World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i22.2696

World J Gastroenterol 2011 June 14; 17(22): 2696-2701
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Belén Beltrán, MD, PhD, *Series Editor*

Inflammatory bowel disease in pregnancy

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Received: April 27, 2010 Revised: June 15, 2010
Accepted: June 22, 2010
Published online: June 14, 2011

Abstract

Crohn's disease and ulcerative colitis affect women in their child-bearing years. Family planning has come to be a common discussion between the gastroenterologist and the inflammatory bowel disease (IBD) patient. Disease control prior to desired conception and throughout pregnancy is the most important thing to keep in mind when caring for the IBD patient. Continued medical management during pregnancy is crucial in optimizing outcomes. Studies indicate that quiescent disease prior to conception infer the best pregnancy outcomes, similar to those in the general population. Active disease prior to and during pregnancy, can lead to complications such as pre-term labor, low birth weight, and small for gestational age infants. Although there are no definitive long term effects of pregnancy on IBD, there are some limited studies that suggest that it may alter the disease course. Understanding the literature and its limitations is important in the modern era of IBD care. Educating the patient and taking a team approach with the obstetrician will help achieve successful outcomes for mother and baby.

Key words: Inflammatory bowel disease; Pregnancy; Crohn's disease; Ulcerative colitis; Breastfeeding

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Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. *World J Gastroenterol* 2011; 17(22): 2696-2701 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i22/2696.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i22.2696

INTRODUCTION

Approximately fifty percent of patients are less than 35 years of age at the time of diagnosis and twenty five percent conceive for the first time after their diagnosis of inflammatory bowel disease (IBD)[1-3]. Advances in the field of IBD have made successful pregnancy outcomes a reality for many women. It is very important that as a gastroenterologist you have input into the conversation regarding management during pregnancy. It is important to understand the effect of pregnancy on IBD and the effect of IBD on a pregnancy. This review discusses the evidence for the important questions that female patients have in regards to this topic, and recommendations based on clinical experience of the authors has also been included.

HOW DOES IBD AFFECT THE OUTCOMES OF PREGNANCY?

The general consensus agrees that the impact of IBD

on pregnancy depends on disease activity at conception. Studies suggest that quiescent disease throughout a pregnancy leads to similar risks to those of the general population in regards to spontaneous abortion, pregnancy related complications, and adverse perinatal outcomes[4-6]. Disease activity at conception has been associated with preterm births, low birth weight (LBW), and fetal loss[4,7-10]. In addition, active disease during pregnancy results in the greatest risk of adverse perinatal outcomes[3,4,11]. This risk appears to be higher in women with Crohn's disease (CD) than in those with ulcerative colitis (UC). However, severe disease relapses during pregnancy in UC are associated with shorter gestation periods and lower birth weights[12]. In the study by Reddy *et al*[12] there was a higher risk of preterm births among women hospitalized for severe UC, with the mean gestational age being 35 wk *vs* 38.7 wk in the control group (without disease relapse).

In 1997, Kornfeld *et al*[13] studied 756 women with IBD and found that IBD was an independent risk factor for LBW and premature infants. However, they did not differentiate between CD and UC. Studies in the US and Denmark have demonstrated an increased risk of preterm delivery, small for gestational age (SGA), and LBW in infants to CD mothers[8,14,15]. In a study of Danish UC women, 1531 infants were included and there was no difference in rates of pre-term delivery, LBW, or SGA compared to controls[16]. The rate of healthy offspring to UC women was similar to the general population[3,8]. Despite a consistent trend of preterm delivery, most of the deliveries occurred after 35 wk with favorable outcomes[14].

Khosla *et al*[17] examined a cohort of 54 pregnant CD patients, and found that those with active disease at conception had rates of miscarriage up to 35% higher than those of patients who were in remission. In 2007, Nørgård *et al*[18] examined the impact of disease activity on birth outcomes in CD, and reported that activity during pregnancy only increased the risk of preterm birth. Furthermore, Moser *et al*[19] concluded that the presence of ileal disease in CD women was a strong predictor for LBW.

In a study by Dominitz *et al*[14] a greater risk of congenital abnormalities was seen in UC women compared to controls (7.9% *vs* 1.7%, $P < 0.001$). This study, however, failed to take into consideration disease activity or medication use, and this finding has not been replicated by other investigators. Indeed, most studies have found no greater risk of malformations in UC or CD[8,10,20]. For example, Lamah *et al*[21] found that there was no increased risk of spontaneous abortions, perinatal mortality, or congenital malformations in their UC cohort.

Using the 2005 Nationwide Inpatient Sample, Nguyen *et al*[22] examined 2372 CD deliveries and 1368 UC deliveries. In this population-based study, the adjusted odds of a cesarean section were higher in women with CD (aOR 1.72) and UC (aOR 1.29) compared to non-IBD controls. The risk of a venous thromboembolism was also substantially higher in IBD pregnancies. Interestingly, protein calorie malnutrition occurred more frequently in IBD women, as did blood transfusions in CD deliveries (aOR 2.82). To date, there are no associated complications of hypertension or proteinuria with IBD pregnancy[5].

Beniada *et al*[11] reported a series of 76 cases of women with their first IBD flare during pregnancy, and observed that they were at increased risk for pre-term delivery and/or LBW. The largest study to date on this topic is the meta-analysis by Cornish *et al*[23] that evaluated 12 studies in regard to the impact of IBD on pregnancy. This study comprised a total of 3907 patients with IBD and 320 531 controls. Based on this analysis, women with IBD were more likely to experience adverse pregnancy outcomes, such as premature birth and LBW. In fact, premature delivery was almost twice as likely compared to the general population. Women with IBD were also 1.5 times more likely to undergo cesarean section. Unfortunately, neither medication use nor disease activity was analyzed as a co-founder, which makes it difficult to put the results into proper perspective. The meta-analysis reported a 2.37 fold greater risk of congenital abnormalities (95% CI: 1.47-3.82, $P < 0.001$), but most of the studies included did not differentiate between minor and major malformations[23].

In 2006, a Spanish study of 124 pregnant CD women looked at pregnancies before and after diagnosis. They concluded that the course of IBD did not adversely affect pregnancy or the postpartum time period. The study determined that diagnosis prior to pregnancy did not influence the number of cesarean sections performed or increase the presence of LBW infants[24].

In 2007, Mahadevan *et al*[25] compared pregnancy outcomes between women affected with IBD and those unaffected. The study comprised of 461 pregnant IBD patients and a randomly selected cohort of age matched controls, and represents the largest US study to date. Women with IBD were more likely to have an adverse pregnancy complication compared to those women without IBD, but there was no difference in adverse newborn outcomes or congenital abnormalities. This difference was seen irrespective of the disease activity. The use of IBD medications was not found to be predictive of adverse outcome in this large, non-referral population. There was no statistically significant difference in newborn outcomes between the IBD and control pregnancies.

In the general population, smoking is a known risk factor for LBW infants and for disease activity in CD women[2]. Pregnant CD patients who smoke are at a substantially increase risk for LBW and preterm delivery[2,21]. Conversely, smoking in UC women does not increase their risk of preterm delivery[26]. However, given the known risk of smoking on the individual and the baby, smoking cessation should be encouraged in all scenarios.

Numerous studies continue to associate preterm birth and IBD; however the majority of these "preterm" deliveries occurred after 35 wk of gestation[14,26]. In UC, if resection is needed during pregnancy, Nielsen *et al*[8] found an increased risk of preterm delivery. Many theories have been put forth for this observation, but the etiology is unclear. One hypothesis is that an increase in circulating

prostaglandin levels during a flare could initiate pre-term labor with the induction of smooth muscle contraction[12,27]. Another theory is that the role of increased gut permeability during increased inflammation could alter nutritional and immunological factors affecting labor[12]. In addition, safety concerns for the mother and baby might prompt induction of early delivery, which would bias the end result of an LBW infant. Although each theory is plausible, more data are needed to clarify IBD and preterm infants.

While the data are conflicting at times, it appears that the disease activity is the main impetus of adverse pregnancy outcomes[28], as miscarriages are seen more frequently with active disease[13-15]. In our practice, we encourage women to be in remission before considering conception, and for those who become pregnant, we monitor closely and treat disease activity aggressively.

HOW DOES PREGNANCY AFFECT THE DISEASE COURSE?

A consistent finding in more recent literature is that the rate of disease flare during pregnancy (26%-34%) is similar to non-pregnant flare rates[7,10,29,30]. An exacerbation rate of 34% per year during pregnancy in UC women and 32% per year when not pregnant was observed by Nielsen *et al*[8]. These rates of relapse were similar in the CD population[10]. The Kaiser cohort, previously discussed, included women with inactive disease throughout their pregnancy, with no sudden increase in activity post-partum[25,29].

UC

When conception occurs during a quiescent state, 70%-80% of UC patients will remain in remission[2,8]. The rate of relapse is thus similar to a non-pregnant UC patient. Unfortunately, when flares do occur, the data is unreliable in relation to the stage of pregnancy. It was initially believed that an increase of disease flare occurred in both the first trimester and post-partum, but timing of a flare appears to more related to disease activity at conception and at term. Moreover, disease flare is often related to discontinuation of medical therapy (first trimester) or resuming smoking after delivery (post-partum)[2,11,31]. Active disease at conception can be associated with a worse prognosis. In a cohort of UC patients, Willoughby *et al*[32] noted that active disease during these times was more resistant to treatment.

The patient who has undergone an ileoanal anastomosis procedure presents a special situation. Ravid *et al*[33] examined 67 pregnancies in 38 UC women with ileal pouch anal anastomosis surgery. It was determined that pregnancy was safe with some alteration of pouch function, almost exclusively during the third trimester. For most of the women, the pouch function returned to its pre-pregnancy state. However, there was a small proportion of women that suffered long term disturbance of pouch function. This long- term effect was not related to the method of delivery. Although the mode of delivery in a pouch patient remains disputed, the method of delivery should not be determined by the presence of a pouch, but by patient and obstetric decisions. There are no long term data on pouch function after vaginal delivery but short-term data showed that pouch function, continence and quality of life are not affected by uncomplicated vaginal delivery[2,34].

CD

CD during pregnancy is similar to patients with UC. As with UC, the key to a good outcome is the disease state at conception and delivery. If the CD is quiescent at conception, 70% of pregnant CD patients will remain quiescent compared to the non-pregnant CD patient[2,17,35]. There has been some suggestion that CD symptoms might improve during gestation and that relapse is more common in the first trimester[2,17,26]. When disease is active at the time of conception, we follow "the rule of thirds". One third of women will get better, one third will stay the same, and one third will worsen. The biological mechanism of this finding has yet to be fully explained, but several studies have suggested that the immune disparity between mother and fetus might play a role in immune regulation, thereby altering immune function and pathology[36].

The recommended mode of delivery in CD patients is still controversial. In comparison to the general population, CD patients undergo cesarean sections more frequently, with the rate of cesareans increasing after diagnosis[37,38]. There are conflicting data on vaginal deliveries and perianal disease. The current recommendation, based on small observational studies, is to avoid vaginal deliveries in the setting of active perianal disease. CD patients with uncomplicated disease should be treated like the general population when deciding on delivery, but episiotomy should be avoided. The presence of a colostomy or ileostomy should not designate delivery choice. Despite the limited data, choice of delivery should be a collaborative decision between the patient, gastroenterologist, and the high-risk obstetrician.

Nursing

Any detriment to maternal health secondary to nursing after delivery is controversial. There have been some reported associations between nursing and increased disease activity, but this is unclear whether this is related to disease course or cessation of medication. Kane *et al*[31] found the odds ratio (OR) of disease flare for women who breastfeed was 2.2 (95% CI: 1.2-2.7) compared to those who did not breastfeed. However, once medication discontinuation was factored in, the OR became non-significant. Moffatt *et al*[39] published a population based study of breastfeeding and found no increased risk of flare in the postpartum period, and a possible protective effect once the discontinuation of medications was taken into account.

Long term effects of pregnancy on IBD

There have not been any data to suggest a long term detrimental effect of pregnancy on IBD and there is

never a role for elective termination. In the specific cases where methotrexate or thalidomide are involved, the decision for a therapeutic abortion may need to be addressed, given that it is a category X drug with known association with fetal abnormalities. Pregnancy has not been shown to definitively alter disease phenotype[38]. Riis *et al*[38] demonstrated that parous IBD patients experienced a reduction in relapse rate in the three years following pregnancy when compared to the three preceding years[2,40]. The rate of relapse decreased in the years following pregnancy in both UC and CD. Riis *et al*[38] looked at 580 IBD pregnancies in a European cohort. The pregnancy itself did not influence disease phenotype or surgery rates, but it was associated with a reduced number of flares in the following years (UC 0.34 flares/year *vs* 0.18 flares/year, $P = 0.008$ and CD 0.76 flares/year *vs* 0.12 flares/year, $P = 0.004$). Nwokolo *et al*[41] demonstrated a negative correlation between increasing parity and number of resections[2]. They found that in parous women with CD, the need for surgical resection was inversely correlated with increasing parity. Castiglione *et al*[42] studied parous IBD women and found that the incidence of relapses in the first three years after pregnancy was lower than that prior to pregnancy. Hormonal changes during and after pregnancy might account for a change in fibrosis and stricture formation[5]. Some studies suggest a down regulation of the immune system with maternal fetal HLA disparity[36]. Maternal immune response to paternal HLA antigens might result in immunosuppression that can in turn affect the maternal immune-mediated response. Kane *et al*[36] looked at 50 pregnancies in 38 women and found 42 disparate (84%) at the DRB1 locus, 34 (68%) at the DQ locus, and 31 (62%) at both loci. A significant difference was found in IBD activity between women mismatched at both loci *vs* only 1 or neither locus (OR 8.4, $P = 0.01$) Improvement of IBD symptoms during pregnancy was associated with disparity in HLA class Ⅱ antigens between mother and fetus. When logistic regression was performed, pre-partum disease activity and disparity at both DRB1 and DQ were significant predictors of overall disease activity during pregnancy. Pregnancy should never be discouraged or terminated in a patient with IBD, but instead, the goal of care should be early counseling and appropriate medical management.

IBD medications and pregnancy outcomes (Table 1)

It is believed that the greatest risk to IBD pregnancy is active disease and not active therapy. In addition to the effect on disease activity during pregnancy, the fear of a medication's effect on the fetus often prompts physician and patient to discontinue all medications. Pregnancy data on outcomes and disease course are complicated by cessation of drugs. One of the earliest available drugs for the treatment of colitis, sulfasalazine, readily crosses the placenta, but has not been linked to any fetal abnormalities in several large studies. However, patients taking sulfasalazine should be supplemented with folic acid to decrease the risk of neural tube defects. A dose of one milligram twice daily is appropriate.

Table 1 Use of medications during pregnancy in inflammatory bowel disease

Benefit clearly outweighs risk	Limited data	Contraindicated
5-ASA, oral and topical	Olsalazine	Methotrexate
Corticosteroids	Natalizumab	Thalidomide
Metronidazole, amoxicillin		
Azathioprine/6-MP		
Anti-TNF agents		

TNF: Tumor necrosis factor.

Aminosalicylates: The safety of 5-ASA compounds during pregnancy has been demonstrated in a number of trials, despite the fact that mesalamine and its metabolite, acetyl-5-aminosalicylic acid are found in cord plasma[43,44]. In two separate studies, women taking 2-3 g/d for either UC or CD had no increased incidence of fetal abnormalities compared to normal healthy women.

Immunomodulators: In the retrospective chart review by Francella *et al*[45], there were 79 women with 325 pregnancies. The compared patients on 6-MP during conception, those that stopped prior to conception, and patients never exposed to 6-MP were compared. Although they did not look at prematurity or LBW, there were no statistical differences in spontaneous abortions, major congenital abnormalities, neoplasia, or increased infection [RR 0.85 (0.47-1.55), $P = 0.59$]. Moskovitz *et al*[46] looked at IBD medications (including 6-MP and azathioprine) taken during pregnancy. In this age-controlled multivariate analysis of 113 patients with 207 conceptions, there was no evidence that medications affected pregnancy outcomes (abortions, premature birth, healthy full-term birth, ectopic pregnancy, congenital abnormalities, birth weight, or type of delivery). Nørgård *et al*[47] combined two large national data registries with a national prescription database to look at therapeutic drug use in women with CD and birth outcomes. Among the women that were exposed to 6-MP/azathioprine throughout their pregnancies, the risk of preterm birth and congenital abnormalities was 4.2 (95% CI: 1.4-12.5) and 2.9 (95% CI: 0.9-8.9), respectively. Preterm births were more prevalent among steroid and 6-MP/azathioprine exposed women compared to the reference group. However, they were unable to stratify disease activity to adverse birth outcomes due to the low number of hospital admissions. Due to model fitting issues, the authors could not adjust for the "disease activity" when looking at the LBW infants at term[48].

In has been our practice to continue immunomodulator therapy through pregnancy. While classified as an FDA category D medication, it received this designation in the 1950s when originally approved to treat leukemia. The doses used to treat IBD are much smaller and the above cited literature suggests this to be a low risk therapy at these doses. Stopping therapy once pregnancy is diagnosed only puts the mother's disease at risk of flaring, as organogenesis has already occurred at this point and the fetus has been exposed at its most vulnerable-

cessation for safety to the fetus has to be 6-8 wk before conception, not after.

Biologics: Biologics are now more commonly used for more aggressive disease, and sometimes are used as first line in the "top-down" therapeutic approach. The first series of intentional infliximab use throughout pregnancy by Mahadevan *et al*[49] examined outcomes in ten women with active CD during pregnancy. All ten pregnancies resulted in live births, with no congenital malformations. There were three pre-term births and one LBW infant, but these were not unexpected in a population of women with CD significant enough to require biologic therapy. Infliximab has been detected in the infants born to mothers receiving infliximab during the third trimester of pregnancy; however, to date, the long term effect of this placental transfer is unknown[50].

A published report for the successful use of adalimumab in pregnancy describes a patient with severely active disease at conception[51]. She was placed on adalimumab one month prior to conception and delivered of a normal growth infant without visible congenital anomalies. A case series recently presented suggested its safety in fetal outcomes in women treated for CD[52]. More recent data presented in abstract form showed that patients exposed to natalizumab during pregnancy had a spontaneous abortion rate comparable to what is expected in the general population[53]. However, the number of exposed patients was too low to draw any definitive conclusions. Therefore, it is important for the physician to discuss with each patient the risk to benefit ratio of biologic therapy to control disease in pregnancy.

It has been our practice to continue biologics at least through the second trimester of pregnancy. Placental transport of IgG begins around week 20 and increases thereafter. Theoretically therefore, no therapy is reaching the fetus until administrations after week 20. If the last infusion of infliximab is timed to be around week 32, then the next infusion can be after delivery. Adalimumab injections are held after week 36.

Other agents: Corticosteroids have not been associated with teratogenicity in humans and can be used as required to control disease activity. Prednisolone crosses the placenta less efficiently than other steroid formulations, such as betamethasone or dexamethasone. Only limited data are available regarding the safety of antibiotics as treatment for CD. Currently, ampicillin, cephalosporins, and erythromycin are believed low risk, as is ciprofloxacin. Metronidazole has been used to treat vaginitis in women during the first trimester of pregnancy but no controlled trials have definitively demonstrated its safety[54].

CONCLUSION

Over twenty years ago it was recognized that IBD patients flaring at the time of conception had a higher chance of spontaneous abortion, still birth, and premature delivery. The classic Miller[6] paper from 1986 is often referenced. For patients with active disease, one third will improve, one third will stay the same, and one third will worsen. This leaves two thirds of patients having to live with active disease during pregnancy[48]. Despite conflicting and sometimes confusing data, it is clear that there are potential risks involved with IBD pregnancies. It is crucial to understand the literature and also recognize its limitations. Ideally, conversations with the patient should occur before conception. Furthermore, decisions should be made with an informed approach with a team effort between the patient, the obstetrician, and her gastroenterologist. The key is continued monitoring and aggressive control of the disease prior to conception and throughout, to achieve optimal outcome for mother and baby.

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