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MINIREVIEWS

Monitoring inflammatory bowel disease during pregnancy: Current literature and future challenges

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Abstract

Inflammatory bowel disease has a high prevalence in women of childbearing age and can have a significant impact on pregnancy, from conceiving to carrying the pregnancy. Active disease during pregnancy is known to have negative effects on pregnancy outcomes; therefore, careful monitoring during this period is an important but challenging aspect of care and is crucial as it affects important management decisions. Recent data seems to suggest that endoscopy is a relatively safe procedure during all trimesters of pregnancy. Serum biomarkers such as C-reactive protein and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further work is necessary to establish standard of care monitoring during pregnancy.

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

Core tip: This review article fills in the gap in the paucity of literature specifically focusing on the monitoring of inflammatory bowel disease during pregnancy. New and emerging literature on the use of non-invasive biomarkers such as fecal calprotectin is discussed, but classic monitoring techniques such as endoscopy and radiographic imaging are also evaluated within the scope of pregnancy.

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INTRODUCTION

Inflammatory bowel disease (IBD) has a high prevalence in young adults and affects many women of childbearing age. Having IBD has many effects on women who are contemplating having children, ranging from conceiving to carrying the pregnancy, concerns about passing the disease onto children, fetal outcomes, and effects of pregnancy on the disease process itself.

Many women with IBD have poor knowledge about their ability to bear children or the effect that IBD will have on their pregnancy, with a tendency to overestimate the effects of IBD on fertility[1,2]. This has led to the phenomenon of voluntary childlessness, which affects up to 18% of women with IBD as compared to 6% in the general population. Women with IBD have misconceptions about a decreased rate of fertility, fear of passing on the condition onto offspring, and concerns over the effects of the disease on pregnancy outcomes[3]. In fact, multiple studies have shown that overall rates of fertility between the general population and women with IBD in clinical remission are comparable[4]. However, this trend excludes women who had pelvic surgical procedures, and in particular ileal pouch-anal anastomosis (IPAA) procedures for ulcerative colitis (UC), which have a relative risk of infertility of 3.91 as compared to the general population[5].

Most women who have a quiescent disease before pregnancy have normal pregnancy outcomes. However, active disease upon conception or during pregnancy has been shown to increase adverse outcomes such as low birth weight, preterm birth, and fetal loss[6]. In a recent retrospective study following 406 pregnant Indian IBD patients, pregnancies after disease onset were associated with higher number of adverse fetal outcomes and cesarean sections compared to before disease onset[7] . Similarly, a study from Denmark sought to evaluate birth outcomes with a cohort of women on anti-TNF therapy during pregnancy. Disease activity was associated with adjusted odds ratio of 2.05 for low birth weight and 2.64 for preterm birth, with the ratio for preterm birth increasing to 3.60 for patients with clinical moderate to severe disease activity[8]. In addition to disease activity, inadequate gestational weight gain in the IBD population has been shown to have a 2-fold increase in risk of low gestational weight compared with non-IBD patients with inadequate gestational weight gain in a Norwegian cohort study[9]. This finding has been reproduced in a prospective American cohort study for Crohn's disease, but not for ulcerative colitis[10].

Given the adverse effects of active IBD and associated effects on pregnancy outcomes, careful monitoring during this period is an important but challenging aspect of care. Ideally, disease activity should be objectively assessed prior to pregnancy as a part of conception planning. Endoscopy showing histological mucosal healing is an important predictor of clinical outcomes. This is particularly important since the correlation of clinical symptoms and histologic disease can be weak, especially in Crohn's disease. Therefore, having an objective assessment of disease activity during pregnancy is crucial as this directly affects important management decisions, such as medication changes, in order to keep the pregnant patient in remission through the prenatal course.

To this end, the purpose of our review paper is to discuss the current landscape of research on the safety, efficacy and utility of various methods of monitoring IBD activity during pregnancy (Table 1).

LOWER ENDOSCOPY

Endoscopy is the most definitive method of monitoring and evaluating disease activity. However, endoscopic procedures have been theorized to pose a threat to the fetus through the possibility of intra-procedural maternal hypoxia and hypotension, which can cause fetal hypoxia and potential demise[11]. Additionally, sedating medications, prolonged procedure times, and maternal positioning during endoscopy can potentially have significant effects on maternal circulation. Here, we have categorized lower endoscopy into colonoscopy and flexible sigmoidoscopy due to their separate risks and benefits.

Colonoscopy

Colonoscopy may be indicated in a pregnancy state, to evaluate the extent of ulcerative colitis that may determine the need for additional immunosuppressive agents or in small bowel Crohn's disease. A systematic review of lower gastrointestinal endoscopies performed in all three trimesters of pregnancy evaluated any adverse pregnancy outcomes that were noted to be in a temporal or etiological relation with the procedure[12]. This review comprised of 100 endoscopies, with a total of six reported adverse events that were related to the procedure. The authors concluded that colonoscopy is not only a low-risk procedure during pregnancy, but also that there were no significant changes in adverse events between the three trimesters. Furthermore, a prospective study done by de Lima *et al*[13] compared 42 pregnant IBD patients who underwent lower endoscopy (13 colonoscopies and 33 sigmoidoscopies) with case-matched pregnant IBD patients who did not undergo endoscopy. The adverse events were two spontaneous abortions, which were likely related to the endoscopic procedure; however, this was not a statistically significant difference when compared to the control group. There remains a gap of literature on safety of endoscopy in pregnant patients; but early studies appear

Table 1 Overview of various disease monitoring modalities and their pros/cons in pregnant inflammatory bowel disease patients

Monitoring modality	Pros	Cons
Lower endoscopy		
Colonoscopy	Gold standard of disease monitoring	Limited studies
	Early studies show no difference in adverse events between pregnant IBD patients who underwent colonoscopy and who did not undergo colonoscopy	Provider/patient hesitancy due to procedural and anesthetic concerns
Flexible sigmoidoscopy	Can be performed without sedation	Limited studies
	No case reports of any procedure-related complications	
Radiologic studies		
Ultrasound	Safest form of radiologic imaging	Sensitivity in pregnancy unknown
	Contrast-enhanced ultrasound shown to have good results in IBD	
Magnetic resonance imaging	No use of damaging ionizing radiation	Currently no well-controlled studies of the teratogenic effects of gadolinium contrast in pregnant women have been performed and the fetal risk is unknown
	Can detect luminal and extraluminal abnormalities	
	Long-term safety after exposure to MRI trimester of pregnancy showed no increased risk of harm to the fetus or in early childhood	
Biomarkers		
Albumin	Low albumin shown to be predictor of poor outcomes in IBD	Limited utility in pregnancy due to pregnancy-induced hemodilution resulting in lower albumin values
ESR	Generally a good marker of inflammation and reflects disease activity	Limited utility in pregnancy due to physiologic increase in ESR (2-3 x upper limit of normal)
CRP	Levels are only slightly raised in normal pregnancy and are still under the normal limits	May not accurately reflect disease activity in second and third trimester
	CRP higher in clinically active pregnant IBD patients at preconception and first trimester compared to clinically inactive pregnant IBD patients	Limited studies in pregnant IBD population
FCP	Measure of GI mucosal inflammatory activity detected prior to signs of systemic inflammation	Conflicting evidence for utility of FCP in IBD during pregnancy
	Multiple studies showing correlation between FCP levels and non-invasive disease activity scores in CD and UC	Limited studies with actual endoscopic data to evaluate clinical activity

IBD: Inflammatory bowel disease; CD: Crohn's disease; MRI: Magnetic resonance imaging; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FCP: Fecal calprotectin.

to suggest that endoscopy when necessary is shown to be a low-risk and safe procedure in any trimester.

Flexible sigmoidoscopy

Unsedated flexible sigmoidoscopy is an alternative approach to evaluate the rectum and left colon, thereby avoiding the risks of anesthesia. It plays an important role in determining the severity of mucosal disease in patients with refractory colitis and to evaluate concomitant infections. Based on reviews of retrospective studies and case series, it seems that performing an unsedated flexible sigmoidoscopy in a pregnant woman is quite safe[14]. None of the studies or case reports indicated any procedure-related complications to either the mother or fetus. In addition, the timing of the procedure did not seem to matter given that sigmoidoscopies were safely performed during all three trimesters.

Safety of anesthetics and colon cleansing agents

According to a joint statement from the American Society of Anesthesiologists and the American College of Obstetrics and Gynecology, none of the currently used anesthetic agents, when used in standard concentrations at any gestational age, have been shown to have any teratogenic effect in humans. There is currently an insufficient amount of data on the safety of colon cleansing agents in the pregnant population. Polyethylene glycol electrolyte isotonic cathartic solutions have not been studied in pregnancy, and are classified as pregnancy category C. Sodium phosphate preparations (category C) may cause fluid and electrolyte abnormalities and should be used with caution. Tap water enemas may be sufficient for flexible sigmoidoscopy in a pregnant patient.

RADIOLOGIC STUDIES

In general, imaging with non-ionizing radiation is preferred over modalities with ionizing radiation in pregnancy. In utero radiation exposure to a developing fetus includes intrauterine growth restriction, microsomia, mental retardation, organ malformation, and childhood cancers. These risks are dependent on the gestational age at the time of exposure and the absorbed radiation dose levels. Traditionally, abdominal plain films and computed tomography (CT) scans are avoided due to their high levels of ionizing radiation. However, consensus statements from the American College of Obstetricians and Gynecologists, American College of Radiology, and International Commission on Radiological Protection have

all concluded that radiation doses less than 50 mGy are shown to have negligible risk to the fetus. Therefore, most properly done diagnostic procedures do not present a measurably increased risk to the fetus and should be performed in cases of diagnostic necessity[15].

Ultrasound

Ultrasound is the safest form of radiologic imaging in pregnancy; it can be used to assess abscess formation along with the location and length of the affected segment of bowel. More recently, contrast enhanced ultrasound has been studied in inflammatory bowel disease with good results. It is an emerging technique to evaluate disease activity, the differentiation between small bowel stricture due to inflammation or mural fibrosis, and for the assessment of response to specific therapies[16]. Its sensitivity in pregnancy needs to be investigated.

Magnetic resonance imaging

The principal advantage of MRI over ultrasonography and CT scan is the ability to image deep soft tissue structures in a manner that is less operator dependent and does not use ionizing radiation. As per the guidelines from the American College of Obstetrics and Gynecologists, there are no precautions or contraindications for MRI specific to the pregnant woman[17]. It is being used now in routine obstetric care. MRI has been used to diagnose terminal ileal CD during pregnancy[18].

Use of gadolinium based contrasts agents (GBCA) in MRI during pregnancy: To date, there have been no known adverse effects to human fetuses reported when clinically recommended dosages of GBCA have been given to pregnant women. A single prospective cohort study of 26 women exposed to gadolinium chelates during the first trimester of pregnancy showed no evidence of teratogenesis or mutagenesis in their progeny[19].

There are no known cases of nephrogenic systemic fibrosis associated to the use of GBCAs in pregnant patients. However, gadolinium chelates may accumulate in the amniotic fluid which has the potential for the dissociation of the toxic free gadolinium ion. This is swallowed by the fetus and enters the fetal circulation possibly conferring risk to the fetus. Currently no well-controlled studies of the teratogenic effects of these media in pregnant women have been performed and the fetal risk is unknown.

Both the American College of Radiology and the American College of Obstetrics and Gynecology conclude that gadolinium contrast with MRI should be used with caution; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome, outweighing the possible but unknown risk of fetal exposure to free gadolinium ions. Lowest possible dose should be used to achieve diagnostic results. Contrast enhanced MRI may be useful to evaluate for abscess or fistulas.

Abdominal X ray

Traditionally X-rays are avoided in pregnancy due to fear of fetal risks from ionizing radiation. The maximal risk attributed to a 1-rad exposure, approximately 0.003%, is thousands of times smaller than the spontaneous risks of malformations, abortion, or genetic disease[20]. One abdominal X ray results in fetal exposure to radiation to 0.1 rad[21]. Therefore, in diagnosis of toxic megacolon, the risks to the fetus of an abdominal X-ray (1 in 30000) compared to the condition being poorly managed (60% fetal mortality rate) indicate that the patient should be imaged as would a non-pregnant patient. In conclusion, in cases of emergent situation or when other modalities are not available, an abdominal X ray would prove to be an important test.

BIOMARKERS

Serum and fecal biomarkers play an important role in non-invasive monitoring of the disease activity in IBD patients.

Albumin

Albumin is routinely used to assess overall disease activity state and its impact on the body. Patients with active disease may lose protein/albumin from the inflamed mucosa. Low albumin has shown to be a predictor of poor outcomes in inflammatory bowel disease. However, there are normal physiological changes in some laboratory parameters in pregnancy that should not be attributed to disease activity. Pregnancy causes hemodilution, resulting in fall in albumin by about 1 mg/dL by the end of 1st trimester. Hence, albumin of 2 mg/L during the third trimester in a patient with baseline albumin of 3 mg/L may not reflect worsening disease activity.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) is a marker of inflammation and reflects disease activity. Pregnancy causes a physiological increase in ESR from increase fibrinogen levels. The increase is about 2 to 3 times upper limit of normal by the first trimester. Hence an elevated ESR of 40 mm/h may reflect normal health in a third trimester pregnancy female. Thus, ESR values merit careful interpretation in evaluation of the disease activity in pregnant state.

C-reactive protein

C-reactive protein (CRP) is another marker of inflammation and reflects disease activity. Its levels are usually unaltered or possibly only slightly raised in normal pregnancy compared to a non-pregnant state, however the levels are still under the normal limits[22]. In a prospective study, Bal *et al*[23] evaluated the association of elevated CRP with clinical disease activity during pregnancy among women with IBD. The median CRP was numerically higher in women with clinically active disease

compared to those with clinically inactive disease at preconception (6.95 *vs* 2.80 mg/L, *P* = 0.559) and first trimester (24.75 *vs* 6.00 mg/L, *P* = 1.000), respectively. However, surprisingly the median CRP was lower in women with clinically active disease compared to those with clinically inactive disease at second trimester (8.85 *vs* 12.40 mg/L, *P* = 0.5923), and third trimester (5.45 *vs* 11.90 mg/L, *P* = 0.592), respectively. Their study shows that CRP remains a potential tool for assessing IBD disease activity in the early trimesters of pregnancy; however, it may not accurately reflect the disease activity in later trimesters. It is possible that in their study, concomitant minor infections in later trimesters might have increased CRP in healthy pregnancy patients with silent IBD. More research is needed to clearly identify the response of CRP in pregnancy state with IBD. At present, most physicians consider CRP as a useful tool in monitoring disease activity during pregnancy.

Fecal calprotectin

Among various different biological markers, fecal calprotectin (FCP) has emerged as the most superior marker to diagnose or monitor inflammatory bowel disease. Calprotectin is a heterodimer of two S100 proteins (S100A8 and S100A9), which are a family of calcium-binding proteins that are linked to innate immune functions through their expression in macrophages, monocytes, phagocytes, and granulocytes[24]. These proteins are released during periods of inflammation from gastrointestinal epithelial cells. Therefore, fecal calprotectin can be used as a measure of gastrointestinal mucosal inflammatory activity that is detected prior to signs of systemic inflammation, such as elevations in CRP or ESR[25].

Elevation of fecal calprotectin concentrations is shown to predict disease relapse in the next 12 mo in IBD, although this association is stronger in UC than in CD[26,27]. A recent prospective study showed that fecal calprotectin level below 50 ug/g is predictive of histologic remission in quiescent UC[28]. While there are a multitude of studies that have successfully shown the use of fecal calprotectin in monitoring IBD, its utility in pregnancy has not been fully elucidated yet.

Does pregnancy affect FCP levels?

To evaluate the utility of FCP as marker for active IBD disease during pregnancy, the effects of normal pregnancy on FCP need to be established. A recent prospective study involving 135 patients compared the concentrations of FCP in healthy non-pregnant and pregnant women and in patients with inflammatory bowel disease[29]. Stool samples were taken during each trimester, and there were no significant difference ($P < 0.092$) between FCP concentrations during each trimester. The mean FCP concentration between pregnant and non-pregnant health women showed no statistically significant difference, suggesting that pregnancy itself does not cause an elevation in FCP markers. While the FCP concentrations between patients with IBD and healthy controls were statistically different, no pregnant patients with IBD were included in this study; therefore, it is difficult to draw a conclusion on the combined influence of IBD and pregnancy on FCP levels.

Evidence for utility of FCP in IBD during pregnancy

To date, there have been a few recent studies assessing the utility of FCP in IBD during pregnancy. Initial results have been conflicting, with some showing good correlation between FCP levels and non-invasive disease activity score in CD and UC, while others showed that it is a poor predictor of IBD relapse during pregnancy. Huang *et al* enrolled seventeen pregnant IBD patients in a prospective study, in which fecal calprotectin was monitored at pre-conception and at each trimester along with modified Harvey Bradshaw Index (mHBI) for Crohn's disease and partial Mayo score for ulcerative colitis patients. The median FCP values for women with clinically active disease (as measured by mHBI $\geqslant$ 5 and partial Mayo score $\geqslant$ 2) were numerically higher than women with clinically inactive disease, but did not reach statistical significance at all-time points[30].

A prospective study by Shitrit *et al*[31] enrolled 33 pregnant women with IBD, and compared fecal calprotectin levels with partial Mayo and Harvey Bradshaw index scores, along with serum ESR, CRP, and albumin levels. No correlation was noted between FCP and clinical scores, albumin, and inflammatory serum markers, although a subsequent study by the same group using 80 samples from 57 pregnant patients did show a positive correlation between stool calprotectin and Crohn's disease activity index and partial Mayo scores (r = 0.60 and r = 0.77, respectively)[32]. FCP showed a high sensitivity and specificity in the occurrence of disease activity (as determined by the clinician) at 81.8% and 80.7% in a prospective study by Kanis *et al*[33]; however, there was no correlation between an elevated FCP and subsequent disease relapse. Ultimately, there is no clear consensus at this time with these small prospective studies showing conflicting results. FCP should be used in conjunction with clinical judgment, and appears to be an unreliable predictor of IBD relapse in the setting of pregnancy.

DISCUSSION

Monitoring IBD during pregnancy continues to be an important challenge for clinicians. Recent data seems to suggest that endoscopy, both colonoscopy and flexible sigmoidoscopy, is a relatively safe procedure during all trimesters of pregnancy. MRI and ultrasound remain the safest methods of imaging during pregnancy. Serum biomarkers such as CRP and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further investigation into these non-invasive biomarkers is necessary. Careful monitoring during this period remains a crucial component for important management

decisions to keep the patient in remission throughout the prenatal course.

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