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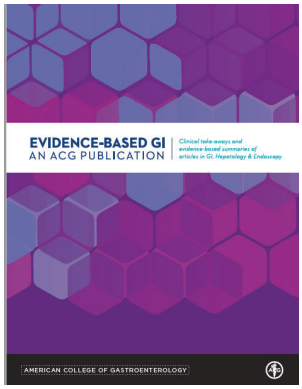

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What to Expect When Expecting — With IBD

Dr. Vasantham Chaudhary
Guest Contributor

Dr. Elie Al Kazzi
Associate Editor

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This article reviews Mahadevan U, Seow CH, Barnes EL, et al. Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease. *Am J Gastroenterol*. Published online August 27, 2025. doi:10.14309/ajg.0000000000003651.

Correspondence to Elie S. Al Kazzi, MD, MPH, Associate Editor Email: EBGI@gi.org

Keywords: pregnancy, preconception, postpartum

STRUCTURED ABSTRACT

Question: How can healthcare providers manage pregnant patients with inflammatory bowel disease (IBD)? How can they counsel patients seeking pregnancy and postpartum care?

Design: The Helmsley PIANO Expert Global Consensus group used GRADE[1] methodology to assess the quality of evidence and formulate recommendations when the evidence is available. For topics lacking data suitable for GRADE, the RAND/UCLA[2] appropriateness method was applied to achieve expert consensus. The population, intervention, comparison, outcome (PICO) format was used. The consensus panel included 39 international experts including gastroenterologists, colorectal surgeons, maternal-fetal medicine specialists, teratologists, and lactation experts.

Patients: Women with IBD before conception, during pregnancy, and in the postpartum period. There is also guidance on vaccine schedules for infants born to

mothers with IBD.

Interventions/Exposure: Ten topics are highlighted in this document: maternal factors impacting pregnancy, fertility, preconception counseling and optimization, management of active disease during pregnancy, management of pregnancy, use of IBD medications during pregnancy, use of IBD medications during lactation, pregnancy adverse events, fetal and neonatal adverse events, and vaccines.

Specific medications were discussed including 5-aminosalicylates, sulfasalazine, corticosteroids, methotrexate, thiopurines, anti-tumor necrosis factor agents, biosimilars, vedolizumab, ustekinumab, IL-23 agents, antibiotics, calcineurin inhibitors, sphingosine-1-phosphate receptor modulators, and Janus kinase inhibitors.

Outcomes: Outcomes discussed included pregnancy adverse events (low birth weight, preterm birth, congenital malformations, spontaneous abortion, and venous thromboembolism), mode of delivery, fetal and neonatal adverse events (neonatal intensive care unit admission, hospitalizations, childhood malignancy, developmental delay, and long-term health outcomes).

Data Analysis: Recommendations were graded as "strong" or "conditional" using the GRADE methodology. With a strong recommendation, providers should recommend the intervention for most patients. A strong recommendation is usually accompanied by High or Moderate Level of Evidence from well-designed randomized controlled trials (RCTs) or RCTs with mild methodologic limitations. With a conditional recommendation, providers might suggest this therapy or diagnostic test, while other providers would not suggest this intervention in similar patients. Conditional recommendations are usually accompanied by Low quality or Very Low quality of evidence from studies without a comparator arm or placebo for comparison. The RAND panel was applied where robust evidence was lacking.

Funding: The Leona M. and Harry B. Helmsley Charitable Trust.

Results: There are 34 recommendations and 35 consensus statements (***Tables 1 and 2***). Topics covered include fertility, management of disease during pregnancy, medications in pregnancy, and fetal and neonatal adverse events.

TABLE 1. GRADE Statements		Recommendation	Level of evidence
Maternal factors impacting pregnancy to be addressed in counseling			
1	We suggest counseling that children with first-degree relatives with IBD, as compared with those without, have an increased risk of development of IBD.	Conditional	Low
Fertility			
2	We suggest counseling that women with IBD may have decreased fertility compared with women without IBD.	Conditional	Very low
3	In women with ulcerative colitis, we suggest counseling that prior ileal pouch anal anastomosis is associated with decreased fertility when compared with women with ulcerative colitis who have not had ileal pouch anal anastomosis.	Conditional	Very low
4	In women with IBD, we recommend counseling that active disease increases the risk of infertility as compared with inactive disease.	Strong	Very low
5	We suggest counseling that women with IBD may have comparable effectiveness of assisted reproductive technology when compared with women without IBD as measured by live birth.	Conditional	Very low
6	We suggest counseling that women with IBD who have undergone pelvic surgery with IBD have similar effectiveness of in vitro fertilization when compared with women without IBD, as measured by live birth.	Conditional	Very low
Preconceptional counseling and optimization			
7	We recommend that women with IBD undergo preconceptional counseling.	Strong	Low
Management of disease activity during pregnancy			
8	We suggest that urgent and emergent IBD surgery during pregnancy be completed when required, and not based on trimester.	Conditional	Very low
Management of pregnancy			
9	We suggest that pregnant women with IBD take low-dose aspirin by 12–16 weeks gestation to prevent preterm preeclampsia.	Conditional	Low
10	We suggest that pregnant women with Crohn's disease and active perianal disease undergo Cesarean delivery.	Conditional	Very low
11	We suggest that pregnant women with IBD and prior ileal pouch anal anastomosis consider Cesarean delivery.	Conditional	Very low
Medications in pregnancy			
12	For women with IBD who are pregnant or attempting conception, we recommend continuing maintenance 5-ASA therapy.	Strong	Low
13	In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance sulfasalazine therapy.	Conditional	Very low
14	In women with IBD who are pregnant, we suggest use of corticosteroid therapy when clinically necessary with appropriate monitoring.	Conditional	Low
15	In women with IBD, we recommend discontinuing maintenance methotrexate therapy prior to conception.	Strong	Very low
16	In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance thiopurine therapy as data does not demonstrate an increased risk of congenital malformations or infant infections.	Conditional	Very low
17	In women with IBD who are pregnant or attempting conception, we recommend continuing maintenance anti-TNF therapy throughout pregnancy.	Strong	Low
18	In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance combination therapy with an anti-tumor necrosis factor and thiopurine therapy throughout pregnancy.	Conditional	Very low
19	In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance vedolizumab therapy throughout pregnancy.	Conditional	Low

(*table continued on next page*)

Table 1 continued

	GRADE Statement	Recommendation	Level of evidence
20	In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance ustekinumab therapy throughout pregnancy.	Conditional	Low
Medications during lactation			
21	We recommend breastfeeding as it is not associated with an increased risk of disease exacerbation in women with IBD.	Strong	Very low
22	We suggest counseling that infants born to mothers on anti-TNF therapy who breastfeed have no increased risk of infection in the first 12 months of life.	Conditional	Very low
Pregnancy adverse events			
23	We suggest counseling that women with IBD as compared with women without IBD have an increased risk of adverse pregnancy outcomes including low birth weight and preterm delivery.	Conditional	Very low
24	We suggest counseling that women with IBD with moderate to severe disease activity have an increased risk of spontaneous abortion as compared with women without IBD or women with mild IBD.	Conditional	Very low
25	We suggest counseling that pregnant women with IBD have an increased risk of VTE during pregnancy as compared with pregnant women without IBD.	Conditional	Low
26	We suggest counseling that pregnant women with IBD have an increased risk of VTE during the postpartum as compared with pregnant women without IBD.	Conditional	Low
Fetal and neonatal adverse events			
27	We suggest counseling that children born to women with IBD have an increased rate of neonatal intensive care unit admissions and hospitalizations in the first year of life compared with children born to women without IBD.	Conditional	Very low
28	We suggest counseling that children born to women with active IBD have an increased rate of small for gestational age and low birth weight compared with children born to women with inactive IBD.	Conditional	Very low
29	We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk for early childhood malignancy.	Conditional	Very low
30	We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk for early childhood developmental delay.	Conditional	Very low
31	We suggest counseling that children born to women treated with thiopurine therapy during pregnancy have no increased risk for early childhood developmental delay.	Conditional	Very low
Vaccines			
32	We recommend that inactive vaccines be provided to children born to mothers with IBD on anti-TNF agents.	Strong	Very low
33	We suggest that live rotavirus vaccine may be provided in children with in utero exposure to biologics.	Conditional	Very low
34	We recommend that live Bacillus Calmette-Guérin vaccine be avoided in the first 6 months[a] of life in children with in utero exposure to anti-TNF therapy due to risk of disseminated tuberculosis and associated mortality.	Strong	Very low

[a]Regional risk should be considered.

5-ASA, 5-aminosalicylate; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; VTE, venous thromboembolism.

Table 2. Consensus statements	
Maternal factors impacting pregnancy	
1	Children born to a parent with Crohn's disease may have a higher risk of developing IBD than children born to a parent with UC.
Fertility	
2	Women with IBD may have reduced fertility compared with women without IBD due to reduced ovarian reserve.
3	Women with IBD may undergo oocyte retrieval without increased risk of flare.
Preconceptional counseling and optimization	
4	Women with IBD desiring contraception should use long-acting reversible contraception over estrogen-containing contraceptives.
5	Women with IBD should be in documented remission and medically optimized prior to elective conception.
Management of disease activity during pregnancy	
6	Endoscopy during pregnancy among women with IBD is low risk but should only be performed if it may change management.
7	If cross-sectional imaging is needed during pregnancy, intestinal ultrasound and MRI without gadolinium are preferred to CT.
8	Fecal calprotectin is useful for monitoring disease activity in pregnant women with IBD.
Management of pregnancy	
9	Pregnancies for women with IBD should be considered as high risk for complications.
10	Women with current or past history of rectovaginal fistulas should deliver by Cesarean delivery.
11	Women with IBD should be assessed early in pregnancy or preconception for nutritional status, weight gain, and micronutrient deficiency.
Medications during pregnancy	
12	Women with IBD who are pregnant and with active disease should start or optimize the same appropriate therapies as in non-pregnant patients, except for thiopurines, methotrexate, JAKis inhibitors, and S1P receptor modulators.
13	In women with IBD who continue thiopurines during pregnancy, precaution should be taken for intrahepatic cholestasis by measurement of liver enzymes, metabolite levels, and consideration of split dosing.
14	Women with IBD who are pregnant and have infections, fistula, or pouchitis that require antibiotics may take an appropriate course of a low-risk antibiotic.
15	Women with IBD may initiate or continue calcineurin inhibitors (cyclosporine and tacrolimus) during pregnancy with careful monitoring if there are no viable alternate treatment options available.
16	Women with IBD who are pregnant or attempting conception should continue biosimilars to existing biologics.
17	Women with IBD who are pregnant or attempting conception should continue anti-interleukin (IL)-23 therapy throughout pregnancy (mirikizumab, risankizumb, guselkumab).
18	Women with IBD should discontinue ozanimod at least 3 months prior to conception unless there is no effective alternative therapy to maintain maternal health.
19	Women with IBD should discontinue etrasimod at least 1–2 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
20	Women with IBD should discontinue tofacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
21	Women with IBD should discontinue upadacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
22	Women with IBD should discontinue filgotinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
Medications during lactation	
23	Mothers with IBD currently on 5-ASA/sulfasalazine may breastfeed.
24	Mothers with IBD currently on thiopurines may breastfeed.
25	Mothers with IBD currently on corticosteroids may breastfeed.
26	Mothers with IBD currently on anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab) may breastfeed.
27	Mothers with IBD currently on anti-integrins (vedolizumab, natalizumab) may breastfeed.

(table continuted on next page)

Table 2 continued	
Consensus statements	
28	Mothers with IBD currently on anti-interleukin-12/23 and anti-interluekin-23 agents may breastfeed (ustekinumab, risankizumab, mirikizumab, guselkumab).
29	Mothers with IBD currently on biosimilars may breastfeed.
30	Mothers with IBD currently on S1P receptor modulators (etrasimod or ozanimod) should not breastfeed.
31	Mothers with IBD currently on JAKis (tofacitinib, upadacitinib, filgotinib) should not breastfeed.
Pregnancy adverse events	
32	Controlling disease activity during pregnancy among women with IBD is critical to reduce adverse outcomes.
Vaccines	
33	Inactive vaccines should be given on schedule to infants of women with IBD regardless of in utero IBD medication exposure.
34	Children exposed to JAKis or S1P receptor modulators in utero may receive live vaccines after 1 month of age.
35	Live vaccines can be given to infants of mothers breastfeeding while on biologics.

5-ASA, 5-aminosalicylate; CT, computed tomography; IBD, inflammatory bowel disease; JAKis, Janus kinase inhibitors; MRI, magnetic resonance imaging; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor.

COMMENTARY

Why Is This Important?

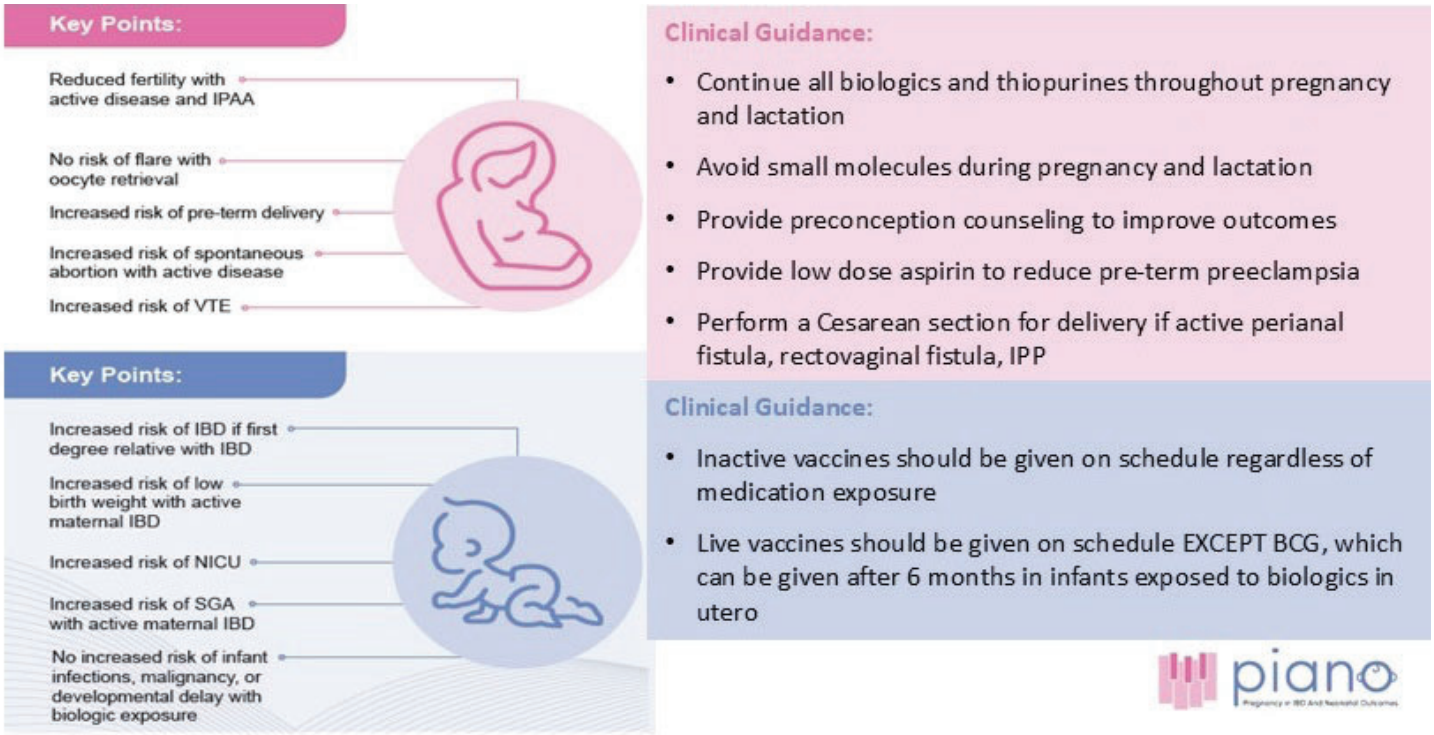
A significant portion of patients with IBD are of child-bearing age and many seek counseling on expectations for fertility, medication use during pregnancy, and pregnancy outcomes. While pregnant women are excluded from clinical trials, there are data from post-marketing registries, insurance databases, and national prospective registries like the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry. This is the first consensus statement on IBD management during pregnancy. Prior publications on this topic, from the United States and Europe, were developed when fewer therapies and less robust safety data were available. Since then, the therapeutic landscape has expanded, with additional biologics and more real-world data supporting safety in pregnancy, lactation and the neonatal period.

Key Study Findings

The guidelines still emphasize the importance of preconception counseling and achieving disease remission prior to conception to lower the risk of adverse pregnancy outcomes. Decreased fertility remains an important outcome in post-surgical patients, especially in patients with ileal pouch anal anastomosis.

There are several new recommendations in this statement.

- A key change is that all biologics, including vedolizumab and IL-23 inhibitors, are now recommended to



Visual abstract: Global Consensus on the Management of Pregnancy in IBD.
BCG, Bacillus Calmette-Guerin; IBD, inflammatory bowel disease; IPAA, ileal pouch anal anastomosis; NICU, neonatal intensive care unit; SGA, small gestational age; VTE, venous thromboembolism.

be continued during pregnancy. Prior recommendations recommended continuing anti-TNF agents but were more cautious around newer agents.

- There is also a recommendation to initiate aspirin between gestational weeks 12 and 16 for pre-eclampsia prevention.
- Another new recommendation is that the live rotavirus vaccine can now be given on schedule even after in utero biologic exposure, and that live vaccines can be given after one month of age after in utero small molecule exposure. Use of small molecules remains cautioned during pregnancy and breastfeeding due to the ability to passively cross the placenta in the first trimester when organogenesis occurs.

Caution

The major limitation is comparative and prospective data on newer therapies, resulting in reliance on expert consensus for many recommendations.

My Practice

Our practice aligns with the new global consensus statement for the management of IBD during pregnancy. We discuss pregnancy planning with patients early when making new treatment decisions and recognize that many patients have contemplated the topic well before bringing it up in clinic. It is a source of apprehension for many patients, and we think the consensus statement provides reassurance that most of our treatment options are safe in pregnancy and breastfeeding. This is particularly

important given the protective role of breastfeeding in reducing the risk of IBD development in offspring.[3]

As an aside, we have also seen patients with prior anti-TNF non-response with severe disease for whom we induce remission with upadacitinib and then transition to a biologic for pregnancy planning. This requires a careful risk-benefit discussion and a recommendation to avoid conception until after the transition. Also, as the consensus statement notes, small molecules should not be withheld from who have no immediate plans for conception, if they represent the most appropriate therapy for their disease.

While obstetricians routinely prescribe aspirin for pre-eclampsia prevention in other populations, we have observed that some defer this decision to gastroenterologists due to concern for IBD exacerbation. We have now begun citing this consensus statement directly in interdisciplinary discussions to support consistent care.

For Future Research

Ongoing data from prospective registries such as PIANO will provide more information on pregnancy outcomes for advanced therapies, including oral biologics currently under investigation. We anticipate the results from ongoing studies, such as the MOMMY-IBD and MELODY trials, examining the impact of maternal diet in pregnancy on the infant microbiome as a potential modifiable factor in the risk of IBD development.[4]

Conflict of Interest

Drs. Chaudhary and Al Kazzi report no potential conflicts of interest related to this study.

Note: An author of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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(Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial design. Contemp Clin Trials Commun. 2020;18:100573.

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The Clinical Significance of Ultrashort Barrett's: Persistence and Progression

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Guest Contributor

Romy Chamoun, MD
Associate Editor

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This article reviews Summarizes Skef W, Haydel J, Rao A, et al. High risk of persistence and risk of dysplasia after diagnosis of ultrashort barrett's esophagus. *Am J Gastroenterol*. 2025; 120(11):2520-2528.

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Keywords: ultrashort Barrett's esophagus, esophagus, dysplasia

STRUCTURED ABSTRACT

Question: What is the prevalence of ultrashort Barrett's esophagus (USBE; <1 cm), how often does it persist on follow-up, and what is the associated risk of dysplasia or neoplasia compared with Barrett's esophagus ≥1 cm?

Design: Retrospective cohort study evaluating long-term endoscopic and histologic outcomes over 32 years.

Setting: Michael E. DeBakey Veterans Affairs Medical Center (Houston, TX), with follow-up through April 2023.

Patients: Adults diagnosed with Barrett's esophagus between 1990 and 2022 with biopsy-confirmed intestinal metaplasia and at least 1 follow-up endoscopy.

- USBE: <1 cm segment with intestinal metaplasia.
- Comparison group: BE ≥1 cm by Prague criteria.

Intervention / Exposure: Diagnosis of ultrashort Barrett's esophagus (<1 cm) with intestinal metaplasia on index endoscopy.

Outcome Measures: Primary—Persistence of BE or intestinal metaplasia on follow-up endoscopy. Secondary—Development of definite dysplasia or neoplasia.

Data Analysis: Descriptive statistics were used for baseline characteristics, comparing continuous variables with Student's t-tests and categorical variables with Pearson's χ^2 or Fisher's exact tests. Multivariable logistic regression—including variables significant on univariate analysis and known BE risk factors—identified predictors of persistent BE after USBE. Cumulative incidence, 95% confidence intervals (CIs), and incidence rates per 1,000 person-years were calculated for any and definite dysplasia. Follow-up time extended from index endoscopy to dysplasia diagnosis, last endoscopy, or death. Differences in incidence rates were evaluated with log-rank tests. Cox proportional hazards models estimated hazard ratios comparing persistent USBE to BE ≥1 cm. Analyses were performed using Stata 15.1, with $P<0.05$ considered statistically significant.

Funding: Supported by U.S. Veterans Affairs institutional resources; no external funding.

Results: Of 739 patients with Barrett's esophagus, 167 (22.6%) had USBE on index endoscopy; 86 patients (11.6% of the total cohort) had persistent BE on follow-up. Clinical characteristics—including age, sex, BMI, reflux risk factors, hiatal hernia, medication use, and biopsy volume—did not differ between persistent USBE and BE ≥1 cm. Persistence was significantly associated with race/ethnicity: non-Hispanic White (adjusted odds ratio [aOR] 3.85; 95% CI 1.37–10.8) and Hispanic patients (aOR 4.78; 95% CI 1.18–19.4) had higher odds of persistent BE compared with non-Hispanic Black patients. Among those with persistent USBE, 41.9% remained <1 cm and the remainder developed short-segment BE. Cumulative incidence of any dysplasia (indefinite, LGD, HGD, or EAC) was 17.4% in persistent USBE vs 31.2% in BE ≥1 cm; cumulative incidence of definite dysplasia/neoplasia was 11.6%

and 17.8%, respectively. Incidence rates of all dysplasia/neoplasia were lower in persistent USBE (30.2 vs 66.2 per 1,000 person-years; HR 0.54; 95% CI 0.32–0.91), while incidence rates of definite dysplasia were not significantly different (19.5 vs 33.8 per 1,000 person-years; HR 0.67; 95% CI 0.35–1.29). No demographic or clinical factors predicted dysplasia among patients with persistent USBE.

COMMENTARY

Why Is This Important?

Ultrashort Barrett's esophagus (USBE), defined as <1 cm of columnar-lined mucosa with intestinal metaplasia, is a common but controversial finding in clinical practice. Many gastroenterologists encounter patients with subtle tongues of salmon-colored mucosa or an irregular Z-line that is biopsied, but guidelines disagree on whether segments <1 cm should be labeled as BE or followed at all. Some societies exclude USBE due to measurement variability and presumed minimal cancer risk. This study provides long-term outcome data to help clinicians understand whether USBE is clinically meaningful, challenging the assumption that these short segments are benign and transient.

Key Study Findings

This study shows that USBE represents nearly one-quarter of newly diagnosed Barrett's cases, highlighting how commonly this issue arises in real-world practice.

Persistence was notable—more than half of USBE cases had ongoing BE or intestinal metaplasia on follow-up, suggesting that many of these segments represent true metaplasia rather than sampling artifact or inflammation.

Race and ethnicity significantly influenced outcomes, with White and Hispanic patients having a markedly higher risk of persistence compared with Black patients, underscoring potential biological or environmental influences. Importantly, persistent USBE was associated with an 11.6% cumulative dysplasia risk, and the dysplasia incidence rate did not differ significantly from that of ≥1 cm BE. These findings collectively suggest that USBE may carry more prognostic weight than previously believed.

Caution

Several limitations must temper the interpretation of these findings. The study population consisted primarily of older male veterans, which may restrict

applicability to women or broader community populations. Measurement of <1 cm mucosa is inherently subjective and susceptible to interobserver variability, particularly across decades of endoscopy. Although the dysplasia risk appears meaningful, the absolute number of dysplasia events in the USBE subgroup remains modest, resulting in wide confidence intervals and limiting precision. Retrospective data collection may also introduce bias, particularly regarding biopsy practices and follow-up intervals. Therefore, while USBE should not be dismissed, these findings should be applied thoughtfully and individualized.

My Practice

In my practice, I do not aim to biopsy an irregular Z line. Biopsies are obtained when there is at least 1 centimeter of proximal displacement of columnar mucosa from the top of the gastric folds. This approach is consistent with guidelines from the American College of Gastroenterology and most other national and international guidelines. Studies show that patients with an irregular Z line rarely progress to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) during surveillance. These potentially low-yield endoscopic surveillance studies may lead to unnecessary burden for patients and increased health care cost. However, the findings of this study highlight that ultrashort Barrett's esophagus may carry a measurable risk of dysplasia, particularly in certain demographic groups. At present, in borderline cases of an irregular Z line vs >1 cm of abnormal appearing columnar mucosa in the distal esophagus, I tend to err on the side of caution and obtain a biopsy or multiple biopsies encompassing the proximal tip of columnar mucosa and normal appearing esophageal mucosa in an effort to only capture esophageal (and not gastric) mucosa. The findings of this study may support this approach, as there is not only benefit in capturing subtle > 1 centimeter tongues of columnar mucosa, but also potential benefit in capturing columnar mucosa that is borderline in length of proximal extent given the rate of definite dysplasia or neoplasia (11.6%) found in surveillance of patients with irregular Z lines in the study. That said, more studies are needed to demonstrate the yield of endoscopic surveillance in patients with irregular Z lines before I routinely biopsy this finding to assess for possible USBE.

Future Research

Future work should include large prospective multicenter cohorts that include women and more racially diverse populations to validate these findings beyond the VA system. Studies are needed to identify endoscopic factors that predict persistence, such as subtle mucosal features or advanced imaging patterns. Research should

clarify optimal surveillance intervals for persistent USBE and determine whether molecular, genomic, or biomarker-based tools can better stratify dysplasia risk. Ultimately, comparative effectiveness trials evaluating selective surveillance versus no surveillance strategies in USBE could help refine guideline recommendations and determine the true clinical significance of these ultrashort segments.

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Cancer Risks in Familial Adenomatous Polyposis

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Dr Timothy Yen
Associate Editor

This article reviews Beck SH, et al. Cancer risks in attenuated and classical familial adenomatous polyposis: A nationwide cohort with matched, nonexposed individuals. Am J Gastroenterol. 2025;120(6):1345-1352.

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Keywords: FAP, cancer, risks, genetics

STRUCTURED ABSTRACT

Question: What are the cancers risks among familial adenomatous polyposis (FAP) patients?

Design: Retrospective matched multiple cohort study.

Setting: National Danish polyposis registry.

Patients/Exposure: Classic (>100 colorectal adenomas before age 25) or attenuated (<100 colorectal adenomas) familial adenomatous polyposis (FAP) with a pathogenic/likely pathogenic variant in the APC gene. These patients were matched 1:4 to patients without FAP on year of birth, sex, and postal code at birth.

Outcomes: Cancer diagnoses (split by organ and overall), colorectal adenomas, and duodenal adenomas.

Data Analysis: Observation began in 1997 or the patient's date of FAP diagnosis, and ended at each cancer diagnosis, death, loss to follow-up, or end of study in 2022. To estimate relative risk of cancer with age, the authors performed Cox hazards regression adjusted for year of birth, sex, and education level. They only included patients without missing data.

Funding: The Misse and Valdemar Risom Foundation, and The Disirée and Niels Yde´s Foundation.

Results: Of 311 patients with classic FAP (cFAP) and 134 patients with attenuated FAP (aFAP), 11.5% developed at least 1 cancer in any organ with an adjusted HR of 4.83 (cFAP) and 3.24 (aFAP) compared to 16,000 matched non-FAP patients. Overall cancer incidence decreased equally over time in all cohorts; 7.7% died during observation, 53% underwent major gastrointestinal surgery, and the incidence of newly diagnosed aFAP increased over time (and exceeded that of cFAP). In all, 9-11% of FAP patients developed colorectal cancer more often than non-FAP patients (HR 2.16-2.72 for colon cancer, HR 9.12-12.66 for rectal cancer) with no significant difference between cFAP and aFAP patients. Ninety percent of FAP patients had rectal cancer preceding colectomy. The risk for colorectal adenomas with HGD (HR 2.72) and any duodenal adenomas (HR 4.02) was higher in cFAP than aFAP. Pancreatic cancer was more common in cFAP compared to non-FAP patients (HR 7.66). See Table for details. The study was inadequately powered for duodenal cancers.

	aHR (95% CI) for cFAP*	aHR (95% CI) for aFAP*	aHR (95% CI) for cFAP vs aFAP
Any cancer	**4.83 (3.63-6.41)**	**3.24 (2.17-4.85)**	1.49 (0.98-2.27)
Colon cancer	2.16 (0.99-4.72)	**2.72 (1.19-6.22)**	0.80 (0.32-2.00)
Rectal cancer	**12.66 (7.04-22.76)**	**9.12 (4.35-19.12)**	1.39 (0.72-2.69)
Pancreatic cancer	**7.66 (1.67-35.26)**	3.19 (0.61-16.42)	2.41 (0.44-13.07)

Table 1. Cancer diagnoses
*Compared to non-FAP patients
Bold indicates $P < 0.05$
aHR: adjusted Hazard ratio; CI: Confidence Interval; cFAP: classic familial adenomatous polyposis; aFAP: attenuated familial adenomatous polyposis

COMMENTARY

Why Is This Important?

FAP is a difficult population to study because it is relatively rare, although it's clinical presentation is quite dramatic due to the burden of colorectal polyps. Many studies on FAP harken back to historical studies before the advent of routine high-definition colonoscopies for screening, as reflected in the increasing incidence of aFAP over time.[1] It is thus helpful to have a more contemporary description of cancer risks and outcomes in both cFAP and aFAP.

Key Study Findings

With presumed standard-of-care prophylactic colectomies and surveillance colonoscopies (in the United States), most FAP patients will fortunately not develop cancer, although the risk overall is still markedly higher than the average-risk patient without FAP.

There is still a subset of FAP patients that can develop rectal cancer after colectomy, thus frequent flexible sigmoidoscopy of the residual rectum (typically every 6-12 months depending on polyp burden) remains important.[2] The burden of duodenal adenomas is still substantial, particularly in the cFAP population, although we still do not fully understand risk factors for duodenal adenocarcinoma otherwise.

Caution

This study does not account for surveillance procedures such as colonoscopy prior to colectomy, as well as surveillance flexible sigmoidoscopy/pouchoscopy (for those with an ileorectal anastomosis or ileo-anal pouch anastomosis) or ileoscopy (for those with an end ileostomy) after colectomy. Prior studies have observed that the risk of ileal adenomas is higher in those with a pouch compared to end ileostomy, which would be an important risk factor to understand given its potential impact on choice of surgery.[3] It is also curious that only about half of patients underwent surgery, which may be from inadequate observation time (i.e. the colectomy has not happened) rather than non-operative colonoscopic management of polyp burden, which is seldomly feasible with substantial resource and colonoscopic burden.[4]

FAP patients are not typically recognized as high risk for pancreatic adenocarcinoma in national guidelines.[5-7] As the authors note, these patients did not undergo genetic re-evaluation to assess for comorbid pathogenic variants. To recognize this as a FAP-associated cancer, future studies must account for differences in other risk factors for pancreatic cancer (alcohol, tobacco, chronic pancreatitis etc.). Finally, the study did not examine desmoid disease, which is a leading cause of

morbidity and mortality in FAP patients despite its non-malignant nature.

My Practice

Upon meeting a newly diagnosed FAP patient, I counsel the patient that although the risk of colorectal cancer is high, the risk can be dramatically reduced with colectomy and subsequent frequent lower endoscopies. Prior to colectomy, I find that the removal of most diminutive/small adenomas and counting the exact number of polyps is practically less useful. Given that the majority of FAP patients require extended or total colectomy, I perform colonoscopy with several diagnostic goals in mind: 1) masses concerning for cancer or advanced polyps; 2) estimating whether the rectal burden of polyps is "endoscopically manageable" over time with repeat procedures; 3) define the anatomic extent of endoscopically "un-manageable" polyposis in collaboration with colorectal surgery to inform whether the patient is a candidate for an ileorectal or even ileosigmoid anastomosis to improve post-operative quality of life. Finally, I do stress to the patient that even after surgery, frequent lower endoscopies are still critical to avoid the risk of rectal cancer.

For Future Research

Larger studies incorporating endoscopic data is still needed to understand how to manage the upper intestinal manifestations of FAP such as duodenal or gastric neoplasia, as well as medication interventions to help manage those with advanced duodenal neoplasia given the morbidity associated with duodenectomy.

Conflict of Interest

The author has no reported conflicts of interest.

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