

Assessment of Physicians' Perceived Risk of Inflammatory Bowel Disease Medications in Pregnant Patients

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Abstract: Many female patients with inflammatory bowel disease (IBD) are affected during their reproductive years, and the benefits of continuing medical therapy to maintain remission during pregnancy generally outweigh the risks of therapy cessation. Knowledge of the current guidelines is important to maximize maternal and fetal outcomes. **Methods:** A total of 116 practitioners (family medicine [FM], n=35; internal medicine [IM], n=22; obstetrics/gynecology [Ob/Gyn], n=23; gastroenterology [GI], n=36) responded to a survey. Respondents were asked about the US Food and Drug Administration classifications of common IBD drugs, the need for caution when administering live vaccines to neonates exposed to biologic agents in utero, and 2 scenarios of patients with IBD who wanted to become pregnant. **Results:** Compared with GI physicians, FM+IM physicians were less likely to correctly identify infliximab (Remicade, Janssen Biotech) as a pregnancy category B drug (67% vs 30%; $P=.0005$). Among all respondents, 38% were unaware of the need to delay administration of live vaccines to infants exposed to anti-tumor necrosis factor agents in utero. GI specialists were more likely to advise patients to continue their IBD regimen (biologic agents and thiopurines) during pregnancy than non-GI (IM, FM, and Ob/Gyn) physicians (biologic agents: 86% vs 46%; $P<.0001$ and thiopurines: 69% vs 15%; $P<.0001$). Overall, 78% of non-GI physicians said that they would change their practice based on the survey. **Conclusion:** Practitioners caring for pregnant patients may lack awareness regarding the safety and management of IBD drugs during pregnancy. Bringing awareness through education may increase the number of physicians following best practice guidelines.

Keywords

Inflammatory bowel disease, pregnancy, biologics, thiopurines

Inflammatory bowel disease (IBD) comprises a spectrum of chronic, immune-mediated inflammatory diseases affecting the gastrointestinal tract. The incidence and prevalence of IBD have been increasing worldwide, with North America having the highest incidence of Crohn's disease (20.2 per 100,000 person-years) and

Europe having the highest incidence of ulcerative colitis (24.3 per 100,000 person-years).¹ Because IBD is currently not curable, remission is an essential component of disease management. Many female patients with IBD are affected during their reproductive years.^{2,3} For female patients hoping to become pregnant, disease remission becomes even more important at the time of conception and throughout the pregnancy to maximize both maternal and fetal outcomes. Active disease at conception and during pregnancy has been shown to increase the risk for spontaneous abortions, preterm delivery, and low birth weight.³⁻⁵ In addition, active perianal disease is an indication for cesarean section, resulting in more surgical procedures and a greater risk for operative and postoperative complications.⁶

Despite the possible side effects of using medication during pregnancy, current guidelines state that the benefits of continuing medical therapy to maintain disease remission during pregnancy outweigh the risks associated with the cessation of medications in the majority of cases.^{7,8} Although medications such as methotrexate and thalidomide remain contraindicated in pregnant patients, many of the medications widely used in the treatment of IBD, such as thiopurines, biologic agents, and corticosteroids, are appropriate treatment options for most pregnant patients.^{2,3} However, physicians involved in the care of pregnant patients with IBD may not be aware of best practice guidelines, resulting in suboptimal patient care.

The purpose of our survey was to assess practitioners in different specialties (family medicine [FM], internal medicine [IM], obstetrics/gynecology [Ob/Gyn], general gastroenterology [GI-general], and gastroenterology with a specialty in IBD [GI-IBD]) who are frequently involved in the care of pregnant patients with IBD and determine their awareness regarding the safety of using IBD medications in this patient population. The study was approved by the institutional review board of the University of Oklahoma Health Sciences Center.

Methods

A regional survey was conducted of practicing physicians in the states of Alabama, Arkansas, Kansas, Missouri, Oklahoma, and Texas. Physicians in the relevant specialties from the listed states were randomly selected based on contact information obtained from university medical faculty directories. In addition, because of the relatively low number of GI physicians compared with other specialists, we randomly selected physicians from the American College of Gastroenterology directory. SurveyMonkey was used to create the survey electronically, and the survey was distributed via a hyperlink sent by electronic mail. In addition, paper surveys were

created and personally delivered to hospitals and clinics located in the Oklahoma City metropolitan area; these surveys were collected in sealed envelopes. The survey was sent to 800 practitioners, and the response rate was approximately 15%.

Participants were asked to complete demographic information: specialty (FM, IM, Ob/Gyn, GI-general, and GI-IBD); number of years of practice within the specialty (trainee, 1-5, 6-10, 11-15, or >15 years); age range (20-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56-60, or >60 years); practice location (academic hospital, public hospital, or private practice); gender; number of patients with IBD seen per year (0, 1-4, 5-10, 11-20, or >20 patients); and comfort level treating patients with IBD (very comfortable, comfortable, neutral, uncomfortable, or very uncomfortable).

Participants were then asked 4 questions. The first question asked them to assign the correct US Food and Drug Administration (FDA) pregnancy categories for infliximab (Remicade, Janssen Biotech), methotrexate, and prednisone. The second question asked, "According to the current literature, caution should be taken when using live vaccines on infants when the mother was exposed to which of the following IBD medications during pregnancy—infliximab, azathioprine, prednisone, or mesalazine?" For the last 2 questions, physicians were given a scenario of managing a patient with IBD who wanted to become pregnant. In the first scenario, the patient was being treated with thiopurines (eg, azathioprine or 6-mercaptopurine), and in the second scenario, the patient was being treated with biologic agents (eg, infliximab or adalimumab [Humira, AbbVie]). For each scenario, the respondents were asked if they should inform the patient to (a) take the medication only as symptoms arise, (b) not take the medication under any condition, (c) continue taking the medication as previously prescribed, or (d, e) discontinue the medication (eg, azathioprine/infliximab) and start a different medication within the same class (eg, 6-mercaptopurine/adalimumab).

After answering these questions, the physicians were educated about the correct answers based on current literature and guidelines. For the FDA pregnancy category question, infliximab is class B, methotrexate is class X, and prednisone is class C. For the live vaccine question, infliximab carries the recommendation that caution be used when live vaccines are given to exposed infants.^{2,9} For the 2 questions regarding the use of thiopurines and biologic agents for patients with IBD who wanted to become pregnant, the current literature recommends continuing the medication in both scenarios.^{2,7,10,11} After being informed of the correct answers, the physicians were asked if they would change their practice based on the education section of the survey.

Table. Demographics of the Respondents

		Respondents (n=116)^a
Specialty	Family medicine	35 (30)
	Internal medicine	22 (19)
	Ob/Gyn	23 (20)
	GI-general	27 (23)
	GI-IBD	9 (8)
Practice location	Academic	64 (55)
	Private	31 (27)
	Public	21 (18)
Length of practice, years	≤5	48 (41)
	6-15	33 (28)
	>15	35 (30)
IBD patients seen per year	0-4	41 (35)
	5-20	47 (41)
	>20	28 (24)
Gender	Male	68 (59)
	Female	48 (41)
Age, years	20-30	16 (14)
	31-35	22 (19)
	36-40	15 (13)
	41-45	19 (16)
	46-50	10 (9)
	51-55	9 (8)
	56-60	9 (8)
	>60	16 (14)
Comfort treating IBD patients	Very comfortable	13 (11)
	Comfortable	23 (20)
	Neutral	22 (19)
	Uncomfortable	37 (32)
	Very uncomfortable	21 (18)

^a The data are presented as count (%).

GI, gastroenterology; IBD, inflammatory bowel disease; Ob/Gyn, obstetrics/gynecology.

Statistical Analysis

SAS 9.2 (SAS Institute) was used for all analyses. Summary statistics were calculated for all continuous and categorical response variables, including the responses to each survey question, as well as the total percentage of the survey questions answered correctly by each respondent. Because of concerns about small frequency counts of the multiple physician characteristics, some of the

variable categories were combined for analysis purposes. The Kruskal-Wallis test was used to detect differences in median total scores (total percentage correct) among the respondent categories listed in the Table. If a difference was detected, pairwise comparisons were made with the Wilcoxon 2-sample rank sum test. The percentage of correct responses for each individual question was compared among groups with a chi-square test. Significant overall tests were followed by pairwise comparisons with a chi-square test. The alpha level was adjusted for pairwise comparisons with a Bonferroni adjustment (adjusted value of $.05/3=.0167$ for 3 pairwise comparisons among respondent groups). A Fisher exact test was used to test for significant associations between categorical variables, instead of a chi-square test, when more than 20% of the expected contingency table frequency counts were less than 5 or any counts were 0.

Results

The demographics of the survey respondents are listed in the Table. Because of the relatively low number of practicing GI-IBD physicians, this group unsurprisingly represented a small percentage of our respondents. As a result, GI-general and GI-IBD physicians were pooled together for the analysis, except when otherwise specified. Additionally, some of the demographic ranges from the survey were further grouped together during analysis, as shown in the Table. Of the 116 practitioners surveyed, 30% were FM practitioners, 19% were IM practitioners, 20% were Ob/Gyn specialists, and 31% were GI practitioners (GI-general, 23%; GI-IBD, 8%). Of the total respondents, 55% reported their practice location as academic, 27% as private, and the remaining 18% as public; 41% of the participants reported practicing 0 to 5 years, 28% had 6 to 15 years of experience, and the remaining 30% reported more than 15 years of experience. Of the total physicians surveyed, 3% had not treated any patients with IBD in the past year, 32% had managed 1 to 4 patients, 41% had managed 5 to 20 patients, and 24% had managed more than 20 patients. Among the combination of family medicine and internal medicine (FM+IM) practitioners, 49% reported seeing fewer than 5 patients with IBD per year, 46% reported seeing 5 to 20 patients, and 5% reported seeing more than 20 patients. Among the Ob/Gyn respondents, 48% reported seeing fewer than 5 patients with IBD per year, 43% reported seeing 5 to 20 patients, and 9% reported seeing more than 20 patients. In contrast, 5% of the GI physicians saw fewer than 5 patients with IBD per year, 31% saw 5 to 20 patients, and 64% saw more than 20 patients. Of the total respondents, 59% were male and 41% were female.

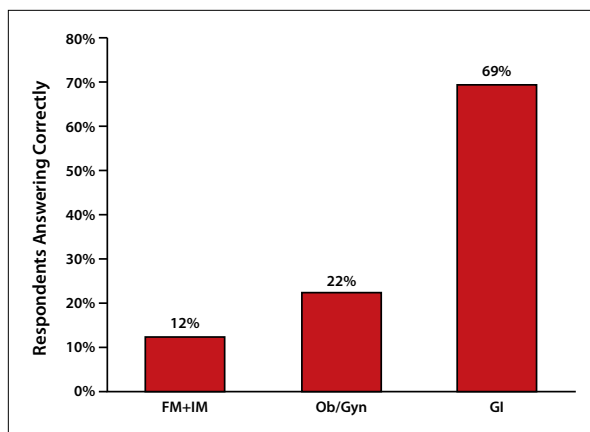


Figure 1. The percentage of respondents who answered the thiopurine management question correctly by specialty.

FM+IM, combined family medicine and internal medicine; GI, gastroenterology; Ob/Gyn, obstetrics/gynecology.

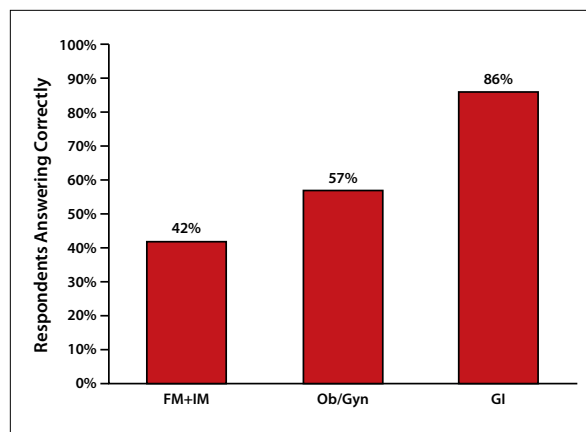


Figure 2. The percentage of respondents who answered the biologic management question correctly by specialty.

FM+IM, combined family medicine and internal medicine; GI, gastroenterology; Ob/Gyn, obstetrics/gynecology.

Compared with the GI physicians, the FM+IM physicians were less likely to correctly identify infliximab as a FDA pregnancy category B drug (67% vs 30%; $P=.0005$). The Ob/Gyn respondents were more likely than the GI respondents to correctly identify prednisone as a FDA pregnancy category C drug (83% vs 39%; $P=.001$).

Of the total respondents, 38% were unaware that the use of live vaccines in an infant exposed to anti-tumor necrosis factor (anti-TNF) medications in utero should be delayed. Within the individual respondent groups, 35% of the FM+IM physicians were unaware, 52% of the Ob/Gyn physicians were unaware, and 33% of the GI respondents were unaware (GI-general, 37%; GI-IBD, 22%). There were no significant differences among specialties (overall chi-square test, $P=.29$).

The FM+IM physicians were less likely than the GI physicians to continue thiopurines in a patient with IBD who wanted to become pregnant (12% vs 69%; $P<.0001$; Figure 1). The Ob/Gyn and FM+IM physicians were less likely than the GI physicians to continue biologic therapy in a patient with IBD who wanted to become pregnant (57% vs 86%; $P=.011$ and 42% vs 86%; $P<.0001$, respectively; Figure 2). Physicians who had treated more than 20 patients with IBD in the past year were more likely than physicians who had treated 0 to 4 patients with IBD in the past year to correctly manage a patient with IBD who wanted to become pregnant in both scenarios (continue thiopurines, 54% vs 17%; $P=.0014$ and continue biologics, 79% vs 46%; $P=.0074$).

Physicians who reported feeling comfortable treating patients with IBD were more likely than physicians who rated themselves as uncomfortable treating patients with IBD to correctly manage a patient with IBD who wanted to become pregnant (continue thiopurines, 50%

vs 19%; $P=.0015$ and continue biologics, 75% vs 48%; $P=.011$). Additionally, there was a significant difference between the median percentage of correct answers of those reporting to be comfortable and the median percentage of those reporting to be uncomfortable treating IBD patients (67% vs 50%; $P=.0014$). There was no significant difference between the percentage of correct responses of those reporting to be comfortable compared with the percentage of correct responses of those reporting a neutral comfort level.

Among the respondents who answered at least 1 patient care question incorrectly, 76% of the FM respondents, 80% of the IM respondents, and 90% of the Ob/Gyn respondents said that they would change their practice based on the education section at the end of the survey; these percentages were higher than the percentage of GI-IBD physicians (17%; $P<.011$ for each pairwise comparison with GI-IBD physicians). Additionally, the percentages did not differ significantly between the GI-general and GI-IBD physicians ($P=.056$; Figure 3).

Physicians practicing in a public hospital setting were more likely to correctly answer a higher overall median percentage of questions than physicians practicing in an academic hospital (67% vs 50%; $P=.016$). Compared with physicians in private practice, respondents practicing in a public hospital were more likely to correctly identify FDA pregnancy category C for prednisone (86% vs 39%; $P=.0008$). However, when the responses of academic and nonacademic (public and private practices combined) physicians were compared, there were no significant differences between the overall median percentages of questions answered correctly ($P=.15$) or individual questions answered correctly ($P>.17$ for each question). In addition, no statistically significant differences were found when

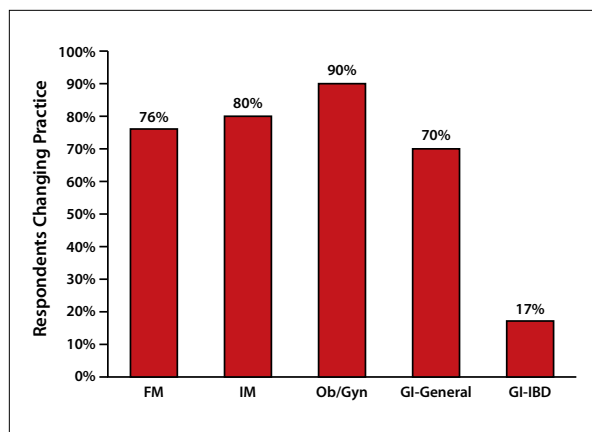


Figure 3. The percentage of physicians who answered at least 1 question incorrectly and stated that they will change their practice based on the survey.

FM, family medicine; GI-general, general gastroenterology; GI-IBD, gastroenterology with a specialty in inflammatory bowel disease; IM, internal medicine; Ob/Gyn, obstetrics/gynecology.

comparing the percentages of correct responses among groups of respondents defined by duration of practice (0-5 vs 6-15 vs >15 years).

Discussion

The results of this study indicate significant variations in the level of knowledge among practitioners taking care of female IBD patients of childbearing age. Practitioners involved in the care of pregnant patients may not have the correct knowledge of the safety and management of IBD drugs during pregnancy. FM and IM physicians were less likely to correctly manage a patient with IBD who wanted to become pregnant. Physicians managing a greater number of patients with IBD seemed to be more aware of current guidelines.

The effect of anti-TNF agents on an infant's developing immune system has not been established.² Regarding the use of live vaccines in infants exposed to anti-TNF therapy in utero, a significant difference was not discovered among physician demographics. However, it is concerning that 38% of all respondents were not aware that fetal exposure to anti-TNF medications necessitates the cautionary use of live vaccines.

This study demonstrates a need to educate physicians potentially involved in the care of pregnant patients with IBD. Of the physicians who correctly answered no more than half of the total number of survey questions, 79% said that they would change their practice based on the education section at the end of the survey. It is reassuring to note that most physicians are willing to change their practice when made aware of the current guidelines. It

is interesting to note that only 17% of the GI physicians specializing in the treatment of IBD who answered at least 1 question incorrectly were willing to change their practice. This may be a consequence of the greater comfort and experience of these specialists in the management of this disease or of their caring for fewer pregnant patients compared with the other specialists. The lack of a statistically significant difference between GI-general and GI-IBD physicians stating that they would change their practice is likely due to the underpowered GI-IBD group.

To our knowledge, this is the first study to investigate the prevalent beliefs of physicians regarding the safety of IBD medications in pregnant patients. The study demonstrates that education could increase the likelihood that physicians will follow best practice guidelines when treating patients with IBD, as indicated by the percentage of physicians reporting that they would change their practice.

This study was limited by a small sample size (116 respondents), and we were not able to collect data for the nonresponders. The results may have been impacted by nonresponse bias, given the low response rate of 15%, which is typical of clinical and public health opinion surveys. It is possible that physicians more frequently involved in the management of pregnancy or IBD were more likely to respond, which may have resulted in a skewed population that is incongruent with nationwide practice. We observed that close to 50% of both the FM+IM and Ob/Gyn groups saw fewer than 5 patients with IBD per year; however, we did not collect information on how many pregnant patients each group managed per year. Additionally, we could not monitor the use of outside resources, such as the Internet, or consultation with colleagues while the practitioners answered the survey questions.

In order to obtain the best estimate of physicians' current knowledge, we chose not to include an option of uncertainty or allow questions to go unanswered. This may have resulted in physicians not completing the survey or making random answer selections, potentially skewing the results toward increased knowledge. Larger studies are needed to validate our findings.

Conclusion

Practitioners involved in the care of pregnant patients may be unaware of how to manage IBD drugs safely during pregnancy. This is especially true of physicians who see relatively few patients with IBD. Bringing awareness through appropriate education may increase the likelihood that physicians will follow best practice guidelines in the management of pregnant patients with IBD.

The authors have no relevant conflicts of interest to disclose.

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