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EDITORIAL

Medication Adherence During Pregnancy in IBD: Compliance Avoids Complications

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Women with IBD commonly have concerns about the safety of continuing IBD medications during pregnancy, particularly the risk of congenital malformations or other adverse fetal outcomes. These concerns contribute to voluntary childlessness in the IBD population [1]. Preconception counseling with regard to the safety of continuing IBD medications as well as the importance of achieving disease remission prior to conception improves outcomes [2].

The preponderance of evidence from the literature supports the safety of continuing most IBD medications during pregnancy. Other than methotrexate, which remains contraindicated and should be discontinued at least 3 months prior to conception, most IBD medications can and should be continued during pregnancy. Although aminosalicylates can be continued, women taking sulfasalazine should increase their folate supplementation to 2 mg daily. Thiopurines should be continued during pregnancy if they are needed for the maintenance of remission but should not be started during pregnancy due to the long onset of action and potential for adverse side effects in the mother, such as cytopenia and drug-induced pancreatitis [3]. Tumor necrosis factor (TNF) antibodies are safe for the induction and maintenance of active disease throughout pregnancy with studies supporting a decrease in disease flares when they are continued throughout pregnancy [4]. For women who are in disease remission while receiving combination thiopurine and an anti-TNF agent, consideration should be given on a case-by-case basis for stopping the thiopurine in the preconception period in order to ensure disease remission prior to pregnancy, as there may be an increased risk of infections in the newborn for up to 1 year after intrauterine exposure to combination therapy [5]. For the newer, non-TNF-directed IBD biologics, vedolizumab and ustekinumab, though there are less safety data, they can safely be continued throughout pregnancy based on the currently available evidence. Tofacitinib, a small molecule agent, should be discontinued at least 1 week prior to conception if other treatment options are available to maintain disease remission [3].

Controlling active inflammation and maintaining remission prior to and throughout pregnancy have the greatest impact on pregnancy and fetal outcomes. There is an increased risk of stillbirth, preterm birth, and low birth weight (LBW) in the setting of active IBD during pregnancy [6, 7]. Even with quiescent disease at conception, women with UC are more likely to experience a flare during pregnancy, commonly in the first or second trimester, and within 6 months postpartum [8]. Due to the increased risk of flare and the adverse impact of active IBD on pregnancy and fetal outcomes, physicians should stress that medication adherence is essential prior to and during pregnancy.

Given this background context, Watanabe and colleagues in this issue of *Digestive Diseases and Sciences* assessed the impact of medication non-adherence in 68 pregnant women with UC [9]. In this prospective, multicenter study, the authors provided surveys to patients and providers from 17 institutions in Japan from 2013 to 2019. The patient surveys were collected 30 days prior to conception, at each trimester, and 30 days postpartum. Survey questions included information regarding medication adherence, disease activity, and pregnancy outcomes, including stillbirth, preterm birth, spontaneous abortion (SAB), and LBW. Medication adherence was defined as consumption of $\geq 80\%$ of the prescribed dose. Surveys to physicians included questions about the patient's IBD history and their estimate of their patient's adherence. Of the 68 women with complete survey results, 65 were taking oral mesalamine (47 on monotherapy), 5 were taking thiopurine, 14 were taking anti-TNF agents, and 5 were taking combination thiopurine and anti-TNF. Though patients remained adherent to anti-TNF agents and steroids

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throughout the study period, adherence to thiopurines and mesalamine declined in the first trimester. The decrease in adherence was more notable for mesalamine intake, which dropped from 90% preconception to 60% in the first trimester. The main reason cited for non-adherence was "fear of negative effect on pregnancy in the first trimester." A total of 15 women experienced a disease relapse with 9 attributed to medication non-adherence, with non-adherence found to be a significant risk factor for disease relapse (odds ratio [OR] 7.659, 95% CI 1.928-30.427, $p=0.038$). In the subset of women who were receiving mesalamine monotherapy, 17 (36.2%) were non-adherent and, of these, 12 (25.5%) experienced a disease relapse and 11 (23.4%) had an adverse pregnancy outcome, including 5 SAB, 4 LBW, and 3 with preterm birth. (One patient had both LBW and preterm birth.) In this subgroup, non-adherence to mesalamine was associated with disease relapse (OR 15.75, 95% CI 2.335–106.227, $p=0.002$) and adverse pregnancy outcomes (OR 8.378, 95% CI 1.35–51.994, $p=0.03$).

These findings further support the importance of preconception counseling, including a discussion on the importance of the induction and maintenance of disease remission and of medication adherence. These data add to the known association between disease relapse and adverse pregnancy and fetal outcomes. Although the authors do not clearly state whether the women who experienced a disease flare were the same women with adverse pregnancy outcomes, other studies support this correlation [6, 7]. Watanabe et al. do show that 11 women resumed their medications after an "educational session including physician consultation," which emphasizes the need for a consistent message during pregnancy to continue their medications throughout pregnancy. As data accumulate on the impact of maintaining disease remission during pregnancy, medication adherence assumes greater prominence in the care of this special population. We clearly still have some work to do in helping our patients understand the importance of continuing medical therapy before and during pregnancy.

Compliance with Ethical Standards

Conflict of interest Neither Dr. Gaidos nor Dr. Kane has any conflicts to disclose.

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