Inflammatory bowel disease (IBD) is frequently diagnosed during the reproductive years. To effectively manage women during pre-conception, pregnancy, and the post-partum period the gastroenterologist must be knowledgeable about the pregnancy and lactation considerations for the medications used to treat IBD. Hesitancy or failure to provide prenatal counseling, to prescribe, or to withhold medications when appropriate, can result in inadequate care and unfavorable outcomes (1).

**Pregnancy categorization**

In 1979, the Food and Drug Administration (FDA) developed pregnancy labeling regulations and a classification tool for drugs during pregnancy and lactation. This categorization was composed of 5-letter risk categories: A, B, C, D, and X (Table 1). Most IBD drugs fell into categories B, C, or D. The categories were widely criticized for emphasizing potential risk rather than potential benefit, for being misinterpreted to be a grading system for safety with category B drugs assumed to be “safer” than C drugs, and for not being routinely updated to reflect new data.

To address these weaknesses, the FDA published the Pregnancy and Lactation Labeling Rule (PLLR) in 2014 (Table 2). The PLLR requires manufacturers to provide detailed clinical information regarding the risks and benefits of medication use during pregnancy and lactation. It also requires removal of all pregnancy risk categories from current drug labeling. Once fully implemented, it should greatly improve the quality of discussions regarding medication use during these periods.

In keeping with the goals of the PLLR, I talk to my IBD patients who are pregnant or considering pregnancy about the clinical studies, which address the effects of their medications on pregnancy and newborn outcomes. I emphasize the data from human pregnancies with maternal IBD where available and draw attention to areas where we have little data and risks remain unmeasured. I balance the discussion of medication risks with the risks of medication cessation and poorly controlled IBD in pregnancy to the well-beings of the mother and baby.

I discuss medication use in pregnancy before conception, when possible. As over 50% of pregnancies in the United States are unplanned, women of reproductive potential should understand the risks and benefits of their drugs in pregnancy when they start them.

**Medication classes**

**5-Aminosalicylates (5-ASAs):** 5-ASAs can be continued during pregnancy with limited exception. As sulfasalazine may increase the risk of neural tube defects by blocking folate metabolism women taking sulfasalazine should increase their supplemental folate to 1 mg twice a day prior to conception. Transitioning women on Asacol or Asacol HD to other 5-ASA agents should be considered due to their containing dibutyl phthalate, a possible developmental and reproductive toxicant, as a coating material. Women breastfeeding while on 5-ASAs should be informed of the rare risk for diarrhea in the newborn.

**Corticosteroids:** Whether maternal use of corticosteroids for inflammatory conditions increases the risk for orofacial clefts in newborns is controversial (2,3). In addition to monitoring for general side effects, pregnant women on corticosteroids should be monitored for gestational diabetes. Infants exposed later in gestation should be monitored for adrenal suppression. Corticosteroids should be reduced to the lowest possible dose during pregnancy but should not be withheld when necessary.

The transfer rate for corticosteroids into breast milk is low, producing concentrations much lower than the baby’s endogenous steroid production. Corticosteroid use is therefore compatible with breastfeeding.

**Thiopurines:** Rodent studies have demonstrated teratogenicity when supra-therapeutic doses of azathioprine and 6-mercaptopurine (6-MP) were used during organogenesis (4). In contrast, animal studies using thiopurine doses within the therapeutic range for humans did not find an increased risk for malformations (5).
Numerous observational studies examining teratogenic risk with thiopurine have been reassuring in both IBD and non-IBD populations. However, there is data suggesting that azathioprine exposure in early pregnancy may increase the risk for cardiac septal defects (6).

Overall, however, the thiopurine safety data from pregnant women with IBD is consistent with the data from the transplant literature, in which neither higher rates nor consistent patterns of malformations have been reported. Thus, continuation of thiopurines during pregnancy appears to be low risk.

Thiopurines are transferred into breast milk at exceedingly low levels and have not been shown to adversely affect the breastfed infant. Thus, thiopurine use does not preclude lactation.

**Methotrexate:** Methotrexate is an abortifacient and known teratogen (7). Women should discontinue methotrexate at least 3 months before trying to conceive. Methotrexate should not be taken during breastfeeding.

**Anti-tumor necrosis factor alpha agents (anti-TNF-αs):** Anti-TNF-αs can be continued during pregnancy. Multiple studies have shown no increased risk of adverse pregnancy outcomes with anti-TNF-α exposure (8,9). Like other IgG1 antibodies, infliximab, adalimumab and golimumab are actively transported into the fetal compartment via the placenta. This transfer is most efficient in the second and third trimesters. Certolizumab crosses the placenta only by passive means.

Giving the last dose of anti-TNFα (other than certolizumab) during pregnancy at 22–24 weeks’ gestation should be considered in selected women in clinical remission to minimize fetal exposure (10). Due to the risk of vaccine-induced infection, babies exposed to anti-TNF-αs in utero should not receive live vaccines such as the rotavirus vaccine until at least 6 months old unless they have no circulating drug.

Women on anti-TNF-αs can be reassured that breast milk transfer occurs at very low levels. This is not believed to be clinically significant.

**Biosimilars to anti-TNFs:** Infliximab-dyyb and adalimumab-atto are FDA-approved biosimilars to anti-TNF-α. Given the absence of safety data for the biosimilars in human pregnancy, originator drugs should be used when possible in women considering childbearing or who are pregnant.

**Integrin antagonists:** Natalizumab is an IgG1 antibody to the α4β1 and α4β7-integrins, and vedolizumab to the α4β7-integrin. Both are actively transferred across the placenta. Preclinical and human newborn studies have found hematologic abnormalities with in utero natalizumab exposure (11). However, other observational studies have not reported a trend towards medication-induced adverse events. Pregnancy studies from women with IBD on natalizumab and vedolizumab are lacking. Although lactation studies are limited, natalizumab has been detected in breast milk. Women on integrin antagonists should be aware of the limited data with in utero exposure. After weighing risks and benefits, continuing drug through pregnancy may be the best choice but decision making must be individualized.

**IL 12/23 receptor antagonists:** Ustekinumab is an IgG1 monoclonal antibody to the p40 subunit common to IL-12 and IL-23. Active transport across the placenta in later pregnancy is likely. In 4 years of pooled data from clinical trials of patients with psoriasis on ustekinumab, no cases of fetal malformations or fetal death were reported in 31 cases with maternal exposure (12). Given the limited pregnancy data, the decision to administer ustekinumab to pregnant women must be individualized. Studies from animal models show low-level transfer of ustekinumab into breast milk. Transfer into human breast milk is also expected to be low and infant absorption minimal because it is a high-molecular weight protein.

**Summary**

Women with IBD who desire pregnancy or are pregnant must make decisions about managing their disease without compromising the health of their babies. In many cases, continuing maintenance drugs and/or starting a new medication to treat active symptoms is

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<th>Table 1. Historical FDA five-letter risk pregnancy categories</th>
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favored over drug discontinuation or drug withholding. Pregnancy is not a time to refrain from making recommendations for treatment as the stakes for un- or undertreated disease are high for both mother and baby. Even in the data-poor areas, clinicians must be prepared to make decisions based on best evidence to guide their patients through pregnancy.

CONFLICT OF INTEREST
Guarantor of article: Sumona Saha, MD, MS.
Specific author contributions: Sumona Saha- review of the literature, manuscript writing.
Financial support: None.
Potential competing interests: Dr Saha is a consultant and scientific advisor for UCB Biosciences, Inc.

REFERENCES
1. 5-ASA and pregnancy
   a. Asacol may increase risk of neural tube defects in the baby, supplement folate
   b. Asacol should be avoided, the coating material may be a reproductive toxicant
   c. Babies of mother taking 5-ASA could develop diarrhea
   d. Sulfasalazine decreases folate absorption, 1mg daily is recommended for women hat could potentially become pregnant

2. Anti-TNF use during pregnancy
   a. Transfer through the placenta is highest during the first trimester
   b. Last dose of anti-TNF should ideally be times at pregnancy weeks 22-24
   c. Certolizumab has the highest rate of placenta transfer to the fetus
   d. Babies born to mothers on anti-TNF should receive no live vaccines until age 6 months.

True or False

3. Corticosteroid use during lactation is safe

4. Thiopurines should not be taken by lactating mothers

5. Methotrexate should be discontinued at least 3 months prior to conception

6. Safety of natalizumab use during human pregnancy is unknown

7. Human studies have shown no increase in teratogenicity when thiopurines are used at therapeutic doses

8. Mothers on anti-TNF should not breast feed infants receiving live vaccines