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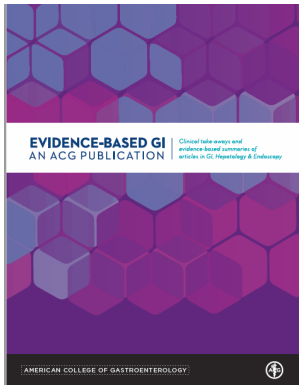

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CRC SCREENING

Time to Increase Adenoma Detection Rate Benchmarks for Screening Colonoscopies

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Jeffrey Lee, MD, MPH
Associate Editor

This summary reviews Schottinger JE, Jensen CD, Ghai NR, et al. Association of Physician Adenoma Detection Rates With Postcolonoscopy Colorectal Cancer. JAMA. 2022 Jun 7;327(21):2114-2122.

Correspondence to Jeffrey Lee, MD, MPH. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: What are the associations between physician adenoma detection rates (ADRs) and patients' risk of post-colonoscopy colorectal cancer (PCCRC) across a broad range of ADR values?

Design: Retrospective cohort study.

Setting: Three community-based integrated healthcare settings in the United States: Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Kaiser Permanente Washington.

Patients: Among 735,396 patients who had 852,624 negative colonoscopies (i.e., negative for CRC) performed by 383 physicians, 51.6% were females and the median age was 61.4 years (interquartile range [IQR]: 55.5-67.2).

Exposure: The ADR of each patient's physician based on screening examinations in the calendar year prior to the patient's negative colonoscopy. ADR was evaluated as a continuous and dichotomous variable (i.e., less than or

equal to or greater than the median). ADR was also evaluated as a categorical variable to assess potential threshold associations (i.e., <20%, 20%-24.9%, 25%-29.9%, 30%-34.9%, 35%-39.9%, 40%-44.9%, 45%-49.9%, and ≥50%).

Outcome: The primary outcome was PCCRC, diagnosed at least 6 months after any negative colonoscopy (all indications). Secondary outcomes were PCCRCs by location, stage, and stratified by sex, and PCCRC-related deaths.

Results: After 2.4 million person-years of follow-up, 619 PCCRCs and 36 related deaths were observed over a median follow-up of 3.25 years (IQR: 1.56-5.01). The median physician ADR was 28.3%. Higher physician ADRs were significantly associated with lower risks of PCCRC (hazard ratio [HR]: 0.97 per every 1% absolute ADR increase, 95% CI: 0.96-0.98) and related deaths (HR: 0.95 per every 1% absolute ADR increase, 95% CI: 0.92-0.99). Compared with physician ADR below the median (i.e., 28.3%), ADRs at or above the median were significantly associated with a lower risk of PCCRC (1.79 vs 3.10 cases per 10,000 person-years; HR: 0.61, 95% CI: 0.52-0.73). There was a similar reduction in PCCRC-related mortality (0.05 vs 0.22 cases per 10,000 person-years; HR: 0.26, 95% CI: 0.11-0.65). Although a clear threshold was not seen across the 8 ADR groups because of overlapping CIs, a physician ADR between 35%-39.9% was associated with the lowest risk of PCCRC compared with ADRs less than 20% (**Figures 1 and 2**).

Funding: National Cancer Institute/National Institutes of Health.

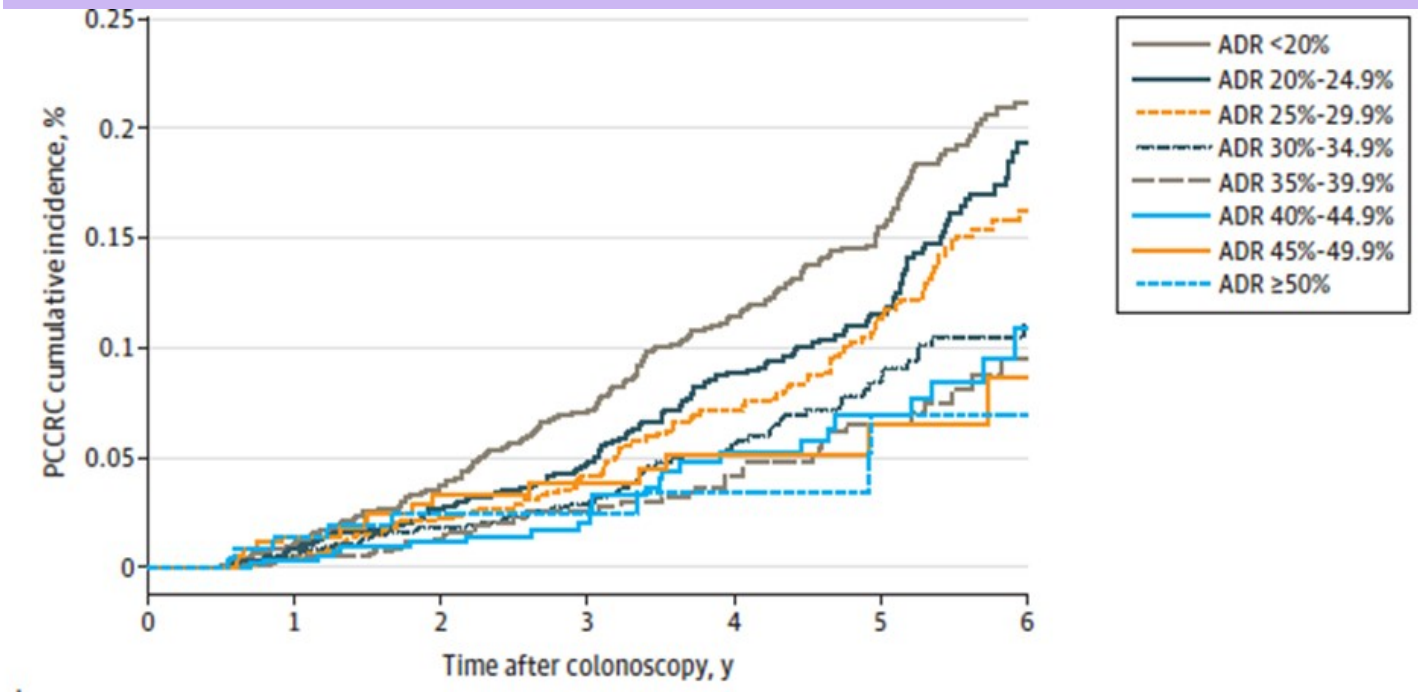

Figure 1. Cumulative Incidence of PCCRC Stratified by ADR

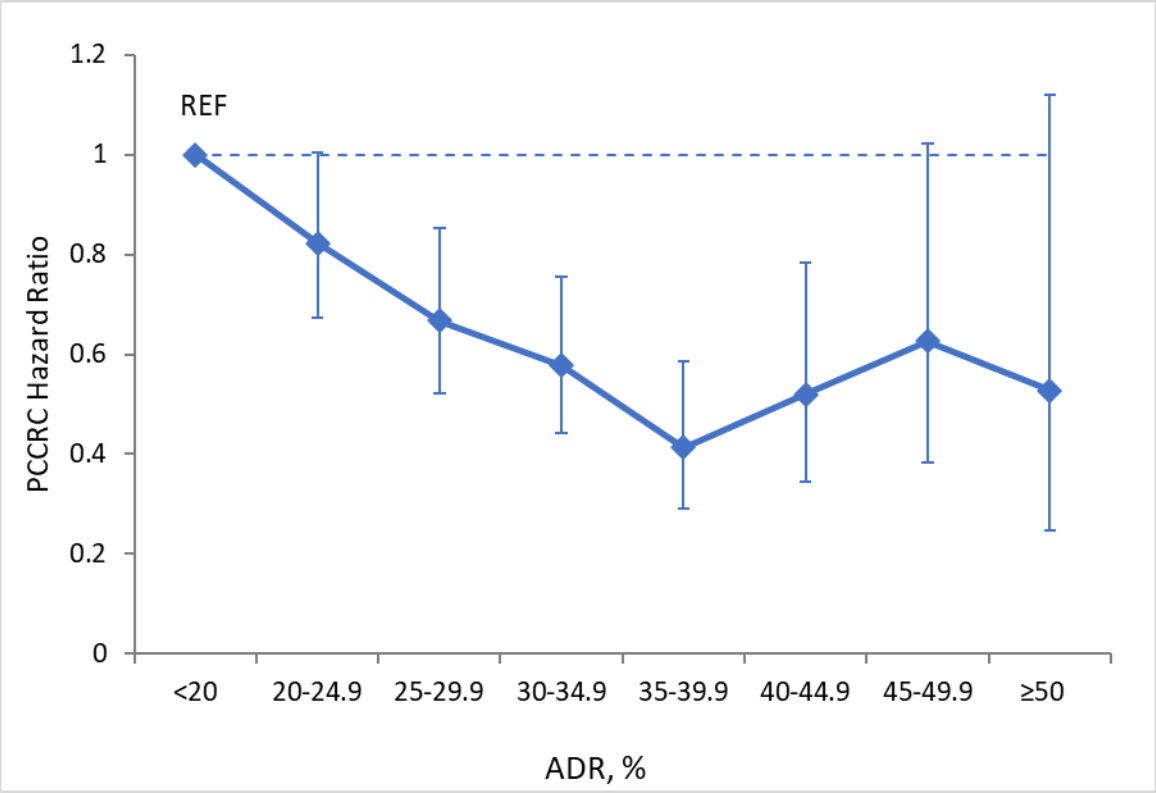

Figure 2: Risk of Post-Colonoscopy Colorectal Cancer (PCCRC) According to Adenoma Detection Rates (ADR)

COMMENTARY

Why Is This Important?

The beneficial effect of colonoscopy on reducing CRC incidence and mortality is largely derived from early detection and removal of adenomas.[1] Studies have consistently shown the magnitude of this benefit varies based on the quality of the colonoscopy examination, particularly the ability to detect adenomas.[2,3] To improve colonoscopy quality, multiple guidelines recommend physician ADR benchmarks of ≥20% for women, ≥30% for men, and ≥25% combined.[4] However, these recommended ADR targets were based on studies that lacked sufficient precision and from time periods when physician ADRs were lower,[2,3] leaving the question of whether ADR benchmarks should be increased or remain the same given improvements in imaging quality and increased emphasis on ADR measurements over the past decade.

This study remedies those limitations. It's the largest cohort study (852,624 negative colonoscopies performed by 383 endoscopists) to demonstrate that higher physician ADR was significantly associated with lower risks of PCCRC, PCCRC-related death, and PCCRC by sex, stage, and location. Also, the study assessed colonoscopies performed between 2010-2017 vs the 1998-2010 timeframe used to identify minimum ADR thresholds of 25%. During the 2010-2017 timeframe, endoscopists routinely reported higher ADRs, partly based on improved bowel preparation techniques, improved endoscopic technology that provide better images, and increased awareness of the importance

of ADRs. Thus, this study provides important data to re-assess minimum ADR thresholds as well as assessing whether or not there is an ADR threshold beyond which higher ADRs do not further lower PCCRC.

Key Study Findings

For each percentage point increase in ADR, the adjusted PCCRC risk and PCCRC-related death was 3% and 5% lower, respectively. Although an ADR threshold was not clearly seen in this study despite its large sample size, an ADR of 35%-39.9% demonstrated the largest reduction in PCCRC risk (HR: 0.41, 95% CI: 0.29-0.59) compared with an ADR <20%. This multi-center cohort study further validates the importance of physician ADR as the key quality indicator for colonoscopy and suggests that minimum and aspirational ADR targets should be increased during the next guideline update.

Caution

Sessile serrated lesions (SSLs) were included in the ADR calculation despite current recommendations in clinical practice to exclude them. Although SSLs are less prevalent compared to conventional adenomas, inclusion of these lesions make comparison across other studies challenging. Nevertheless, flat SSLs in the ascending colon are easily missed and known to be a common etiology for PCCRC.

My Practice

In our medical group, ADRs from screening colonoscopies are provided annually to all gastroenterologists along with other important colonoscopy quality indicators (e.g., cecal intubation rate) to facilitate self-assessment and performance improvement. In addition to measuring ADR, there are several tools and techniques I use to optimize adenoma detection. First, it is critical to use a high-definition colonoscope with image enhancement capabilities (e.g., narrow band imaging) to help detect and evaluate subtle lesions. Second, it is important to have a mindset for detecting flat polyps since these lesions are often missed. Third, I maximize mucosal exposure by "working the folds" (i.e., deflecting the tip of the colonoscope into the inner-haustral valley and exposing the proximal sides of each haustral folds), cleaning and suctioning any stool debris, and distending the lumen adequately. Fourth, I perform 2 or 3 passes in the right colon since adenomas are often missed in this location. Lastly, when available, I often use a distal attachment device such as a clear translucent cap to help expose the proximal sides of each haustral fold and improve mucosal exposure.

For Future Research

Larger studies with more power and longer follow-up are needed for identifying an ADR threshold. The current study lacks statistical power to determine if ADRs > 40% further lower PCCRC because relatively few endoscopists in this cohort had these very high ADRs. Future studies are also needed to evaluate the impact of ADR improvement over time on PCCRC and PCCRC-related deaths. Ultimately, future guidelines and position statements

will update recommendations about including SSLs in ADR calculation, whether to limit ADR to only screening colonoscopies, and comment on whether an ADR > 25% is still an appropriate minimum threshold.

Conflict of Interest

Dr. Lee was a co-author and investigator of this study.

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

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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

Dr Jessica Allegretti
Associate Editor

Dr Rahul S. Dalal
Guest Contributor

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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.

Correspondence to Jessica Allegretti, MD, MPH. Associate Editor. Email: EBGI@gi.org

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**).

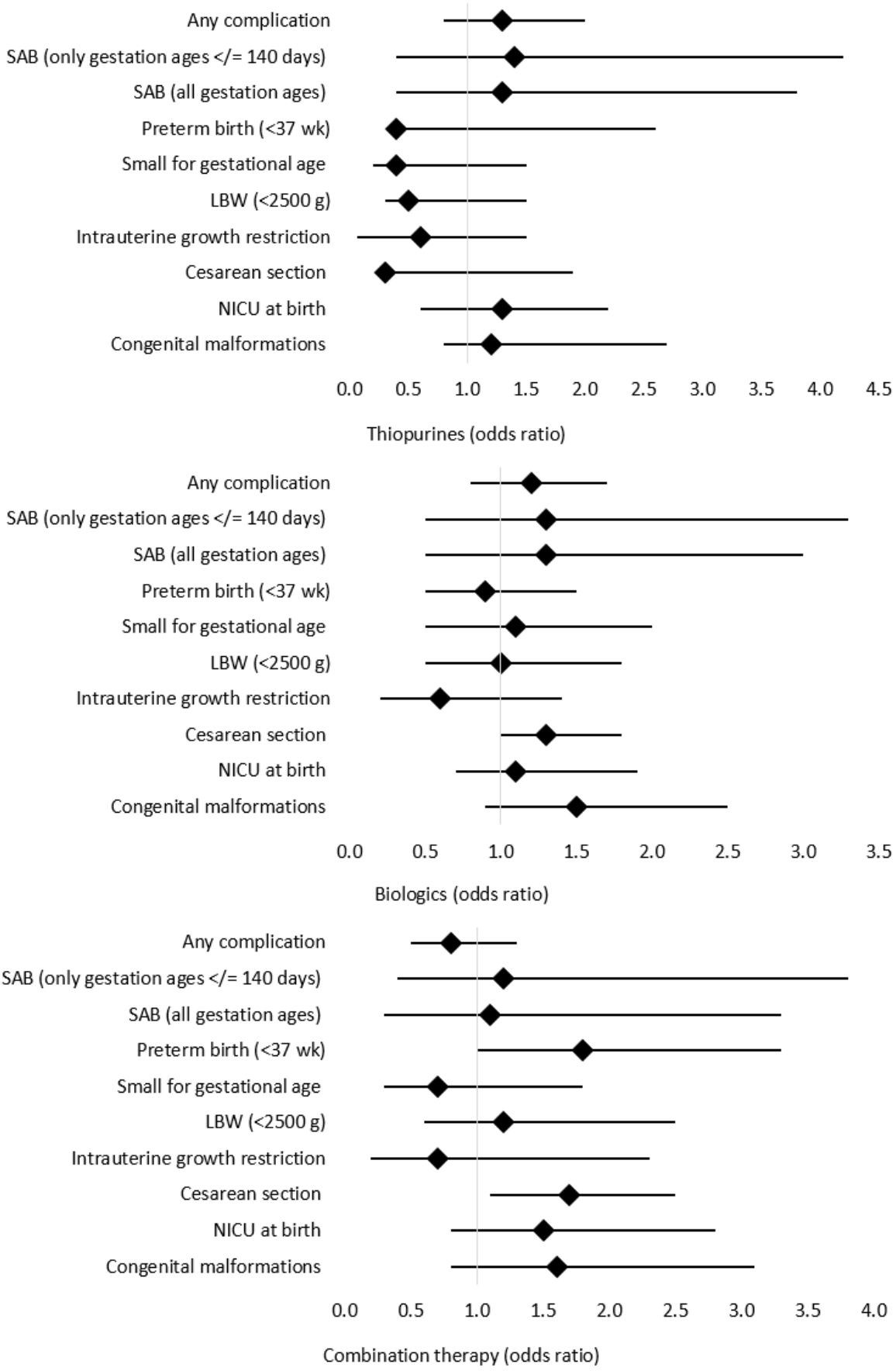

Figure 1. Adjusted odds ratios for the association of inflammatory bowel disease (IBD) therapies with adverse pregnancy-related outcomes (controlling for maternal age, steroid use, and IBD activity). LBW, low birth weight; NICU, neonatal intensive care unit; SAB, spontaneous abortion.

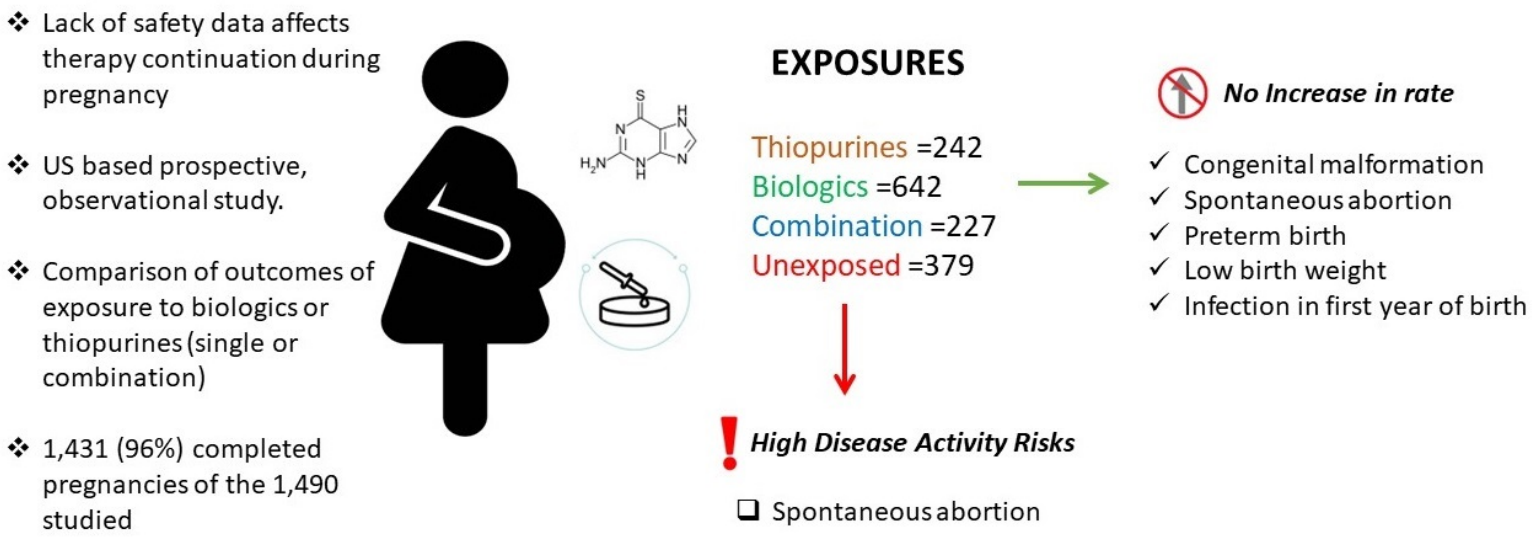

Figure 2: Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease

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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Achieve IBD Remission Before Pregnancy: PIANO Registry Data Shows Adverse Perinatal Outcomes For Infants Associated with IBD Flares and Steroid Use

IBD

Dr Philip Schoenfeld
Editor-in-Chief

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Guest Contributor

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This summary reviews: Odufalu FD, Long MD, Lin K, Mahadaven U for PIANO Investigators. Exposure to Corticosteroids in Pregnancy Is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with Inflammatory Bowel Disease. Gut 2022; 71: 1766-72.

Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Cheif. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is corticosteroid use in inflammatory bowel disease (IBD) patients during pregnancy associated with increased adverse maternal and fetal outcomes?

Design: A prospective, multicenter, observational cohort study.

Setting: Thirty centers in the United States.

Patients: The study enrolled 1,712 pregnant women with IBD between 2009 and 2019, representing 1,490 completed pregnancies, 1,431 live births, and 1,010 infants with one-year developmental measurements available.

Exposures: Corticosteroid use by oral, enema, or IV routes of administration stratified by 4 points in time: preconception, first trimester, second trimester, and third trimester. Study patients completed detailed questionnaires at study entry, each trimester, and 4, 9, and 12 months after birth. Questionnaires pro-

vided demographic data, IBD history, IBD activity, medication exposure, pregnancy outcomes, postpartum outcomes and complications. IBD activity was measured with modified Harvey Bradshaw Index for Crohn's Disease (CD) and the simple clinical colitis activity index (SCCAI) for ulcerative colitis (UC)

Outcome: Primary outcomes were infant outcomes, including adverse pregnancy-related events, congenital malformations, infections, and neurocognitive development during the first 12 months. Secondary outcomes were maternal outcomes of delivery complications, preterm labor, caesarean sections, and trends in IBD activity.

Data Analysis: Bivariate statistics and multivariate logistic regression models were used to compare pregnancy outcomes by corticosteroid exposure. Odds ratios were adjusted for relevant confounders, including preterm birth, maternal disease activity, and classes of medication use.

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: Corticosteroid use was associated with preterm birth (odds ratio [OR]= 1.79; 95% confidence interval [CI]: 1.18-2.73); low birth weight (OR= 1.76; 95% CI: 1.07-2.88), and NICU admission (OR= 1.54; 95% CI: 1.03-2.30). (**Table 1**) Late corticosteroid use (second and/or third trimester) was associated with serious infant infections at 9 months (4% vs 2%, *P*= 0.03) and 12 months (5% vs 2%, *P*= 0.001). Orofacial clefts were also more numerous among infants exposed to corticosteroids in utero: 5 vs 1.

Event	No steroid exposure (n = 1058)	Steroid exposure (n = 432)	P value
Spontaneous Abortion (SAB)	4% (n = 39)	6% (n = 15)	0.14
Preterm birth (< 37 weeks)	8% (n = 81)	13% (n = 51)	0.008
Small for Gestational Age	4% (n = 34)	6% (n = 24)	0.03
Low Birth Weight (< 2500g)	6% (n = 54)	10% (n = 37)	0.008
Intra-Uterine Growth Retardation	2% (n = 16)	3% (n = 14)	0.03
NICU Admission	9% (n = 87)	13% (n = 50)	0.03
Any congenital malformation	9% (n = 86)	10% (n = 40)	0.37

Table 1. Pregnancy Complications in Mothers with IBD and Corticosteroid Exposure

COMMENTARY

Why Is This Important?

Corticosteroid use and IBD flares have each been associated with adverse maternal and fetal outcomes.[1] However, there is very limited data about the risk of corticosteroid use during pregnancy in IBD patients. In order to appropriately counsel IBD patients prior to conception and during pregnancy, precise data about the risks of corticosteroids, IBD flares, and medications that produce steroid-free remissions were needed. The Pregnancy in IBD and Neonatal Outcomes (PIANO) Study is the largest prospective cohort study about this topic and provides comprehensive data to address these issues. Prior reports from the PIANO Study have demonstrated no increased risk of adverse maternal or fetal outcomes with thiopurines or biologic agents.[2]

Key Study Findings

In the largest (n= 1,712) prospective cohort study of pregnant IBD patients, corticosteroid use was associated with an increased risk of preterm birth, low birth weight, and intra-uterine growth retardation. Both disease activity and steroid use probably contributed to these outcomes.

Caution

Again, the occurrence of IBD flares and corticosteroid use are linked, so the precise impact of steroid use vs IBD flares on pregnancy outcomes cannot be completely separated. Also, due to the self-reporting nature of study questionnaires, specific data on dose and duration of steroid use is unavailable.

My Practice

Achieving corticosteroid-free endoscopic and clinical remission prior to conception is the goal with IBD patients. We educate our IBD patients of child-bearing age that immunomodulators and biologic agents should be used, if needed, and that these treatments should be continued during pregnancy to minimize the risk of IBD flares.[2] If steroids are needed to manage IBD flares during pregnancy, we focus on using the lowest possible dose for the shortest period.

For Future Research

Larger cohorts of steroid-using pregnant patients will be needed to precisely define the risk of oro-facial clefts in their infants, although available data suggests that steroids increase the risk of this congenital malformation.

Conflict of Interest

Dr. Schoenfeld has no relevant conflicts of interest. Dr. Charabaty has served as a consultant/advisory board member for AbbVie Pharmaceuticals, Takeda Pharmaceuticals, Pfizer Pharmaceuticals, Bristol Myers Squibb Pharmaceuticals, and Janssen Pharmaceuticals.

Note: The authors of the article published in *Gut* are active on social media. Tag them to discuss their work and this EBGI summary.
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EVIDENCE-BASED GI
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In Case You Missed It: To PPI or not to PPI: Pantoprazole Prophylaxis Does Not Reduce 90-day Mortality and Clinically Significant Adverse Events in ICU Patients

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This summary reviews: Krag M, Marker S, Perner A et al. Pantoprazole in Patients at Risk for Gastrointestinal for Gastrointestinal Bleeding in the ICU. N Engl J Med 2018; 379; 2199-2208.

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STRUCTURED ABSTRACT

Question: Does prophylactic pantoprazole reduce the risk of gastrointestinal (GI) bleeding in critically ill patients admitted to the intensive care unit (ICU)?

Setting: From January 2016 through October 2017, 33 ICUs in Denmark, Finland, the Netherlands, Norway, Switzerland, and the United Kingdom served as study sites.

Participants: Patients considered for the study were 18 years of age or older and admitted to the ICU for an acute condition with at least 1 risk factor for clinically important GI bleeding including shock, anticoagulation use, renal-replacement therapy, mechanical ventilation expected to last >24 hours, history of liver disease or ongoing coagulopathy.

Intervention/Exposure: The study was an international, multicenter, stratified, parallel-group, placebo-controlled, and blinded clinical trial. Enrolled patients were randomized to receive intravenous (IV) pantoprazole 40 mg or placebo as a single daily dose from randomization until ICU discharge or death (maximum of 90 days).

Outcomes: The primary outcome was death within 90 days of randomization. Secondary outcomes included clinically important GI bleeding (i.e. overt GI bleeding with at least 1 of the following within 24 hours of bleeding onset: spontaneous decrease in systolic blood pressure, mean arterial blood pressure, or diastolic blood pressure of 20 mmHg or more, treatment with a vasopressor or a 20% increase in vasopressor dose, decrease in hemoglobin of at least 2 g per deciliter, or transfusion of 2 or more units of packed red cells); infectious adverse events in ICU (new-onset pneumonia or *Clostridioides difficile* infection); serious ICU adverse reactions; acute myocardial infection; and percentage of days alive without the use of life support. Outcome data were assessed by chart review while mortality was identified using regional and national registries, or direct contact with participants or surrogates.

Data Analysis: Intention-to-treat and per protocol analyses were performed. Binary logistic regression was used to estimate the relative risk of the primary outcome adjusted for the trial site. The primary outcome in the per-protocol population was also assessed in prespecified subgroups. Dichotomous secondary outcomes were also evaluated using a binary logistic regression of the intention-to-treat population adjusted for stratification variables and predefined risk factors. Unadjusted chi-square testing for binary outcome measures was also performed. Importantly, there was no adjustment for multiple comparisons of the secondary outcomes. A 2-sided *P*-value of <0.05 was considered statistically significant for the primary outcome with 95% confidence intervals (CI).

Funding: Innovation Fund Denmark.

Results: During the study period, 3,298 patients were enrolled with 1,645 randomly assigned to the pantoprazole arm, while 1,653 were assigned to the placebo arm. Ninety-day vital data were obtained for

99.5% of participants. Baseline characteristics were comparable in both groups except for chronic lung disease, coagulopathy, and emergency surgery. At 90 days after randomization, no difference was seen in mortality rate, 31.1% (n=510) in the pantoprazole group vs 30.4% (n=499) in the placebo group (relative risk [RR] = 1.02; 95% CI 0.91-1.13, *P*=0.76). In addition, no difference was seen between both groups for the composite secondary outcome of clinically important ICU events, 21.9% (n=360) in the pantoprazole group vs 22.6% (n=372) in the placebo group (RR = 0.96, 95% CI 0.83-1.11). While fewer patients in the pantoprazole group had a clinically important GI bleed compared to the placebo group (2.5% vs 4.2%; RR = 0.58, 95% CI: 0.40-0.86), the absence of correction for multiple comparisons limited the interpretation of the relative risk. Results were similar with adjustment for baseline risk factors and in the per-protocol population. The proportions of patients in either group with the other secondary outcomes and with single components of the composite outcome were similar between groups.

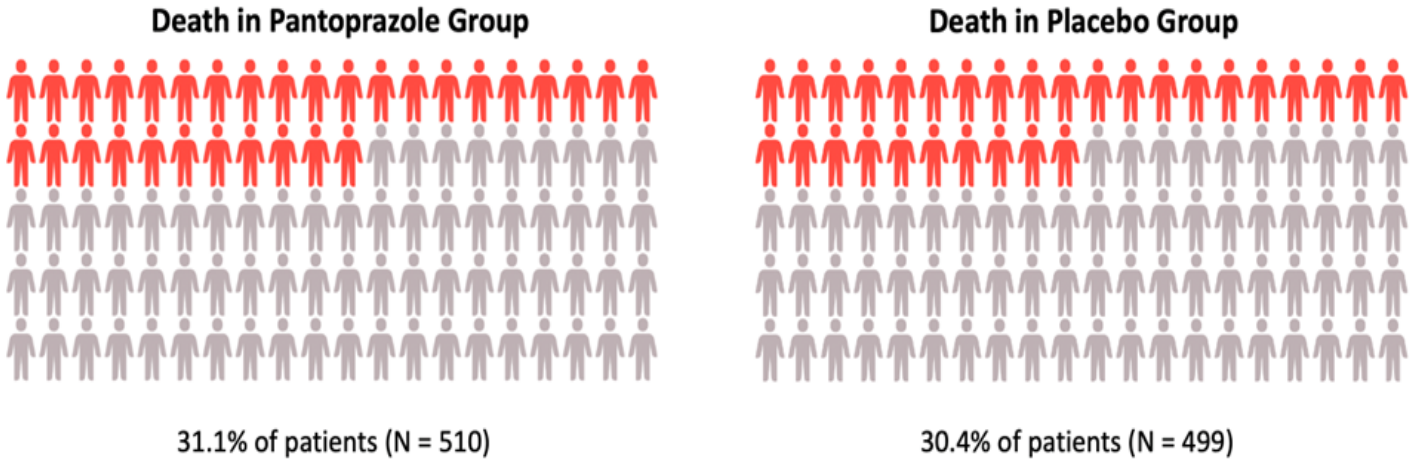

Figure 1: Death by 90 days after randomization to pantoprazole and placebo group (relative risk, 1.02; 95% confidence interval, 0.91 to 1.13).

Figure 2: Occurrence of at least 1 clinically important intensive care unit event (relative risk, 0.96; 95% CI, 0.83 to 1.11).

COMMENTARY

Why Is This Important?

It is estimated that 2.5% of adults admitted to the ICU develop upper GI bleeding.[1] Historically, antisecretory therapies including proton pump inhibitors (PPI) or histamine-2 receptor blockers (H2RB) have been used for stress ulcer prophylaxis.[2] However, the quantity and quality of the evidence supporting stress ulcer prophylaxis is low.[3] Results of the landmark Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit (PEPTIC) trial did not show any difference in in-hospital mortality among ICU patients receiving either PPI or H2RB, although clinically important upper GI bleeding was reported in fewer patients in the PPI group (1.3% vs 1.8%, RR = 0.73; 95% CI: 0.57-0.92).[4] Other trials have also reported similar findings.[3,5] Recently, PPI use has been associated with infection-related complications in the ICU,[6] raising a debate about the benefits vs risks of PPI prophylaxis in the ICU. This international multicenter study by Krag et al attempts to provide more evidence on the utility of proton pump inhibitors in the ICU for the prevention of clinically significant outcomes.[7]

Key Study Findings

It is important to first note that the overall rate of clinically significant GI bleeding in the ICU was low in general.

The investigators showed that among adult patients in the ICU who were at risk of GI bleeding, there was no difference in mortality at 90 days or the number of clinically important ICU events between patients that received pantoprazole or placebo.

Caution

While this study by Krag et al suggests that PPI prophylaxis does not impact ICU outcomes of mortality, comparable with the results of the PEPTIC trial, it is important to emphasize that the trial was not powered to detect differences in certain outcome measures, including the subgroup analyses. The GI bleeding rate of 4.2% in the placebo group was higher than the 2.5% observed in the pantoprazole group. Unfortunately, no *P*-value was computed because no adjustment for multiple comparisons was performed. The study design also did not mandate diagnostic endoscopy to assess the source of the bleeding.

Importantly, the authors also allude to the fact that the 5%-point difference in 90-day mortality that the study was powered for might be considered large. Finally, a sub-group analysis based on receipt of enteral nutrition which could have impacted the outcomes was also not performed.

My Practice

We have not systematically examined the patterns of PPI use for prophylaxis among our ICU patients. However, anecdotally, practice patterns vary among ICU healthcare providers with stress ulcer prophylaxis for ICU patients still

being commonly prescribed. This may stem from the fact that GI bleed risk assessment is yet to be standardized,[8] and as such, ICU providers would initiate prophylaxis based on their subjective risk assessment. We also routinely initiate enteral feeding via nasojejunal tubes as early as possible, which may play a role in reducing GI bleed risk in our patient population.

For Future Research

More research is needed to standardize GI bleed risk assessment among patients admitted to the ICU.[8] Not only would this help define the highest risk cohorts that may indeed benefit from stress ulcer prophylaxis, but this improved risk stratification could be incorporated in future trials' study design to make results more clinically relevant. In addition, the composite secondary outcomes used in this study (comparable to those in the PEPTIC trial) have been described as difficult to interpret and unvalidated.[8] Future studies exploring the impact of PPI use on ICU outcomes should also consider composite outcomes that may be more similar in pathophysiological mechanisms.

Conflict of Interest

Drs. Okafor and Barkun reported no potential conflict of interest.

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