Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Aydin M, Tolunay HE, Aksar M, Boza B, Cim N, Dulger AC, Yildizhan R. Clinical management and outcomes of pregnant women with inflammatory bowel diseases Turk J Womens Health Neanotol 2020; 2(4): 122-127

Original Article

Clinical management and outcomes of pregnant women with inflammatory bowel diseases

İnflamatuar bağırsak hastalığı olan gebelerin klinik yönetimi ve sonuçları

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Abstract

Aim: Inflammatory bowel diseases (IBD); ulcerative colitis (UC) and Crohn's disease (CD) are chronic pathologies affecting young adults. Pregnancy and IBD are multidimensional and could be affected by many variables. In this study, we aimed to present our pregnants with IBD, and their clinical management and pregnancy outcomes.

Material and method: Pregnants with IBD were retrospectively evaluated and grouped as those with UC and CD. A total of nine cases were included in this study.

Results: The mean age of the patients was 28.5 ± 4.9 years. The mean gravida and parity numbers were 2.6 ± 1 and 1.55 ± 1.13 respectively. Six patients with IBD had UC, and three patients had CD. Two patients were newly diagnosed, and seven patients had a history of IBD. The mean gestational week of the eight patients was 34.2 ± 4.55 weeks. The mean birth weight, and first and fifth minute APGAR scores of the eight patients were 2530 ± 956 gr, 7.6 ± 0.91 and 8.87 ± 0.83, respectively (n=8).

Conclusion: IBD affects a large group of women of childbearing age. Pregnancy, maternal and fetal outcomes are widely affected by disease activity. Becoming pregnant can be advised if the disease is quiescent, with rapid and efficient management of possible flare-ups. Controlling IBD is the main factor for obstetrical prognosis in pregnancy.

Key words: Inflammatory bowel diseases; ulcerative colitis; Crohn's disease; pregnancy; management

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Received: 11.06.2020 Accepted: 25.12.2020
DOI: 10.46969/ezh.751082

Öz

Amaç: İnflamatuar Bağırsak Hastalıkları (İBH); ülseratif kolit (ÜK) ve Crohn hastalığı (CH) genç yetişkinleri etkileyen kronik patolojilerdir. Gebelik ve İBH çok boyutludur ve birçok değişkenden etkilenebilir. Bu çalışmada İBH'ı olan gebelerimizin klinik yönetimlerinin ve gebelik sonuçlarının sunulması amaçlandı.

Gereç ve Yöntem: İBD'si olan gebeler retrospektif olarak incelendi ve ÜK'i ve CH olan hastalar olarak gruplandırıldı. Toplam dokuz olgu çalışmaya dahil edildi.

Bulgular: Hastaların ortalama yaşı 28,5 ± 4,9 idi. Ortalama gravida ve parite sayıları sırasıyla 2,6 ± 1 ve 1,55 ± 1,13 idi. İBD'si olan altı hastada ÜK, üç hastada CH mevcuttu. İki hastaya gebelikleri sırasında yeni tanı konuldu, yedi hastada ise İBH tanısı gebelik öncesinde de mevcuttu. Sekiz hastanın ortalama gebelik haftası 34,2 ± 4,55 hafta idi. Ortalama doğum ağırlığı, birinci ve beşinci dakika APGAR skorları sırasıyla 2,530 ± 956 gr, 7,6 ± 0,91 ve 8,87 ± 0,83 idi (n=8).

Sonuç: İBH, çocuk doğurma çağında olan birçok kadını etkilemektedir. Gebelik, maternal ve fetal sonuçlar hastalık aktivitesinden büyük ölçüde etkilenebilmektedir. Hastalık sessiz ise, olası alevlenmelerin hızlı ve etkili yönetimi ile gebe kalınması tavsiye edilebilir. İBH'nın kontrolü obstetrik prognoz için ana faktördür.

Anahtar kelimeler: İnflamatuar bağırsak hastalığı; ülseratif kolit; Crohn hastalığı; gebelik; yönetim

1. Introduction

Inflammatory Bowel Diseases (IBD); ulcerative colitis (UC), and Crohn's disease (CD) are chronic pathologies affecting young adults. The severity of these diseases, characterized by swollen and damaged tissues on the intestines' inner wall, varies over time and from patient to patient. Exacerbations and remission periods describe the natural course of these diseases. Some of the patients, especially those with CD, undergo surgical intervention at some time in their lives. Significant side effects of the drug usage and surgical interventions' results impose additional problems on the patients (1-3).

Although most young adult patients want to have children, fears, drug usage, surgical interventions, and the disease's inflammatory activity can be dissuading. Pregnancy and IBD are multidimensional and could be affected by many variables. Physicians concerned with IBD should consider pregnancy as a physiological process requiring a specified period based on chronic disease, and treatment should be planned accordingly (4).

In this study, we aimed to present the maternal and fetal results and clinical management of pregnant women with IBD and discuss this issue in light of the current reviews and meta-analysis.

2. Material and Method

The pregnant women with IBD monitored in a tertiary health center between 2014 and 2017 were evaluated and grouped as those with CD (5) and those with UC. In this study, nine cases were included. We retrospectively collected and analyzed clinical data, which did not interfere with medical treatment. According to the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" principles, the current study was organized.

The follow-ups of the patients were performed by gastroenterology and perinatology departments. The gastroenterology clinic specialists performed the laboratory examinations, including hemogram, biochemistry, C-reactive protein (CRP), International Normalized Ratio (INR), albumin, and bilirubin level measurements. They followed the patients clinically for clinical signs, including abdominal pain, diarrhea (usually without blood), and bloating¬. Gastrointestinal endoscopy was performed in all of the patients to evaluate the bowel lumen. Concurrently, the biophysical evaluation of the fetuses and obstetrics follow-ups was performed with ultrasonography by obstetricians. The route of delivery was either vaginal delivery or cesarean section at the time of labour.

For the literature review; the meta-analysis conducted in 2015 by Otoore et al. was used for the literature research until 2015 (6). From 2015 to May 2020, PUBMED was researched with the keywords "inflammatory bowel disease" and "pregnancy" and related articles included in to study.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 20.0 software (IBM Corporation Software Group, New York, United States of America). Our categorical data included age, gravida number, parity number, gestational week, birth weight, and APGAR score were evaluated using descriptive statistics for analysis. Descriptive statistics for these continuous variables were presented as mean ±standard deviation (SD).

3. Results

The mean age of the patients was 28.5 ± 4.9 years. The mean gravida and parity numbers were 2.6 ± 1 and 1.55 ± 1.13, respectively. Six patients with IBD had UC, and three patients had CD. Two patients were newly diagnosed, and seven patients had a history of IBD. Pregnancy ended with an abortion in the 8th week of pregnancy in one patient with refractor CD. The mean gestational week of the remaining eight patients was 34.2 ± 4.55 weeks. Among eight patients, vaginal delivery was performed in three patients, and the cesarean section was performed in five patients due to the obstetric indications. The mean birth weight, and first and fifth minute APGAR scores were 2,530 ± 956 grams, 7.6 ± 0.91 and 8.87 ± 0.83, respectively. The exploratory laparotomy was required in two patients with CD in the 26th and 27th weeks of gestation. Sigmoidoscopy was performed to confirm inflammation. Prematurity complications were observed in two babies born at 26th and 28th weeks of gestation **(Table 1)**. All cases are shown in **Table 1** in detail.

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Table 1. Clinical features of the patients

Case	Age	Gravida	Parity	Diagnosis	Intervention	Pregnancy Outcome	Complications	Additional information
Case 1 (CD)	24	2	0	First time at 27th pregnancy week. Acute abdominal pain. The threat of premature birth.	Emergent exploratory laparotomy (ileocolectomy with primary anastomosis was performed) Ileal perforation with small bowel fistula was observed	She went on to deliver a healthy term infant at 37th pregnancy week	Maternal bowel perforation. Fetal complication none.	Azathioprine medication after delivery
Case 2 (UC)	31	3	2	Seven-year history of UC. She admitted with rectal bleeding and pain at 30th pregnancy week	IV steroid treatment. Multiple ulcers were diagnosed in colonoscopy	In the 36th week of pregnancy, she delivered spontaneously.	No complications	Remission with mesalazine
Case 3 (UC)	34	2	1	A 13-year history of UC. An acute flare of UC in the 14th week of pregnancy.	Mesalazine, steroid and cyclosporine treatment. Diagnosis confirmed by sigmoidoscopy	In the 26th week of pregnancy, she underwent an emergency cesarean section for suspected placental insufficiency	Maternal complication none. Fetal complication: Femur fracture, intracerebral hemorrhage, respiratory distress syndrome	Remission with mesalazine
Case 4 (UC)	32	4	3	Two-year history of refractory disease. She reported an unintended pregnancy in 8th week under anti-TNF treatment	Anti-TNF treatment was canceled at 4th week of pregnancy	Miscarriage at eight weeks of gestation.	Maternal complication none. Fetal complication: miscarriage	anti-TNF
Case 5 (CD)	34	3	2	Three years of history of CD. The disease is in remission	Remission. No treatment	38th week of pregnancy, Cesarean section, healthy infant	No complications	No medications
Case 6 (UC)	29	4	3	Two years of history of UC. The disease is in remission. Flare in 20th pregnancy week.	Rectal steroid and, mesalazine medication	36th weeks of pregnancy, Cesarean section due to obstetric indication. Healthy infant	No complications	Remission in the postpartum period
Case 7 (CD)	19	1	0	Two years of history of CD. She had pregnancy under mesalazine treatment.At26th week of pregnancy ileus symptoms was diagnosed	Emergent exploratory laparotomy Adhesiolysis was performed. Surgical resection of the involved segment was not required	28th week of pregnancy, Cesarean section, (Prematurity, 890 gr)	Maternal bowel adhesions. Fetal complication: Respiratory distress syndrome	Azathioprine
Case 8 (UC)	28	3	2	First time at 24th pregnancy week. Rectal bleeding.	Rectal steroid and mesalazine treatment.	37th weeks of pregnancy. Cesarean birth (Due to obstetric indication) Healthy infant	Maternal complication: Flare of disease in the postpartum period No fetal complication	Mesalazine
Case 9 (UC)	26	2	1	One year's history of CD. The disease is in remission	Remission. No treatment	36th weeks of pregnancy. Vaginal birth. Healthy infant	No complications	No medications

CD: Crohn's Disease, UC: Ulcerative Colit

Table 2. A comprehensive review of the latest literature about IBD and pregnancy

Author (Year)	Study Type	Study Period	Type of IBD and Number of Patients (n)	Findings	Recommendations
O'Toole A, et al. (2015) (6)	Meta-Analysis	1980-2014	Fifteen thousand seven pregnancies in women with inflammatory bowel disease and 4,614,271 pregnancies in women without the condition. 6559 patients with ulcerative colitis and 5449 patients with chron disease	1) The disease is associated with increased odds of preterm birth, SGA birth weight, and stillbirth. 2) A significant association between inflammatory bowel disease and congenital anomalies was found.	1) Study reveals that women with inflammatory bowel disease are at an increased risk of three, often interrelated, primary adverse pregnancy outcomes: preterm birth, SGA birth weight, and stillbirth. Preconception counseling offers an opportunity to address patient concerns regarding potential risks and to encourage delay of conception until clinical remission is established, and nutrition is optimized. 2) Early consultation with maternal-fetal medicine specialists, gastroenterologists, and colorectal surgeons (as indicated) is recommended to plan appropriate pregnancy management and mode of delivery.
Hashash JG & Kane S. (2015) (8)	Review	2015		Active disease contributes to decreased fertility, and although this finding is still controversial, active disease at the time of conception has been shown to lead to worse pregnancy outcomes.	1) If surgery is needed for a female patient's health, then alternative methods of conception, such as in vitro fertilization, should be considered. 2) All IBD medications except for thalidomide and methotrexate should be continued in young female patients who plan to conceive and those who are pregnant.
Boyd HA, et al. (2015) (26)	Cohort Study	1996-2002	Ninety-six thousand pregnancies and 700 with IBD. Approximately 300 of them with chron disease and 400 of them with ulcerative colitis	IBD was strongly and significantly associated with preterm premature rupture of membranes and preterm delivery in women using systemic corticosteroids during pregnancy. IBD was also related to premature preterm rupture of membranes in women using local corticosteroid medications and with medically indicated preterm delivery in non-medicated women. Furthermore, IBD was associated with a low 5-minute Apgar score in term infants. Finally, Crohn's disease (but not ulcerative colitis) was associated with significant congenital abnormalities in the offspring.	Women with IBD are at increased risk of severe pre-eclampsia, medically indicated preterm delivery, preterm premature rupture of membranes, and delivering infants with low Apgar score and significant congenital malformations. These associations are only partly explained by severe disease, as reflected by systemic corticosteroid use.
Ban L, et al. (2015) (20)	Cohort Study	1990-2010	9639 patients with IBD	Women with CD and in women who had surgical intervention is related to decreased fertility rates when compared to the general female population.	The lifetime effect of pouch vs. Nonpouch surgery on fertility is small; the reduction of post-pouch operation should be interpreted with caution.
Shand AW, et al. (2016) (13)	Cohort Study	2001-2011	A total of 630,742 women who delivered at ≥20 weeks of gestation. 1960 women (0.31%) with IBD, who had 2781 births (1183 UC, 1287 CD, and 311 IBD-indeterminate)	Women with IBD were more likely than women without IBD to have a cesarean section, severe maternal morbidity, preterm birth, and their infants to be small-for-gestational-age.	Pregnancies complicated by IBD at or near the time of birth have significantly higher rates of adverse pregnancy outcomes than pregnancies of women without IBD.
Bar-Gil Shitrit A, et al. (2016) (10)	Review	1983-2015		1) The mode of delivery did not influence the natural history of IBD, and vaginal delivery was not associated with an increased risk of subsequent perianal disease in women with CD. 2) In two-thirds of cases, women who become pregnant during IBD remission can expect to have a stable condition during pregnancy. In contrast, if pregnancy begins when the disease is active, the severity of the disease will remain the same or worsen during pregnancy in approximate two-thirds of cases. 3) These patients must be made aware of the critical importance of conceiving during a period of disease remission. More than two-thirds of pregnancies conceived during disease remission have an average outcome, with remission continuing throughout pregnancy. These pregnancies are similar to those occurring in the healthy population.	Women with IBD have an increased risk of adverse events during pregnancy. Therefore, pre-pregnancy consultation with a multi-disciplinary team is recommended. Attention should be paid to suitable drug selection, and appropriate treatment should be maintained in women with IBD who wish to conceive, to decrease the risk of a flare-up during pregnancy. When IBD is in remission, pregnancy can be safe and have a favorable outcome.
Padhan RK, et al. (2017) (9)	Cohort Study	2004-2013	514 females with ulcerative colitis (UC) or Crohn's disease (CD) aged between 18 and 45 years were screened, and patients with data on pregnancy status were included (n = 406)	Pregnancies after the disease onset were associated with more cesarean sections and adverse fetal outcomes than pregnancies before disease onset in both UC and CD patients.	Among pregnant UC patients, the disease course was worst when pregnancy coincided with disease onset. Pregnancy and fetal outcomes were worse in pregnancy after disease onset than pregnancy before disease onset.
Pervez H, et al. (2019) (18)	Review	2015-2019		1) In patients whose IBD was active during pregnancy, higher rates of preterm birth and LBW were noted 2) An increase in preterm birth, LBW, congenital abnormalities, and C-section rates was determined 3) Women with UC have a cesarean section rate compared with the general population unlike women with CD, who are more prone to undergo C-sections	The disease should be kept in sustained remission to limit the morbidity and mortality in the mother and the fetus. It should be emphasized to have a regular pre-conception and intrapartum obstetric followups. The nutrition of the mother should also be kept under consideration with the introduction of supplemental vitamins and minerals. In addition to this, the medications used to keep the activity of the disease low should be regulated according to their side effects.
Lavie I, et al. (2020) (21)	Retrospective case-control study	2011-2019	49 women with IBD-ART were matched using propensity score and compared in a 1:1 ratio with three control groups, IBD patients who conceived spontaneously (IBD-SP), women using ART (H-ART) and women who conceived spontaneously (H-SP)	1) Women with IBD who underwent ART do not have a significant increase in preterm birth or other pregnancy complications. 2) Women with IBD who underwent ART did not have a considerable decrease in the rate of spontaneous vaginal delivery.	Patients with IBD undergoing ART have comparable pregnancy outcomes to women using ART and to patients with IBD with spontaneous pregnancy.

4. Discussion

CD is primarily diagnosed with the highest rates in the second and third decades of life. When a woman with CD gets pregnant, the condition should have no adverse effects on pregnancy, and pregnancy should not lead to an exacerbation of CD (5).

If conception occurs during the remission period of the IBD, the risk of relapse does not change. Therefore, patients should be advised to become pregnant at a quiescent period of the disease. In con¬trast, if fertilization occurs during a period of exacerbation, there is a risk of persistent activity or higher relapse rates during pregnancy (7, 8). Pregnancy and fetal outcomes become worse in pregnancy after disease onset than pregnancy before disease onset (9, 10). Six of the patients included in our study had an IBD history; four experienced exacerbations in the disease. Only one of the patients underwent an exploratory laparotomy in the 26th week of gestation due to bowel adhesions and delivered the baby in the 28 week of gestation. The two disease-activated patients were delivered at 26th and 36th weeks of gestation. IBDs mostly affect a young population at reproductive age. Despite recent medical treatment improvements, an increased risk of adverse pregnancy outcomes in patients with IBD still exists (11). Adverse outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (12, 13), and small size regarding the gestational age of birth (SGA) (14, 15). O-Toole A. et al. have found that IBD is associated with preterm birth, SGA, and stillbirth (6). One of our patients that had a delivery in the 26th week of pregnancy had chronic placental insufficiency. She was under immunosuppressive and anti-inflammatory treatments. Some data associated with these drugs show an increased preterm birth rate, stillbirth and low birth weight. However, these adverse pregnancy outcomes may also be associated with active IBD (16, 17). The current study results showed that the activation of the disease might cause preterm birth. Pervez H et al. have found IBD to be associated with preterm delivery (18). Morales et al. studied the effects of CD on the course of pregnancy, and they reported that exacerbation of the disease was associated with an increased risk of premature labour. In contrast, conception during exacerbation was associated with an increased risk of miscarriage (19). Similarly, one of the patient in our series, refractory for two years, and who received anti-TNF, had a miscarriage.

IBD is considered to be related to low fecundability rates. Ban L et al. have found that women with CD and women who had surgical intervention are related to decreased fertility rates compared to the general female population (20). Hashash JG et al. reported that if surgery is needed for a female patient's health, then alternative methods of conception, such as in vitro fertilization, should be considered (8). Opposite to this study, Lavie I et al. have released that women with IBD who underwent ART do not significantly decrease the rate of fertilization (21).

Suppose complications occur during the pregnancy of a patient with CD or UC. In that case, the decision of surgery should be guided by the principle that if a surgical intervention is the best option for the patient, it is usually the best option for the unborn child (22). Laparotomy was done in two patients with exacerbation of the disease. Adhesiolysis was performed in one of those patients (due to rectal bleeding), and surgical resection (due to ileus) was conducted in the other patient.

According to European Crohn's and Colitis Organisation (ECCO) guidelines (23), standard endoscopic procedures (gastroscopy, colonoscopy) are generally considered safe during pregnancy. We safely performed endoscopy in patients with suspected disease exacerbation. 5-ASA compounds and corticosteroids commonly used are very safe for use in IBD treatment during pregnancy (24). No association of combination therapy with a higher risk for spontaneous abortion, low birth weight, congenital abnormalities, and cesarean section was confirmed with the data from the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry (25). Boyd HA et al. have found that women with IBD are at increased risk of significant congenital malformations. These associations are explained by severe disease, as reflected by systemic corticosteroid use (26).

Shand AW et al. and Pervez H et al. have determined that pregnancies complicated by IBD have higher cesarean section rates (13, 18). Bar-Gil SA et al. have found that delivery mode does not influence the natural history of IBD, and vaginal delivery is not associated with an increased risk of subsequent perianal disease in women with CD (10). When choosing the type of delivery, only patients with active perianal disease or fistulas with acute inflammation should be advised to have a cesarean section (27). In our study, we performed the cesarean section only in the presence of obstetric indications.

IBD affects a large group of women of childbearing age. IBD patients are as fertile as other women in society. Pregnancy, maternal and fetal outcomes may widely be affected by disease activity. Both CD and UC patients can experience a healthy, disease-free pregnancy if they become pregnant during remission. This period should not be considered a crisis, and pregnancy follow-up should organize in a multidisciplinary process (10). Patients expect guidelines from obstetricians on how to prepare themselves for pregnancy, as well as information on whether the disease affects fertility, the course of pregnancy, or whether there is a risk of congenital defects associated with inflammation of the bowel or treatment thereof, or whether children may inherit the disease. The agents used in the disease can be used in multiple pregnancy and lactation period. Additionally, information on pregnancy and lactation on the course is essential to making fully conscious decisions regarding pregnancy and lactation. Access to factual information reduces the concerns of patients, reducing the rate of voluntary childless patients.

All these findings show that IBD makes pregnancy complicated, so many trials have been conducted to explore the impact of IBD on pregnancy and the fetus. A comprehensive review of the literature on the subject is shown in **Table 2**.

In conclusion, control of IBD is the main factor for obstetrical prognosis in pregnancy. Becoming pregnant can be advised if the disease is quiescent, with rapid and efficient management of possible exacerbations. The delivery route should be determined on a case-by-case basis, considering pregestational faecal incontinence and the perineum's clinical appearance.

Declaration of Interest

The authors report no conflicts of interest.

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