Med. J. Cairo Univ., Vol. 91, No. 1, March: 437-443, 2023
www.medicaljournalofcairouniversity.net

Monitoring of Ulcerative Colitis Disease Activity During Pregnancy Using CRP/Albumin Ratio

MOHAMED A. EL-NADY, M.D.* and HYAM FATHY, M.D.**

The Department of Internal Medicine, Faculty of Medicine, Cairo and Assiut** Universities*

Abstract

Background: Ulcerative colitis (UC) is a recurrent form of gastrointestinal inflammation that mostly involves the large bowel. Because of the variations in levels of hormones that occur during pregnancy, as well as the increased risk of complications in this period, managing UC can be extremely difficult. Tracking and following UC disease activity when a woman is pregnant is of utmost importance to make sure that both the mother and the fetus remain healthy.

Aim of Study: The aim of our study is to study laboratory tools used for monitoring of ulcerative colitis disease activity during pregnancy. In this study, the relevance of monitoring the activity of UC throughout pregnancy, as well as the methods that are utilized to check for it, will be addressed.

Patients and Methods: This is a retrospective descriptive study of pregnant UC patients. We collected data from ulcerative colitis patients during their pregnancy-related follow-up visits. We registered their sociodemographic data, history of their condition, clinical data, and laboratory findings. For each trimester, disease activity of the patients was assessed. During the appointment, serum levels of C reactive protein (CRP) and albumin were determined and documented.

Conclusion: Ulcerative colitis is a chronic illness that primarily affects young people and is defined by alternating bouts of activity and quiescence. In our study analysis, both CAR and fecal calprotectin were directly correlated to occurrence of complication in pregnancy. The proper treatment of ulcerative colitis in pregnant women is essential to ensuring the mother's and her child's overall well-being and good health. It calls for careful monitoring as well as regular visits at specialized referral institutions.

Results: In our study analysis, both CRP albumin ratio (CAR) and fecal calprotectin were directly correlated to occurrence of complication in pregnancy. The proper treatment of ulcerative colitis in pregnant women is essential to ensuring the mother's and her child's overall well-being and good health. It calls for careful monitoring as well as regular visits at specialized referral institutions.

Correspondence to: Dr. Mohamed A. El-Nady,
The Department of Internal Medicine, Faculty of Medicine, Cairo University

Key Words: *Pregnancy – Ulcerative Colitis – Inflammation – C Reactive Protein – Fecal Calprotectin.*

Introduction

ULCERATIVE colitis (UC) is a recurrent form of gastrointestinal inflammation that mostly involves the large bowel. Because of the variations in levels of hormones that occur during pregnancy, as well as the increased risk of complications in this period, managing UC can be extremely difficult **[1]**. Tracking and following UC disease activity when a woman is pregnant is of utmost importance to make sure that both the mother and the fetus remain healthy **[2]**.

Assessing the activity of UC is critical for a multitude of purposes. To begin, it is helpful to detect early any possible flare-ups or complications that may emerge due to the changes in hormone levels during pregnancy **[3]**. This can help reduce the risk of future potential events and assist in lowering the likelihood of problems occurring for either the mother or the child. Finally, monitoring the activity of UC while a woman is pregnant can be helpful in ensuring that the mother is receiving the appropriate therapy and care for her disease so that she can achieve safe delivery and to prevent risk of pretermlabor, low birth weight, and other issues **[4]**.

Regular checkups in a specialized medical center, laboratory testing, and imaging investigations are some of the methods that are used in the process of monitoring the activity of UC during pregnancy **[5]**. A healthcare practitioner will evaluate the patient's symptoms and make any necessary adjustments to their treatment protocol. Laboratory examinations, such as blood tests and stool samples, can be performed to evaluate the level of inflam-

mation and look for evidence of an infection. It is possible to determine how severe the inflammation in the intestines is by the use of imaging techniques such as ultrasounds and CT scans [6].

Radiation-based procedures and endoscopies are generally avoided whilst pregnant because of worries about anesthesia and circulatory changes associated with the latter, both of which have the potential to be harmful to the developing child [7].

The Truelove-Witts criteria are among the commonly used clinical indicators in the determination of severity of UC. Determining the activity of the disease by the use of non-invasive indicators may be helpful in taking decision about suitable treatments, includinghospital admission or the administration of steroids intravenously [8].

It has been shown that high serum levels of C-reactive protein (CRP) and low levels of serum albumin are strongly linked with aggressive disease. These signs are also linked to a lack of response to therapy using corticosteroids and anti-tumor necrosis factor-alpha (anti-TNF), as well as an increased likelihood of undergoing a colon resection [9].

Recent interest in a new measure of inflammation known as the CRP to albumin ratio, sometimes known as CAR, has been demonstrated to have a predictive significance in several different forms of malignancies, as well as acute pancreatitis. An increase in this ratio is related with a higher inflammatory load, a negative outcome, and increased risk of death [10].

Aim of the study:

The aim of our study is to study laboratory tools used for monitoring of ulcerative colitis disease activity during pregnancy. In this study, the relevance of monitoring the activity of UC throughout pregnancy, as well as the methods that are utilized to check for it, will be addressed.

Patients and Methods

A total of 19 UC pregnant patients were included in our study. This study was conducted in the outpatient clinic of both Assiut University Hospitals and Cairo University Hospital in the duration between January 2021 and January 2022.

This is a retrospective descriptive study of pregnant UC patients. We collected data from ulcerative colitis patients during their pregnancy-related follow-up visits. We registered their sociodemographic data, history of their condition, clinical data, and laboratory findings. For each trimester, disease activity of the patients was examined. During the appointment, CRP and albumin levels in the serum were determined and documented.

Patients having cancer, connective tissue disease, chronic liver disease, chronic renal disease, and heart failure were excluded from this study, as were patients with a history of systemic infection during the previous four weeks. Patients with current systemic infections were excluded from this research.

Acute severe UC is defined as more than six bloody stools per day in addition to one or more of the following: Temperature >37.8 °C; Pulse >90 beats per minute; Hemoglobin level (Hb) 10.5g/dL; or ESR >30mm/h. Moderate activity is classified as more than four bloody stools per day in addition to the following: Temperature 37.8 °C; pulse 90 beats per minute; haemoglobin 10.5g/dL; ESR 30mm/h. Truelove-Witts criteria defined mild activity as less than four bloody stools per day in addition to the following: temperature 37.8 °C; pulse 90bpm; Hb >11.5g/dL; ESR 20mm/h [11].

Preterm labor, low birth weight for gestational age, and caesarean section delivery were identified as complications related to pregnancy.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 26.0. The Shapiro-Wilk was used to verify the normality of distribution of variables; Comparisons between groups for categorical variables were assessed using Chi-square test (Monte Carlo or Fisher Exact). Student *t*-test was used to compare two categories for normally distributed quantitative variables while Mann Whitney test was used to compare between two categories for not normally distributed quantitative variables, Regression To detect the most independent/affecting factor for affecting Need for Endoscopy during pregnancy, Need for Radiology and Pregnancy Complications. Significance of the obtained results was judged at the 5% level.

Results

The mean age of pregnant UC patients in this study was 27.68±4.52 years. The mean of the disease duration was 6.16±3.0 years. Three patients were actively smoking (15.8%) while 6 patients

(31.6%) were under biological therapy before pregnancy and the rest 13 patients were under conventional therapy (68.4%) as described in Table (1).

The distribution of disease activitybefore conception was as follows: Mild activity in 13 patients (68.4%), Moderate activity in 4 patients (21.1%) and Severe activity in 2 patients (10.5%). Inflammatory markers were recorded for each trimester and described in Table (1).

Endoscopy was needed during pregnancy to evaluate disease activity in 5 patients (26.3%) while radiological examination was needed in 7 patients (36.8%).

Complications related to pregnancy in UC patients were found in 8 patients (42.1 %).

Qualitative parameters was expressed as number and percent, normal distributed quantitative parameters was expressed as mean ± standards deviations while not normally distributed quantitative parameters was expressed and median (interquartile range).

Relations of different factors to pregnancy related complications were described in Table (2).

Use of biological therapy before pregnancy, disease activity before pregnancy, biological markers of inflammation as well as CAR were related to occurrence of complications related to pregnancy in UC patients.

Qualitative parameters was expressed as number and percent, normal distributed quantitative parameters was expressed as mean ± standards deviations while not normally distributed quantitative parameters was expressed and median (interquartile range).

Univariate and multivariate regressive analysis of these factors revealed that only CAR and fecal calprotectin were in positive relation with the pregnancy related complications that were noted on follow-up Table (3).

Table (1): Distribution of the studied cases according to different parameters.

	N = 19
Age	27.68±4.52
Duration of the disease	6.16±3.0
Active Smoking (yes)	3 (15.8%)
Treatment before pregnancy:	
Biologic/ Conventional	6 (31.6%) / 13 (68.4%)
Disease activity:	
Before pregnancy:	
Mild	13 (68.4%)
Moderate	4 (21.1%)
Severe	2 (10.5%)
Serum Albumin (gm/dL):	
1st trimester	3.32±0.23
2nd trimester	3.18±0.22
3rd trimester	3.07±0.21
Serum CRP (mg/L):	
1st trimester	23 (16.5-30)
2nd trimester	28 (20-35)
3rd trimester	40 (24-260)
CRP/Albumin Ratio:	
1st trimester	6.57 (4.85-10.17)
2nd trimester	8.48 (6.12-12.13)
3rd trimester	14.29 (7.50-80.84)
Fecal Calprotectin (mcg/gm):	
1st trimester	285 (200-360)
2nd trimester	310 (207.5-410)
3rd trimester	360 (235-550)
Need for Endoscopy during pregnancy (yes)	5 (26.3%)
Need for Radiology (yes)	7 (36.8%)
Pregnancy Complications (yes)	8 (42.1%)

Table (2): Statistical relation between different factors to pregnancy relatedcomplications (total number of cases = 19 pregnant UC patient).

	Pregnancy complications				Test of sig.	*p*-value
	No (n=11)		Yes (n=8)			
	No.	%	No.	%		
Age	26.91±4.50		28.75±4.62		*t*=0.870	0.396
Duration of the disease	6.81±2.96		5.25±3.01		*t*=1.132	0.273
Active Smoking:						
No	11	100.0	5	62.5	χ^2=4.898	FE*p*=0.058
Yes	0	0.0	3	37.5		
Treatment before pregnancy:						
Biologic	0	0.0	6	75.0	χ^2=12.058*	FE*p*=0.001*
Conventional	11	100.0	2	25.0		
Disease activity:						
Before pregnancy:						
Mild	11	100.0	2	25.0	χ^2= 11.200*	MC*p*= 0.001*
Moderate	0	0.0	4	50.0		
Severe	0	0.0	2	25.0		
Serum Albumin (gm/dL):						
1st trimester	3.45±0.11		3.14±0.22		*t*=4.121*	0.001 *
2nd trimester	3.32±0.13		3.0±0.19		*t*=4.376*	<0.001 *
3rd trimester	3.21±0.08		2.89±0.20		*t*=4.365*	0.002*
CRP (mg/L):						
1st trimester	18 (13.5-22.5)		31 (29-37)		U=4.50*	<0.001 *
2nd trimester	25 (14-28)		37 (32.5-42)		U=7.50*	0.001 *
3rd trimester	28 (18.5-121.5)		52.5 (40-520)		U=15.0*	0.016*
CRP/Albumin Ratio:						
1st trimester	5.28 (3.8-6.5)		10.53 (9.2-11.5)		U=4.0*	<0.001 *
2nd trimester	7.58 (4.2-8.4)		12.58 (10.7-13.5)		U=7.50*	0.001 *
3rd trimester	8.75 (5.8-39)		17.44(14.5-182)		U=15.0*	0.016*
Fecal Calprotectin (mcg/gm):						
1st trimester	205 (180-282.5)		440 (305-540)		U=7.50*	0.001 *
2nd trimester	215 (195-302.5)		472.5 (320-585)		U=9.0*	0.003 *
3rd trimester	250 (197-305)		565 (530-615)		U=0.0*	<0.001 *

χ^2 : Chi square test.
MC : Monte Carlo.
FE : Fisher Exact.
t : Student *t*-test.
U : Mann Whitney test.
* : Statistically significant at $p \leq 0.05$.

Table (3): Univariate and multivariate analysis for factors predicting pregnancy related complications (total number of cases = 19 pregnant UC patient).

	Univariate		Multivariate	
	p	OR (95% CI)	*p*	OR (95% CI)
Age	0.375	1.103 (0.888-1.369)		
Duration of the disease	0.259	0.824 (0.589-1.153)		
Albumin (gm/dL):				
1st trimester	0.031 *	0.0 (0.00-0.287)		
2nd trimester	0.063	0.0 (0.0-2.971)		
CRP (mg/L):				
1st trimester	0.031 *	1.481 (1.037-2.115)		
2nd trimester	0.039*	1.311 (1.014-1.697)		
3rd trimester	0.174	1.003 (0.999-1.008)		
CRP/Albumin Ratio:				
1st trimester	0.037*	3.582 (1.080-11.883)	0.894	1.002 (0.975-1.030)
2nd trimester	0.033 *	2.332 (1.070-5.084)		
3rd trimester	0.151	1.011 (0.996-1.026)		
Fecal Calprotectin (mcg/gm):				
1st trimester	0.049*	1.021 (1.001-1.043)	0.116	3.354 (0.742-15.16)
2nd trimester	0.034*	1.016 (1.001-1.031)		

-® Reference group. -Variables with *p*-value !90.05 included in multivariate. -*: Statistically significant at $p \leq 0.05$.

Discussion

Pregnancy is considered a very sensitive and fragile period, especially for women with a chronic illness. A specialised multidisciplinary team of professionals who are familiar with IBD should be involved in the care of the patients, and they should keep a strong contact with the expectant female [12]. This will help to guarantee that patients have access to a supportive environment. In an ideal scenario, members of a multidisciplinary team should periodically meet with pregnant patients, particularly those patients displaying signs linked with a poor illness course [13]. IBD and pregnancy interacts together in both ways that impacts corse of each condition; IBD can have an effect on fertility and the outcome of a pregnancy, on the other side pregnancy can have repercussions for how active IBD progress [14]. Impact of pregnancy on the progression of inflammatory bowel disease was compared to non-pregnant women with UC, pregnant UC patients had a greater risk of flare of the disease activity throughout pregnancy and in the postnatal period [15].

Females who have inflammatory bowel disease who get pregnant while their condition is high activity (as determined by the specialist) appear to be prone to have severe disease than patients who conceive when their disease is in quiscence [16]. Patients who already have active illness at the time of conception are more likely to experience a resurgence or a worsening of their condition if they become pregnant. The European Crohn's and Colitis Organization recommends that IBD should be in remission before pregnancy [1].

In our study, we have shown that previous exposure to biological agents, disease activity before pregnancy, inflammatory markers as well as the level of CRP/Albumin ratio were directly related to complications during the pregnancy in UC patients.

In patients with UC, relapse during pregnancy occurred more frequently than in patients with Crohn's disease [17].

Several research have shown that females who have IBD had a greater chance of having a pregnancy related complications in the form of: Preterm labor, low birth weight for gestational age, and caesarean section delivery [18]. Interestingly, the studies do not imply that there is a higher incidence of congenital defects [14].

It is essential to be aware that the physiological changes that accompany pregnancy might induce fluctuations to serological markers of inflammation

such as albumin, and C-reactive protein [CRP]. In a pregnancy that is developing normally, the concentrations of haemoglobin and albumin will fall, but CRP levels may rise **[19]**. It does not appear that pregnancy has a significant effect on the level of faecal calprotectin. It is possible to accurately detect disease activity throughout pregnancy using this marker according to ECCO guidelines **[1]**.

CAR demonstrated a better specificity and positive predictive value than CRP in predicting severe ulcerative colitis, and there was a significant link between CAR and UC disease activity **[10]**. In our study analysis, both CAR and fecal calprotectin were directly correlated to occurrence of incidences in pregnancy upon regressive analysis.

Exposure to radiation and contrast material entangle high risk for the foetus. If imaging modality is needed to evaluate an acute severe relapse of UC, then the imaging method of choice is magnetic resonance imaging (gadolinium is not recommended during the first trimester), however several reports have shown interest in the use of intestinal ultrasound to monitor disease activity during pregnancy **[20]**. In our study no factor was correlated to need for radiological examination during pregnancy in UC patients.

During the second trimester of pregnancy, a colonoscopy may be performed if it is highly suggested to do so. Colonoscopy during the second trimester of pregnancy may be performed quite safely, without posing significant dangers to the developing foetus **[21]**. We did not show any direct relation between laboratory tests to the need of endoscopy during pregnancy in UC patients.

References

1- TORRES J., CHAPARRO M., JULSGAARD M., et al.: European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. J. Crohns Colitis., 17 (1): 1-27, 2023.

2- CHODEN T., MANDALIYA R., CHARABATY A., et al.: Monitoring inflammatory bowel disease during pregnancy: Current literature and future challenges. World J. Gastrointest Pharmacol. Ther., 9 (1): 1-7, 2018.

3- SELINGER C.P., NELSON-PIERCY C., FRASER A., et al.: IBD in pregnancy: Recent advances, practical management. Frontline Gastroenterol., 12 (3): 214-24, 2021.

4- COSTA R.V., SIMÕES C., CORREIA L., et al.: Inflammatory Bowel Disease and Pregnancy: Is It a Marker for Adverse Outcomes? Rev. Bras. Ginecol. Obstet., 44 (10): 915-24, 2022.

5- PERVEZ H., USMAN N., AHMED M.M., et al.: The Impact of Inflammatory Bowel Disease on Pregnancy and the Fetus: A Literature Review. Cureus, 11 (9): e5648, 2019.

6- SCHMIDT M., KÜHNERT M., KUSCHEL B., et al.: Care of Women with Chronic Inflammatory Bowel Disease (Chronic IBD) During Pregnancy: Recommendations of the Obstetrics and Prenatal Medicine Working Group of the DGGG. Geburtshilfe Frauenheilkd, 81 (12): 1348-53, 2021.

7- ALI M.F., HE H. and FRIEDEL D.: Inflammatory bowel disease and pregnancy: Fertility, complications and treatment. Ann. Gastroenterol., 33 (6): 579-90, 2020.

8- MAGRO F., GIONCHETTI P., ELIAKIM R., et al.: Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J. Crohns Colitis, 11 (6): 649-70, 2017.

9- MIRANDA-GARCÍA P., CHAPARRO M. and GISBERT J.P.: Correlation between serological biomarkers and endoscopic activity in patients with inflammatory bowel disease. Gastroenterol. Hepatol., 39 (8): 508-15, 2016.

10- SAYAR S., KURBUZ K., KAHRAMAN R., et al.: A practical marker to determining acute severe ulcerative colitis: CRP/albumin ratio. North Clin. Istanb., 7 (1): 49-55, 2020.

11- TRUELOVE S.C. and WITTS L.J.: Cortisone in ulcerative colitis; final report on a therapeutic trial. Br. Med. J., 2 (4947): 1041-8, 1955.

12- SHAND A.W., CHEN J. S., SELBY W., et al.: Inflammatory bowel disease in pregnancy: A population-based study of prevalence and pregnancy outcomes. BJOG, 123 (11): 1862-70, 2016.

13- HOFFMANN P., KRUEGER J., BASHLEKOVA T., et al.: Pregnancy with inflammatory bowel disease: Outcomes for mothers and their children at a European tertiary care center. J. Obstet. Gynaecol. Res., 48 (3): 621-33, 2022.

14- LAUBE R., PARAMSOTHY S. and LEONG R.W.: Review of pregnancy in Crohn's disease and ulcerative colitis. Therap Adv. Gastroenterol., 14: 17562848211016242, 2021.

15- PEDERSEN N., BORTOLI A., DURICOVA D., et al.: The course of inflammatory bowel disease during pregnancy and postpartum: A prospective European ECCO-EpiCom Study of 209 pregnant women. Aliment Pharmacol. Ther., 38 (5): 501-12, 2013.

16- ABHYANKAR A., HAM M. and MOSS A.C.: Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol. Ther., 38 (5): 460-6, 2013.

17- DE LIMA-KARAGIANNIS A., ZELINKOVA-DETKOVA Z. and VAN DER WOUDE C.J.: The Effects of Active IBD During Pregnancy in the Era of Novel IBD Therapies. Am. J. Gastroenterol., 111 (9): 1305-12, 2016.

18- MEYER A., DROUIN J., WEILL A., et al.: Pregnancy in women with inflammatory bowel disease: A French nationwide study 2010-2018. Aliment Pharmacol. Ther., 52 (9): 1480-90, 2020.

19- KLAJNBARD A., SZECSI P.B., COLOV N.P., et al.: Laboratory reference intervals during pregnancy, delivery

and the early postpartum period. Clin. Chem. Lab. Med., 48 (2): 237-48, 2010.

20- GOTTLIEB Z.S., DOLINGER M., KAYAL M., et al.: Clinical Challenge: Proactive Precise Management of Active Ulcerative Colitis During Pregnancy-Advantages of Point-of-Care Intestinal Ultrasound and Therapeutic Drug Monitoring. Dig. Dis. Sci., 67 (8): 3557-61, 2022.

21- CAPPELL M.S., FOX S.R. and GORREPATI N.: Safety and efficacy of colonoscopy during pregnancy: An analysis of pregnancy outcome in 20 patients. J. Reprod Med., 55 (3-4): 115-23, 2010.

مراقبة نشاط مرض التهاب القولون التقرحى أثناء الحمل باستخدام نسبة CRP/الألبومين

التهاب القولون التقرحى هو شكل متكرر من التهاب الجهاز الهضمى الذى يصيب الأمعاء الغليظة فى الغالب. بسبب الاختلافات فى مستويات الهرمونات التى تحدث أثناء الحمل، بالإضافة إلى زيادة خطر حدوث مضاعفات فى هذه الفترة، يمكن أن يكون التحكم فى التهاب القولون التقرحى صعباً للغاية. يعد تتبع نشاط مرض التهاب القولون التقرحى ومتابعته عندما تكون المرأة حاملاً أمراً فى غاية الأهمية للتأكد من بقاء كل من الأم والجنين فى صحة جيدة.

الهدف من دراستنا هو دراسة الأدوات المختبرية المستخد مة لرصد نشاط مرض التهاب القولون التقرحى أثناء الحمل. فى هذه الدراسة، سيتم تناول أهمية مراقبة نشاط التهاب القولون التقرحى طوال فترة الحمل، بالإضافة إلى الطرق المستخدمة للتحقق من ذلك.

هذه دراسة وصفية بأثر رجعى لمرضى التهاب القولون التقرحى الحوامل. قمنا بجمع البيانات من مرضى التهاب القولون التقرحى خلال زيارات المتابعة المتعلقة بالحمل. سجلنا بياناتهم الاجتماعية والديموغرافية وتاريخ حالتهم والبيانات السريرية والنتائج المعملية. تم فحص نشاط المرض لكل ثلاثة أشهر. تم تحديد مستويات بروتين سى التفاعلى والألبومين وتوثيقها .

فى تحليل دراستنا ، ارتبط كل من CAR و calprotectin البرازى ارتباطاً مباشراً بحدوث مضاعفات فى الحمل. يعد العلاج المناسب لالتهاب القولون التقرحى عند النساء الحوامل أمراً ضرورياً لضمان صحة الأم وطفلها بشكل عام وصحة جيدة. وهو يدعو إلى المراقبة الدقيقة والزيارات المنتظمة لمؤسسات الإحالة المتخصصة.