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EDITORIAL

Pregnancy and IBD: Timing Is Everything

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Since the peak age of reproduction coincides with the peak incidence of inflammatory bowel disease (IBD), many female patients worry about the effect of pregnancy on disease activity, the effect of IBD on pregnancy and birth outcomes, and the effect of IBD medications on the developing fetus. As the study of pregnancy in IBD is complex, current research must attempt to separate the effects of confounders such as disease activity at conception and during pregnancy, medication use, comorbidities, gestational weight gain, and history of IBD surgery. Most pregnancy studies are performed in Europe or the USA with little data from Asia, an area in which IBD incidence is increasing rapidly. Since therapeutic monoclonal antibodies (biologics) are increasingly used to treat IBD in the USA and Europe, much of the recent research focuses on their safety during pregnancy. In India, where treatment with biologics is less common, Padhan et al. [1], writing in this issue of *Digestive Diseases and Sciences*, were able to measure the effect of IBD on pregnancy and vice versa in cohort of women, most of whom were not treated with biologic therapy. What makes this study unique is that for the first time the authors compare non-pregnant patients to patients whose pregnancy antedated disease onset, coincided with disease onset, or occurred after the onset of disease. The authors also examine the pregnancy outcomes of mode of delivery, abortion, stillbirth, preterm, full term, and postdated.

This study was performed at the All India Institute of Medical Sciences (AIIMS), a premier medical research university and hospital located in New Delhi, India. The cohort of 406 women included both non-pregnant IBD patients and IBD patients who had had one or more pregnancies. Almost half of the patients had a pregnancy before IBD onset [49.3% ulcerative colitis (UC) and 45.7% Crohn's disease (CD)] A small percentage of patients had a pregnancy that coincided with onset of disease (5.1% UC and 7.1% CD). The remaining patients had pregnancies before and after disease onset (8.6% UC and 17.1% CD), only after disease onset (12.5% UC and 7.1% CD), or had never been pregnant (23.8% UC and 23% CD). Though it is helpful to group patients in this way to compare results, the groups were small. Since only ~25% of patients had both IBD and a pregnancy at the same time (110 patients; 88 UC and 22 CD) (Padhan et al., Table 3), important outcomes may have been missed. The group of patients heretofore never reported in the IBD literature, and perhaps the most interesting group, is those whose pregnancy coincided with the onset of IBD, consisting in this study of only 22 patients (17 UC and 5 CD).

While 52% of patients received treatment with azathioprine/6-mercaptopurine, only 3% received biologics. Although initiation of corticosteroid treatment was incorporated into the authors' definition of a disease exacerbation, no data on overall steroid use were available in these patients. Given the lack of use of biologic therapy, it is possible that this group of patients had more active disease than is typically seen in the West. Since the authors' definition of disease activity does not separate out exacerbations during the pregnancy itself but rather examines the overall disease course, data on disease activity or medication use exclusively during each pregnancy are not available. The authors' stated purpose, to examine the overall disease course over years among the different groups of patients, was, however, achieved. While no

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difference existed in terms of overall disease course in the groups of UC patients who had been pregnant, fewer CD patients with pregnancy before disease onset were in remission compared to patients with pregnancies before and after, after, or coinciding with disease onset (Padhan et al., Table 3). The authors then examined the disease course in all non-pregnant and pregnant patients. Pregnancy was protective: Compared to patients who had been pregnant, patients who had never been pregnant had significantly lower chances of being in remission. This correlation was significant for UC patients although in CD patients a similar trend was observed (Table 1).

A novel finding in this study is the analysis of women whose pregnancy coincided with the onset of IBD. This small group of patients, particularly those with UC, did poorly. More UC patients who had a pregnancy before and after or after disease onset were in remission compared to patients whose pregnancy coincided with onset of disease. This finding was not observed in CD patients. Clinically this finding makes sense as many clinicians have seen more severe and intractable disease in women with UC who are unlucky enough to have IBD present at the same time as pregnancy. The mechanism by which UC may be triggered very early in pregnancy is not entirely understood. In pregnancy, since T helper 2 cell (Th2) responses are increased, this may increase the risk of a UC exacerbation. Perhaps in certain groups of patients with susceptible genetics and/or altered gut microbiota, this Th2 response may provoke the onset of UC. There was no difference in disease course in women who had 1 pregnancy versus >1 pregnancy.

In terms of adverse pregnancy outcomes, the authors reported a higher frequency of Caesarian sections when delivery occurred after disease onset or coincided with onset of disease as compared to delivery before disease onset (Table 2). There was a significantly higher probability of full-term birth in pregnancies that occurred before disease onset when compared to other groups. In 50 pregnancies that occurred before the onset of CD, there was 1 (2%) abortion compared to 8 (36.4%) abortions in 22 pregnancies after onset of disease. Among pregnancies after disease onset or pregnancies coinciding with disease onset, preterm deliveries were significantly more common in CD patients as compared to UC patients.

The significant findings are that pregnancy is protective; women, especially those with UC, who had been pregnant, experienced a superior disease course compared with those who had never been pregnant. Furthermore, the timing of pregnancy seems important; women with CD who had a pregnancy prior to IBD diagnosis had inferior outcomes compared with those whose pregnancy occurred after IBD onset. Of all women who had been pregnant, the patients who had the poorest outcomes were those unlucky enough to have their pregnancy coincide with a new diagnosis of UC. The surprising adverse pregnancy outcome is the number of abortions in CD patients whose pregnancy occurred at or after disease onset. It is not known whether the abortions were spontaneous or voluntary. Although a higher rate of spontaneous abortions in CD patients was reported by Riis et al. [2] in 2006, no more recent reports exist addressing this outcome or early pregnancy general outcomes in IBD patients.

Patients with IBD diagnosed prior to pregnancy have increased adverse pregnancy and birth outcomes, as reported in Mahadevan's 2007 study of the Kaiser Permanente database [3], a study resembling the Padhan study in that very few pregnant patients had received biologic therapy [3]. In Mahadevan's study as in the current study, there were increased adverse pregnancy and birth outcomes in women with IBD. Nevertheless, Mahadevan did control for disease activity and medication use during pregnancy. Riis et al. [2] examined the effect of pregnancy on disease course in a European cohort study from 2006. They reported similar results to Padhan et al. in that there is a higher rate of Caesarian sections in women whose IBD was diagnosed prior to pregnancy and also a decreased rate of relapse in women with IBD in the years following a pregnancy. In the Riis study, very few patients were prescribed biologic therapy or azathioprine; furthermore, there was no control group of non-pregnant women as in this current study.

Table 1 Ulcerative colitis (UC) and Crohn's disease (CD) course in pregnant and non-pregnant women

Patient groups	UC			CD		
	Remission	Intermittent exacerbation	Chronic continuous	Remission	Intermittent exacerbation	Chronic continuous
All pregnant patients	127 (56.7%)	84 (37.5%)	13 (5.8%)	17 (53.1%)	13 (40.6%)	2 (6.3%)
Not pregnant	33 (43.4%)	33 (43.4%)	10 (13.2%)	7 (43.8%)	7 (43.8%)	2 (12.8%)

Table 2 Pregnancy outcomes in women with ulcerative colitis (UC) and Crohn's disease (CD)

	UC		CD	
	Pregnancy before onset	Pregnancy after onset/precipitating disease	Pregnancy before onset	Pregnancy after onset/precipitating disease
Abortion	17 (4.7%)	7 (6.8%)	1 (2%)	8 (36%)
Preterm	0	2 (1.9%)	1 (2%)	2 (9%)
Full term	346 (95%)	91 (88.3%)	48 (96%)	12 (55%)
Vaginal delivery	327 (96.7%)	81 (88%)	44 (93.6%)	9 (75%)
Caesarian delivery	11 (3.3%)	11 (12%)	3 (6.4%)	3 (25%)

In summary, Padhan et al. make a strong effort to better define the interaction between pregnancy and the course of IBD. Given the paucity of available information on this question, particularly in non-Western countries, this study is an important contribution to the literature. Despite the limited number of patients, there is a clear warning that particularly good care must be taken of patients whose disease coincides with pregnancy, or who are already pregnant prior to their IBD diagnosis. It is hoped that these authors will investigate the high rates of abortions in CD patients whose IBD was diagnosed at or after pregnancy as this phenomenon could be due to multiple factors. A superior understanding of early IBD pregnancy outcomes in general and the effect of biologic therapy on all of these reported outcomes is needed. Fortunately, a large prospective cohort US study addressing these questions is ongoing [4] with sufficient patients enrolled to enable examination of the effects of all important factors on pregnancy and birth outcomes and also the overall course of disease.

References

1. Padhan R, Kedia S, Garg SK, et al. Long term disease course and pregnancy outcomes in women with inflammatory bowel disease: an Indian cohort study. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-016-4353-5.
2. Riis L, Vind I, Politi P, et al. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:1539–1545.
3. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterol*. 2007;133:1106–1112.
4. Mahadevan U, Martin CF, Sandler RS, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. *Gastroenterology*. 2012;142:1:S-149.