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Continuing Anti-TNF Agents Past 24 Weeks of Pregnancy Associated with Fewer IBD Relapses with No Increase in Adverse Fetal Outcomes

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This summary reviews Meyer A, Neumann A, Drouin J, et al. Benefits and Risks Associated With Continuation of Anti-Tumor Necrosis Factor After 24 Weeks of Pregnancy in Women With Inflammatory Bowel Disease: A Nationwide Emulation Trial. Ann Intern Med. 2022 Oct;175(10):1374-1382

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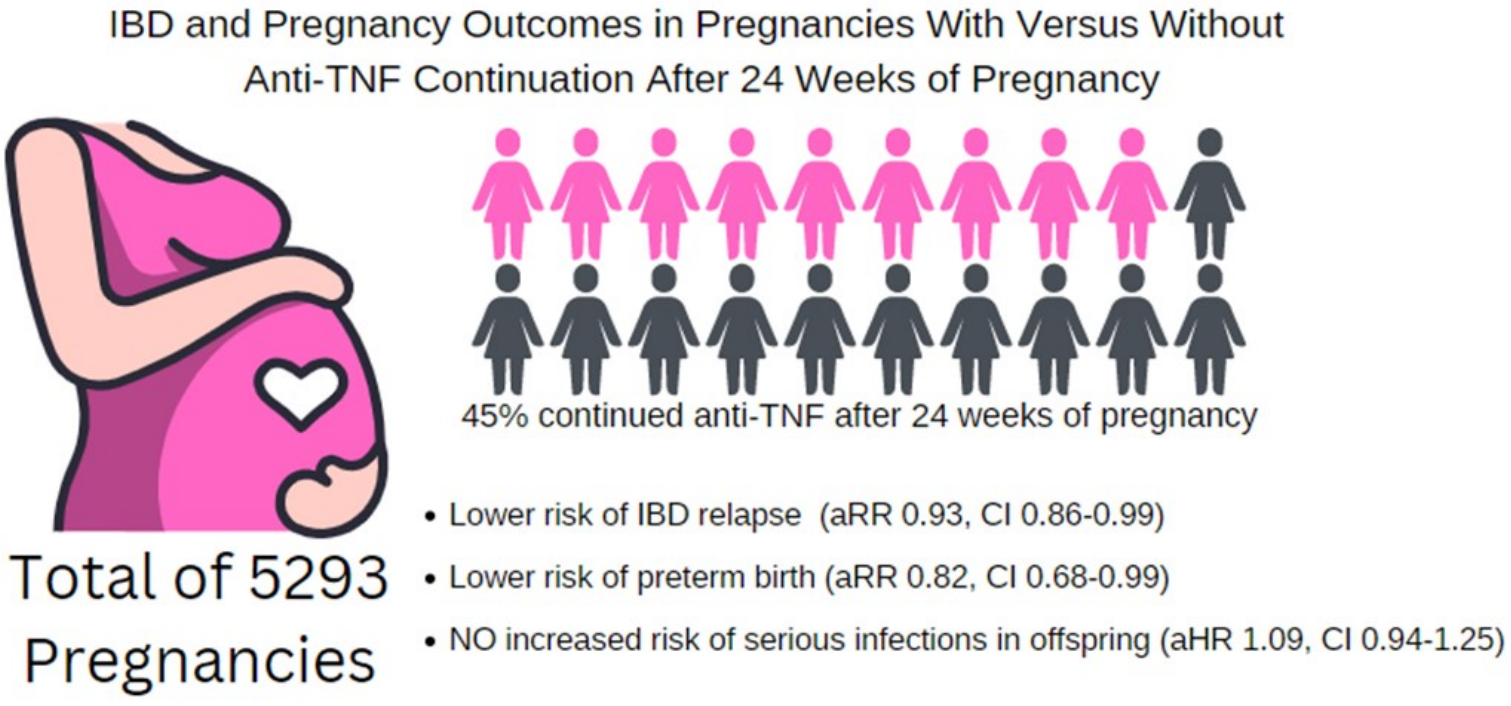

STRUCTURED ABSTRACT

Question: Does continuing anti-TNFs beyond 24 weeks in pregnancy have an impact on maternal IBD relapse, adverse pregnancy outcomes, or serious infections in the offspring during the first 5 years?

Design: Retrospective, observational cohort study.

Setting: Nationwide population-based study using the French National Health data system (Système National des Données de Santé).

Patients: A total of 5,293 pregnancies with inflammatory bowel disease (IBD) between 2010 and 2020, with a prescribed anti-TNF (infliximab, adalimumab, golimumab, or certolizumab) between conception and 24 weeks of pregnancy. Median age of 29 years, with approximately 80% of patients with Crohn disease. Pregnancies exposed to methotrexate, vedolizumab, ustekinumab, or tofacitinib before 24 weeks were excluded.

Exposure: The "anti-TNF continue" group included any pregnancy with administration or a prescription of an anti-TNF (infliximab, adalimumab, golimumab, or certolizumab) after 24 weeks of gestation, whereas the "anti-TNF stop" group included pregnancies where anti-TNFs were not administered/prescribed beyond 24 weeks.

Outcomes: Three primary outcomes were maternal IBD relapse, adverse pregnancy outcomes, and serious infection in the offspring. IBD relapse was defined by at least 1 oral or rectal corticosteroid dispensing, IBD-related hospitalization, or surgery between 32 weeks and the end of pregnancy, or postpartum (within 6 months after delivery). Adverse pregnancy outcomes included pregnancy-related hospitalizations, cesarean section, stillbirth, prematurity (births before 37 weeks), and low (below tenth percentile) or large (above ninetieth percentile) birthweight. Serious infection in offspring was defined as any infection requiring hospitalization as the primary diagnosis. Children were followed from birth until onset of a serious infection, 5 years of life, or end of the study in December 2020.

Data Analysis: All pregnancies that occurred in women with IBD during the 11-year period were included in the analyses. A comparison of the risks for IBD relapse and adverse pregnancy outcomes between the 2 groups, anti-TNF continue and anti-TNF stop groups, was performed. A multivariate logistic regression model was used to predict risks and their ratios. A marginal Cox model with inverse probability weighting to compute hazard ratios was used to compare risk for serious infections in the offspring.

Funding: No private funding, done at the initiative of French National Health Service.

Results: Approximately 55% of pregnant women treated for IBD discontinued anti-TNF treatment before 24 weeks of pregnancy. Prescription of anti-TNF during pregnancy beyond 24 weeks of gestation was associated with less IBD relapse (adjusted rate ratio [aRR] 0.93, 95% confidence interval [CI] 0.86–0.99), a lower rate of prematurity (aRR 0.82, CI 0.68-0.99), and no difference in the overall rate of serious infections in the offspring (adjusted hazard ratio [aHR] 1.08, CI 0.94-1.25). **(Figure 1)** Importantly, 88.3% of women who had continued anti-TNF after 24 weeks of pregnancy were still treated with anti-TNF after 6 months of delivery, whereas only 71.1% of those who had stopped anti-TNF therapy before 24 weeks had it restarted. This study followed infants for risk of serious infections up to 5 years of age showing no increase in overall risk of infections throughout the first 5 years of the infants' life.

COMMENTARY

Why Is This Important?

Pregnant women with IBD are more likely to have pregnancy-related complications.[1] Studies have shown that women are likely to stop anti-TNF treatment during pregnancy, often on the recommendation of their physician, with discrepancy among the North American and European guidelines on continuing anti-TNF therapy in late pregnancy.

North American IBD guidelines recommend continuing anti-TNF agents in pregnant IBD patients beyond 24 weeks.[2] However, previous European guidelines recommend stopping anti-TNF agents around week 24-26 of gestation to limit neonatal exposure, due to concerns about levels of inflixi-

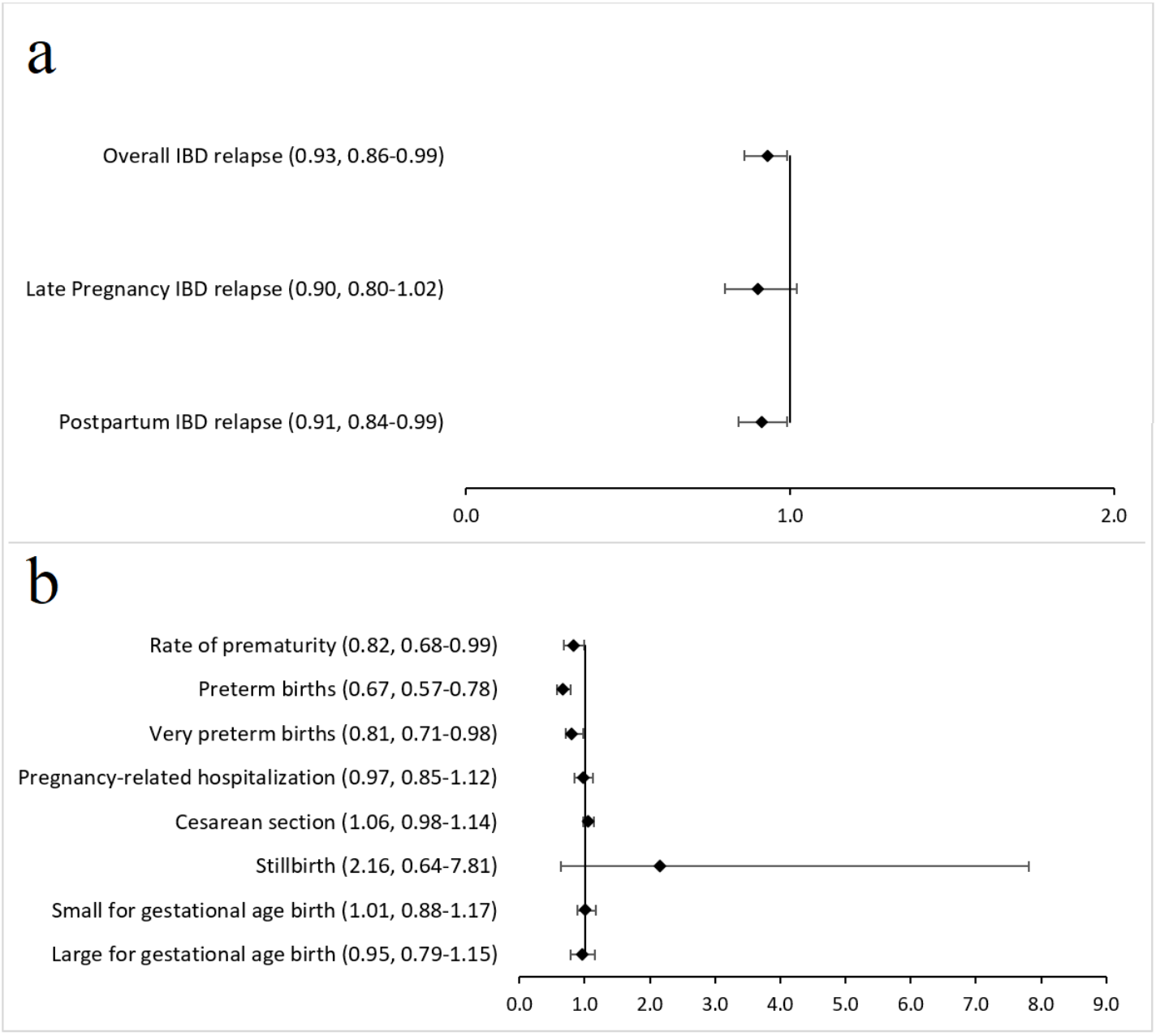

Figure 1: (a) IBD related outcomes. **(b)** Pregnancy related outcomes. Adjusted rate ratio, 95% confidence interval.

mab and adalimumab in the fetus that can persist up to 7 months.[3] Results from the recent PIANO study, a large prospective cohort study of 1,712 pregnant women with IBD on either no therapy, thiopurine, biologic, or combination therapy revealed no increase in adverse pregnancy or fetal outcomes in patients on therapy, however, higher disease activity in patients not on therapy was associated with worse outcomes[4] These data are partly responsible for updated guidelines from the European Crohn's and Colitis Organisation, which now support continuing anti-TNF agents through the third trimester.[5]

Key Study Findings

This large study from France revealed that 55% of pregnant patients discontinued anti-TNF therapy after 24 weeks of gestation. Patients who continued anti-TNF therapy had better pregnancy outcomes overall, with lower IBD relapses and lower risk of premature births, without an increase in overall serious infections in infants up to 5 years of age.

Caution

This study was conducted using the French National Health data system, and algorithms rather than actual clinical data were used to identify patients with IBD, pregnancies, or serious infections. Drug administration was identified by either a dispensed prescription of a subcutaneous drug or facility administration of an infusion, however, subgroup analyses based on the infliximab group (administered in-hospital in France) yielded similar results. This study also evaluated only anti-TNF agents, and as such results cannot be generalized to non-anti-TNF biologics.

My Practice

Guided by the Toronto Consensus statement, the AGA care pathway, and evidence from the PIANO study, we discuss the overall safety of anti-TNF agents during pregnancy versus the risk of active disease. We strongly counsel my patients based on available evidence to continue their biologic therapy through pregnancy. This study provides further evidence that the use of anti-TNF agents throughout pregnancy is not associated with worse outcomes, but rather lower disease relapse and risk of adverse pregnancy outcomes. We discuss with patients the importance of optimizing disease control prior to conception and throughout the pregnancy with emphasis on the importance of adequate disease control in late pregnancy to minimize adverse pregnancy outcomes for mother and child.

For Future Research

With the introduction and more widespread use of non-anti-TNF biologics and small molecules, we are faced with similar questions regarding the safety of these newer agents. Future research should focus on the safety of these medications during pregnancy and lactation as well as impact on response to vaccine and long-term risks of infection, immune-mediated disease, and other health outcomes. This will improve our shared decision making with patients regarding the use of these agents in IBD pregnancy–a high risk state with an increase in adverse maternal and fetal outcomes.

Conflicts of Interest

Dr. Abu-Heija and Dr. Schoenfeld report no potential conflicts of interest for this summary. Dr. Mahadevan reports being a consultant for AbbVie, Janssen, Takeda, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Protagonist, Prometheus Biosciences, Rani Therapeutics, Surrozen, Gilead, and Eli Lilly.

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