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Continue Thiopurines and Anti-TNF Agents If Your IBD Patient Becomes Pregnant: Results from the Pregnancy in IBD and Neonatal Outcomes (PIANO) Study

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IBD

This summary reviews Mahadevan U, Long MD, Kane SV, et al. Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease. Gastroenterology 2021;160 (4):1131-1139.

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STRUCTURED ABSTRACT

Question: Are biologic, thiopurine, or combination therapy for inflammatory bowel disease (IBD) during pregnancy associated with increased adverse maternal and fetal outcomes?

Design: Prospective, multicenter, observational cohort study.

Setting: Thirty centers in the United States.

Patients: There were 1,712 pregnant women with inflammatory bowel disease (IBD) enrolled between 2009 and 2019, representing 1,490 completed preg-

nancies, 1,431 live births, and 1,010 infants with 1-year developmental measurements available.

Exposures: Primary exposures included thiopurines or biologics used in the 3 months before the last menstrual period or during pregnancy. Women were divided into 4 exposure groups: unexposed (no use of thiopurines or biologics, but could include use of antibiotics, mesalamine, or steroids), thiopurine exposed, biologic exposed, and combination therapy (thiopurine and biologic) exposed. Study patients completed detailed questionnaires at study entry, each trimester, and 4, 9, and 12 months after birth.

Outcome: Five primary outcomes were spontaneous abortion (SAB), preterm birth, low birth weight, congenital malformations, and infant infections (serious or non-serious). Secondary outcomes were stillbirth, intrauterine growth restriction, small for gestational age, placental abruption, eclampsia, pre-eclampsia, cesarean section, fetal distress, and infant intensive care unit admission. Developmental milestones were also assessed at 12, 24, 36, and 48 months, and included communication, fine and gross motor skills, personal, social, and problem solving.

Data Analysis: Incidence of pregnancy and neonatal outcomes among women exposed to thiopurines, biologics, or combination therapy were compared to those of women who were unexposed to these agents. Adjusted odds ratios (OR) were calculated using multivariable logistic regression adjusting for relevant confounders (including disease activity, maternal and infant characteristics, and prior SAB) (**Figure 1**). Cox proportional hazard models were constructed to assess predictors of SAB within 20 weeks.

Funding: The study was funded by the Crohn's & Colitis Foundation, Lisa and Douglas Goldman Foundation, Lab and Valibhav Goel Foundation, and the National Institutes of Health.

Results: Exposure to thiopurines, biologics, or combination therapy were not associated with an increased risk of congenital malformations, SAB, preterm birth, low birth weight, or infections during the infant's first year of life. Higher IBD activity was associated with a greater risk of SAB (hazard ratio [HR]= 3.41; 95% confidence interval [CI]: 1.51-7.69), and preterm birth was associated with an increased risk of infant infections (OR= 1.73; 95% CI: 1.19-2.51) (**Figure 2**).

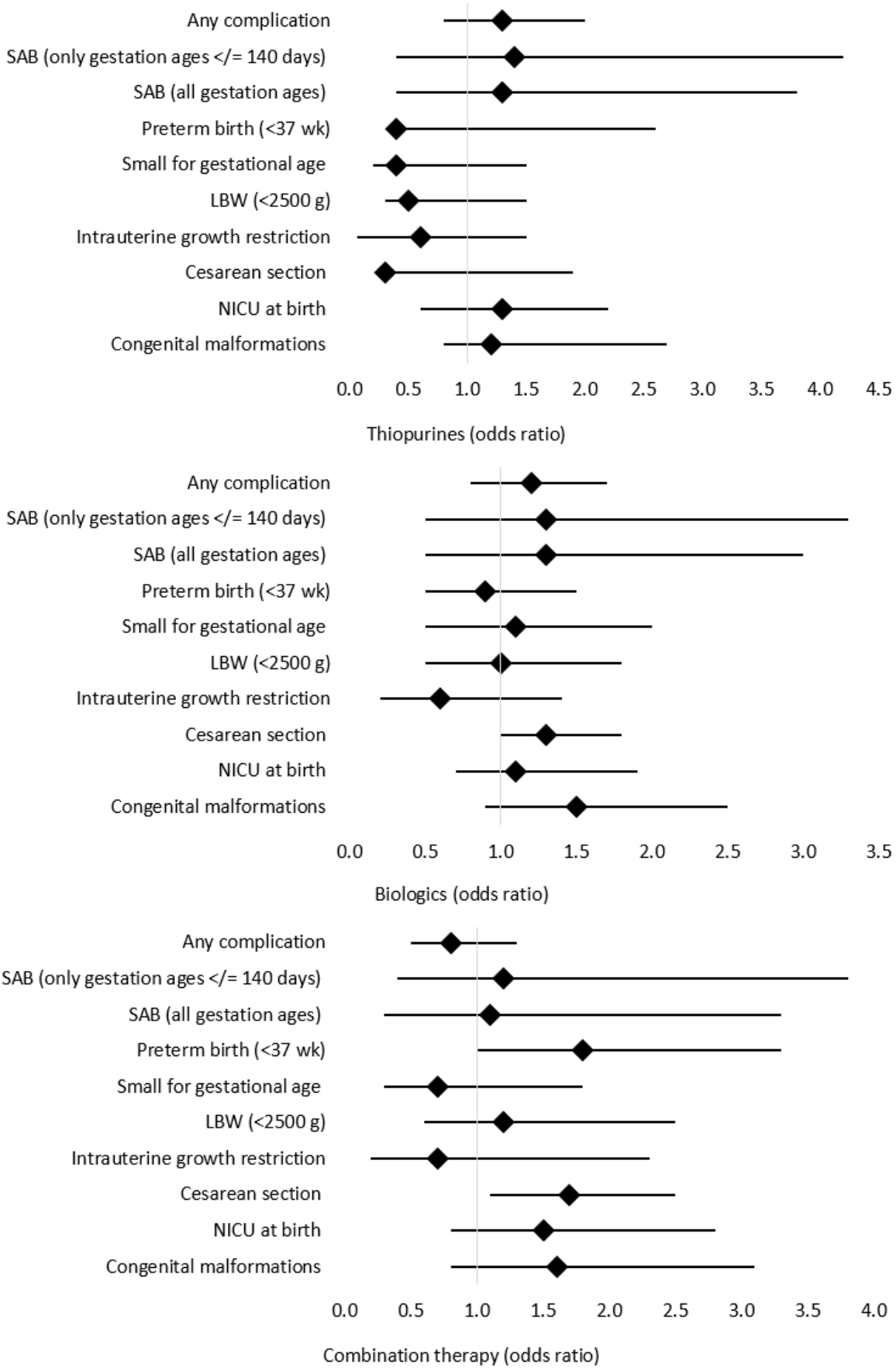

Figure 1. Adjusted odds ratios for the association of inflammatory bowel disease (IBD) therapies with adverse pregnancy-related outcomes (controlling for maternal age, steroid use, and IBD activity). LBW, low birth weight; NICU, neonatal intensive care unit; SAB, spontaneous abortion.

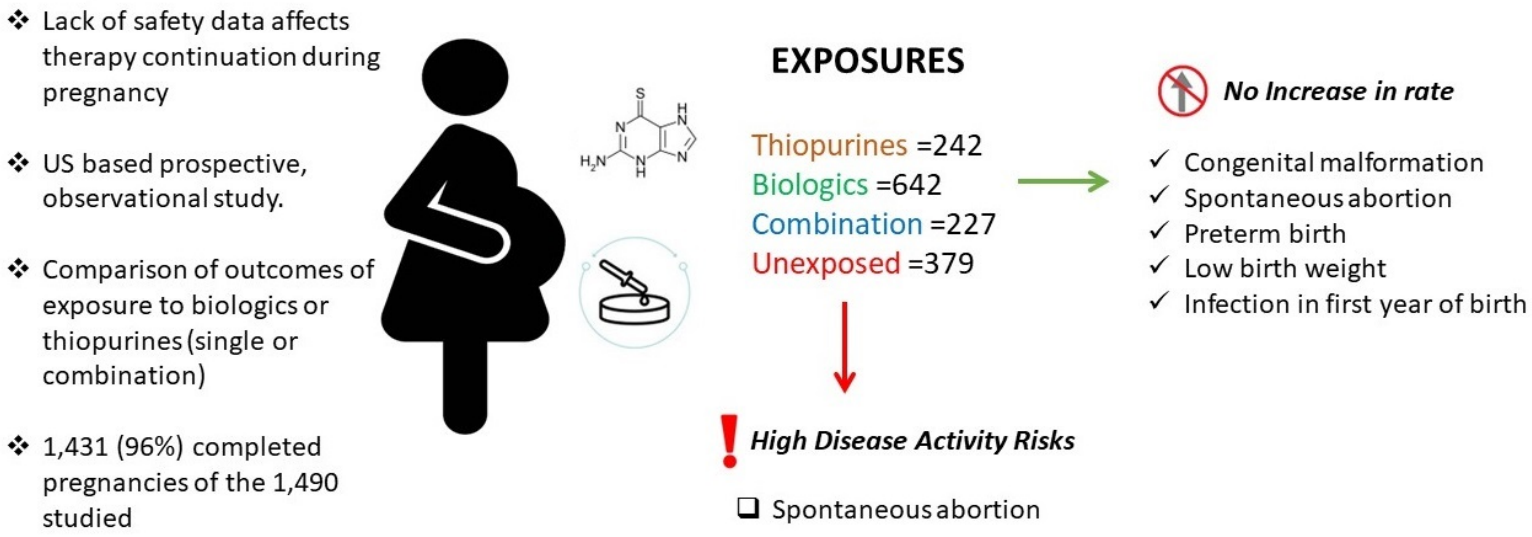

Figure 2: Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease

COMMENTARY

Why Is This Important?

Women with IBD are more likely to have pregnancy-related complications compared to women without IBD.[1] Higher disease activity is associated with adverse pregnancy outcomes, and retrospective data from France indicated that discontinuation of anti-tumor necrosis factor (TNF) therapy before week 24 of pregnancy increases the risk of an IBD flare.[2,3] However, there has been hesitancy among patients and providers to continue thiopurine and biologic therapies during pregnancy due to the potential risk of maternal complications, congenital malformations, and infections.[2] In fact, European guidelines suggest stopping biologics at 22 weeks gestation, although this may increase the risk of IBD flares.

Recent American guidelines recommended continuation of thiopurines and anti-TNF agents during pregnancy, but this was based on low-quality evidence (4). Therefore, additional data was sorely needed to demonstrate the safety of continuing thiopurines and biologics during pregnancy, as this practice would minimize the risk of disease flares and subsequent complications.

The Pregnancy in IBD And Neonatal Outcomes (PIANO) Study greatly expands our knowledge as the largest prospective study assessing the safety of biologics and thiopurines in pregnancy. It provides comprehensive information about demographics, changes in disease activity and maternal and infant outcomes.

Key Study Findings

In this prospective cohort study of 1,712 pregnant women with IBD, thiopurine and biologic use were not associated with an increased risk of congenital malformations, SABs, preterm birth, low birth weight, or infant infections within 1 year, but increased IBD

activity was associated with an increased risk of SAB (hazard ratio= 3.41; 95% confidence interval: 1.51-7.69). Also, these drug exposures were not associated with any differences in developmental milestones in the first year of life.

Caution

Data regarding maternal and neonatal outcomes are self-reported by the mothers, rather than obtained and confirmed by the medical record. This raises the potential of misclassification bias. Selection bias is also possible due to loss to follow-up; however, this was not observed differentially by drug exposure group.

The study also did not assess small molecule therapies (e.g., tofacitinib, upadacitinib, and ozanimod) or recently approved biologic agents for IBD such as risankizumab. Additionally, the makeup of biologic users was predominantly anti-TNF (e.g., infliximab, adalimumab), with only 8.6% of patients exposed to anti-integrin (e.g., vedolizumab) or anti-interleukin 12/23 agents (e.g., ustekinumab). Therefore, the results of this study may not apply to users of non-anti-TNF biologics.

My Practice

When my female patients with IBD on biologic or thiopurine therapies become pregnant, I continue these agents throughout pregnancy to minimize the risk of IBD flares and the need for corticosteroids. I also counsel my patients regarding the importance of optimizing disease control prior to pregnancy, as data indicates that IBD flares and corticosteroid use are associated with adverse pregnancy outcomes (3,5). I currently discontinue small molecules such as tofacitinib, upadacitinib, and ozanimod, which do not have adequate safety data for use during pregnancy.

For Future Research

Data regarding the use of non-anti-TNF biologics during pregnancy are limited. As the spectrum of biologic therapies for IBD continues to expand, future research should expand on the safety of utilizing agents such as vedolizumab, ustekinumab, and risankizumab during pregnancy. Additionally, research is needed regarding the impact of biologic and thiopurine exposures on infant developmental milestones beyond 1 year.

Conflicts of Interest

Dr. Dalal has received grant support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs. Dr. Allegretti has received grant support from Janssen Pharmaceuticals, Pfizer Pharmaceuticals, and Merck Pharmaceuticals, and has served as a consultant for Janssen Pharmaceuticals, Pfizer Pharmaceuticals, AbbVie Pharmaceuticals, Ferring Pharmaceuticals, Merck Pharmaceuticals, Bristol Myers Squibb, Seres Therapeutics, Finch Therapeutics, Iterative Scopes, and Takeda Pharmaceuticals.

Note: The authors of the article published in *Gastroenterology* are active on social media. Tag the to discuss their work and this EBGI summary!

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REFERENCES

1. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology 2007;133(4):1106-12.
2. Luu M, Benzenine E, Doret M, et al. Continuous Anti-TNFα Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION). Am J Gastroenterol 2018;113(11):1669-1677.
3. 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 Sep 2007;102 (9):1947-54.
4. Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group. Gastroenterology 2019;156(5):1508-1524.
5. Odufalu FD, Long M, Lin K, Mahadevan U, et al. Exposure to corticosteroids in pregnancy is associated with adverse perinatal outcomes among infants of mothers with inflammatory bowel disease: results from the PIANO registry. Gut 2022;71 (9):1766-1772.