TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS
TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

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Ulcerative colitis and pregnancy

Ülseratif kolit ve gebelik

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INTRODUCTION

Ulcerative colitis (UC) is a disease that particularly affects women in the reproductive period. About 25% of female patients become pregnant after the establishment of a diagnosis of inflammatory bowel disease (IBD). Potential adverse effects of disease activity on fertility, potential pregnancy complications due to UC, potential adverse effects of the pregnancy itself on the course of UC, and the teratogenic potential of medications used in UC are troublesome issues for both patients with UC and physicians. Several studies have investigated the effects of UC on fertility and pregnancy and obtained contradictory results (1-6).

No comments regarding "Pregnancy and Lactation" are found in the guidelines published by ECCO (European Crohn's and Colitis Organisation) in 2008; those comments have been declared to be forthcoming later (7). In this study, our objective was to investigate the effects of UC on fertility and the course of pregnancy as well as the effects of pregnancy on UC.

MATERIALS AND METHODS

The 3e systematic literature screening method was used in this study to investigate the following questions that were not included in the 2008 guidelines of ECCO: "Does UC affect fertility in women?", "Are there any evidences indicating that pregnancy increases disease relapses in UC", and "Does disease activity in UC affect the course of pregnancy?".

The PubMed database was used to perform a systematic literature screening. In addition, literature references were screened to reach other studies. Key words included "Ulcerative colitis and pregnancy"; however, only literature in English was screened. Studies performed with patients older than 18 years were included. Odds ratios (OR) values were calculated to determine the development of infertility in women with UC compared to those without UC, development of relapse in pregnant UC patients compared to those who are not pregnant, and the rate of gestational complications (abortion, in utero exitus, premature delivery, low birth weight (LBW), development of congenital malformations, cesarean section, and infant small for gestational age [SGA]) in pregnant women with UC compared to those without. Definitions of the terms premature delivery, LBW and SGA infant are presented below:

- Premature delivery: Birth at <37 weeks of gestation.
- LBW: Infant <2500 g at birth.
- SGA: Infant whose birth weight, length or head circumference is below 10 percentile appropriate for his/her gestational age.

RESULTS

Five studies related to the effects of UC on fertility and the course of pregnancy as well as the effects of pregnancy on UC were identified as a result of the 3e systematic search. Determination of OR values of infertility, gestational complications and development of relapse in pregnant patients with UC were targeted while evaluating the studies. The types of these five studies are stated in Table 1.

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A-Does UC affect fertility in women?

Most clinicians used to consider patients with UC as subfertile. In the study of De Dombal et al. (8) performed in 1965, only 31% of patients with UC were found to be fertile. In their study performed in 1980, Willoughby et al. (1) concluded that fertility rates corrected for age and desire for pregnancy were normal (92%). In 1990, Baird et al. (9) reported that IBD was associated with decreased fertility with regard to the total number of pregnancies. However, correction for influencing factors (decreased fertility whether desired or not, secondary fertility, duration allowed for the occurrence of pregnancy) demonstrated that decreased fertility was indeed associated with the patients' own choice, rather than IBD.

A recent study from Australia reported lower rates of fertility in subjects with IBD compared to those without IBD (76% vs. 58%). Infertility was determined in 32% and 49% of patients with UC and Crohn's disease (CD), respectively. However, the frequency of referral due to fertility treatment was found comparable in patients with and without IBD despite these low rates (19.4% vs. 20%). It was thus suggested that the decrease in fertility rates might partially be a result of personal choice (10).

Fertility rates have also been reported to decrease due to the postoperative effects of ileal pouch anal anastomosis (IPAA) operations including pelvic adhesions and reproductive organ injuries. Similarly, decreased fertility has been reported after the performance of IPAA due to familial adenomatous polyposis (11). In a meta-analysis on the effects of IPAA on infertility, fertility rates were recorded as 19.9% and 50.1% in UC subjects who received medical treatment and underwent IPAA, respectively. The results of this meta-analysis demonstrated that there is no exact response to the question of whether laparoscopic IPAA and rectal stump and subtotal colectomy with ileostomy increase the rates of infertility (12). In a study performed on 21 subjects to determine the effects of surgery on gynecological anatomy using hysterosalpingography (HSG), no abnormalities were determined in 14 subjects (67%). The most common abnormality noted in that study was adhesion of the tubes to the pelvis in 10 (48%) subjects. Despite this high rate of anatomic abnormality, no exact correlation could be established between surgery and radiographic signs since pre-operative HSGs were not available in these subjects (13).

The only study that conformed to the screening criteria in the systematic literature screening was that of Hudson et al. (14) performed on patients with IBD to compare women receiving medical treatment for UC and women with a history of IPAA in terms of development of infertility in comparison to the normal population. Statistical analysis of the data obtained in their study suggested that OR for infertility was 1.42 (95% confidence interval [CI]: 0.648-3.129, p=0.3) and 12.6 (95%CI: 3.703-42.957, p<0.001) in women with UC receiving medical treatment and IPAA history, respectively. OR for the infertility rate in women with UC as a personal choice was found to be 3.4 (95%CI: 2.029-5.724, p<0.001) (Table 2).

Table 1. The types of studies analyzed

Type of study	Number of studies
Retrospective study	1
Retrospective case-control study	2
Prospective case-control study	1
Meta-analysis	1

B-Are there any evidences indicating that pregnancy increases disease relapses in UC?

The effect of pregnancy on UC has been separated into four different groups according to the classification by Abramson et al. (15):

1. Patients diagnosed with UC and in remission prior to conception
2. Patients with active disease during conception

Table 2. Voluntary and involuntary infertility risks of patients with UC

	OR	CI (95%)	p value
Women with UC receiving medical treatment	1.42	0.648-3.129	0.3
Women with UC and IPAA history	12.6	3.703-42.957	<0.001*
Voluntary infertility rate in women with UC	3.4	2.029-5.724	<0.001*

UC: Ulcerative colitis. IPAA: Ileal pouch anal anastomosis. OR: Odds ratio. CI: Confidence interval. *: Statistically significant

3. Patients developing UC during the period of pregnancy
4. Patients developing UC during puerperium (during the first 3 months after delivery)

There are studies suggesting that disease exacerbation rates are similar in pregnant and non-pregnant women with IBD. The mean rate of relapse was 34% in studies investigating the relapse rate in pregnant UC patients who were in remission during conception (2). Nielsen et al. (4) found the yearly rate of disease exacerbation as 34% in pregnant patients and 32% in non-pregnant patients.

There are also studies in the literature suggesting that the course of UC in pregnancy is associated with disease activity during conception. Active UC during conception might deteriorate during the period of pregnancy in the absence of medical treatment (4). In a study investigating the effect of disease activity during conception on pregnancy, 90% of patients who were in remission during conception were recorded to remain in remission throughout pregnancy, whereas 27.3% of patients who had active disease during conception presented with active disease and even exacerbation in 25.5%. Most relapses during pregnancy occur in the first trimester. This has been associated with the fact that most patients quit their medications at the onset of pregnancy for fear of potential teratogenic effects (1,4).

Pregnancy itself might sometimes present with improvement in disease activity or clinical remission. A significant decrease was determined in the relapse rates in pregnant women compared to non-pregnant women with UC in the year following pregnancy in a European cohort study examining a 10-year period (0.18 attacks/year vs. 0.34 attacks/year, p=0.008) (16). Although the etiologic basis of this finding has not been clarified yet, maternal and fetal HLA class II antigens have been suggested to be associated. Maternal immune response against paternal antigens has been accused of the immune suppression observed in subjects with IBD and rheumatoid arthritis (17,18).

Occasionally, the initial presentation of UC might occur during pregnancy. Additionally, some subjects might become symptomatic only in pregnancy, remain asymptomatic between pregnancies, and present with disease activations in recurrent pregnancies (19). In the study of Willoughby et al. (1), the initial UC episode was recorded during pregnancy in 7.7% of subjects, and 50% of these occurred in the first trimester. In addition, the initial attack was noted during puerperium in 4.3% of the cases.

Only one study was found that suited the screening criteria in the systematic literature screening. However, no UC-CD separation was made in that study. In that study, development of relapse was not a statistically significant finding in pregnant subjects who were in remission at baseline when pregnant and non-pregnant patients with IBD were compared (OR: 2.076, 95%CI: 0.068-63.421, p=0.6) (20).

C-Does disease activity in UC affect the course of pregnancy?

Population-based studies have demonstrated that the risk of occurrence of delivery complications including premature delivery, LBW and SGA was increased in pregnant women with IBD. Although the rate of congenital abnormalities was increased, the association with IBD medications administered during pregnancy remains to be clarified (21,22). In a population-based study comparing 461 subjects with IBD with 495 control subjects, both from the Kaiser district of North California, increased risk was determined in terms of spontaneous abortion (OR: 1.65 (95%CI: 1.09-2.48)) and pregnancy complications (*in utero* exitus, premature delivery, SGA) (OR: 1.54 (95%CI: 1.0-2.38)) among subjects with IBD. However, the risk of development of congenital malformations was not increased in subjects with UC or CD (23).

Previous studies have suggested that disease activity is a predictor of gestational complications. They suggested that the rates of fetal death and premature delivery were increased in subjects with active disease during conception, whereas the rates of LBW and premature delivery were increased in subjects with active disease during pregnancy (3,24).

Active disease was not a predictor of any one of the gestational complications in pregnant women with UC in the Kaiser population. Indeed, these complications were recorded at a higher frequency in subjects with mild-moderate UC compared to those with severe UC (23). In another population-based study performed in Denmark, calculated corrected risk values of LBW, premature delivery and congenital abnormalities (OR, 95%CI) were: 0.2 (0.0-2.6), 2.4 (0.6-9.5) and 0.8 (0.2-3.8), respectively. However, premature delivery risk (OR, 95% CI) was 3.4 (1.1-10.6) in subjects with moderate-severe risk (25).

The frequency of cesarean section is increased in subjects with IBD. Decision of cesarean section should be given taking into consideration the obstetric issues. There are only two exceptions to this rule:

- Perianal disease: Vaginal birth might aggravate perianal disease in patients with active perianal disease (26).
- Presence of ileal pouch anal anastomosis: Vaginal birth might be performed in subjects with IPAA without any harm to the pouch. Pouch function returns to normal postpartum even if it is disrupted during pregnancy; however, sphincter injury due to vaginal birth might lead to incontinence and increased bowel movements when aggravated by the effects of aging. Therefore, the type of delivery should be determined in cooperation with an obstetrician, gastroenterologist and the patient herself in subjects with IPAA (27).

A total of 1,952 subjects with UC and 78,235 control subjects were compared in a meta-analysis examining eight studies performed between 1986 and 2005. No difference was determined between the groups in terms of LBW, SGA and cesarean section, whereas the rates of premature delivery (OR: 1.34, 95%CI: 1.09-1.64, p=0.005) and congenital abnormalities (OR: 3.88, 95%CI: 1.41-10.67, p=0.009) were increased (Table 3). No discrimination of major-minor malformations was performed in studies reporting congenital abnormalities; one study had included chromosomal disorders, which might have resulted in overestimation of the risk. Authors have emphasized that the risk of congenital malformations should be determined in extensive prospective studies and the specific type of malformation with increased risk should be determined (28). Studies examined in this meta-analysis had not analyzed the relationship between disease activity and pregnancy complications (28). However, previous studies had demonstrated a relationship between disease activity and premature delivery and LBW (3,9). The authors of that meta-analysis concluded that prospective studies are required to investigate the relationship between disease activity and pregnancy complications.

In the sub-analysis of a retrospective case-control study, no elevated risk was determined in terms of premature delivery, cesarean section and spontaneous abortion in subjects with UC compared to controls. However, the risk of development of congenital deformity was elevated in subjects with UC (OR: 21.2, 95%CI: 1.081-415.855, p=0.04). In that study, subjects with disease activation during conception were compared with subjects with mild disease in terms of spontaneous abortion, intrauterine fetal death, premature delivery, and congenital malformations and obtained similar results (29) (Table 3).

In a recent Asian population study, the risks of

Table 3. The risks of adverse events of pregnancy in women with UC

Pregnancy Outcomes	OR	95% CI	p value
Cornish et al. (2007) (28)			
LBW	1.66	(0.48-5.66)	0.4
Prematurity	1.34	(1.09-1.64)	0.005*
SGA	1.05	(0.51-2.16)	0.9
Cesarean section	1.3	(0.86-1.96)	0.21
Congenital malformations	3.88	(1.41-10.67)	0.009*
Bortoli et al. (2007) (29)			
Prematurity	1.17	(0.402-3.406)	0.2
Cesarean Section	1.43	(0.744-2.758)	0.2
Congenital malformations	21.2	(1.081-415.855)	0.04*
Spontaneous abortion	1.16	(0.536-2.545)	0.6
Lin et al. (2010) (30)			
LBW	2.49	(1.55-3.99)	<0.001*
Prematurity	1.99	(1.23-3.23)	0.004*
SGA	1.44	(0.99-2.09)	0.052
Cesarean section	1.18	(0.86-1.60)	0.3

UC: Ulcerative colitis. LBW: Low birth weight. SGA: Small for gestational age. OR: Odds ratio. CI: Confidence interval. *: Statistically significant

SGA and cesarean section were not increased, whereas the risks of LBW (OR: 2.49, 95%CI: 1.55-3.99; p<0.001) and premature delivery (OR: 1.99, 95%CI: 1.23-3.23; p=0.004) were increased in pregnant subjects with UC compared to the controls (30) (Table 3).

The risks of LBW and premature delivery were found to be increased in subjects with IBD in the study of Reddy et al. (31) performed on subjects with IBD in comparison to healthy controls (OR for both: 29.5 (4.925-177.361), p=0.0002). On the other hand, in the study of Szepes et al. (32), the rates of early therapeutic termination and premature delivery were found to be higher in subjects with IBD compared to the controls. IBD was observed not to influence the development of congenital diseases (IBD: 9/97 vs. Control: 2/70, p=0.305). Disease activity was not statistically significantly associated with an increased rate of pregnancy complications in UC or CD.

CONCLUSION

The results of this systematic literature study have demonstrated that the increased rates of infertility observed in UC patients resulted from voluntary infertility. The rates of involuntary infertility were increased in subjects with a history of IPAA; however, no such increase was determined in subjects receiving medical treatment for UC. In terms of the effects of pregnancy on UC, it might be suggested that disease activity during conception is a predictor of disease activity during pregnancy. In addition, it has been determined that disease becomes active mostly in the first trimester, which is probably due to discontinuation of medications at the onset of pregnancy. In terms of the effects of UC on pregnancy, the risks of LBW and premature delivery were increased in pregnant women with UC. Data regarding the effects of disease activity on the course of pregnancy and development of congenital malformations are inadequate.

Recommendation:

Does UC affect fertility in women?

The decreased rate of fertility in subjects with UC is associated with previous surgical history. ***(EL 2b, RG B)***

The decreased rate of fertility in subjects with UC receiving medical treatment is mostly a result of voluntary infertility. ***(EL 3b, RG C)***

Recommendation:

Are there any evidences indicating that pregnancy increases disease relapses in UC?

The disease often follows an active course during pregnancy in subjects with active disease during conception. ***(EL 3b, RG C)***

The rate of relapse is higher in the first trimester in pregnancy even in subjects who are in remission during conception. ***(EL 3b, RG C)***

Relapses are often associated with discontinuation of medications. Therefore, proper treatment should be continued during pregnancy in pregnant subjects with UC who enter remission with medication. ***(EL 5, RG D)***

Patients with UC should be advised to become pregnant during periods of remission in order to decrease the rates of relapse during pregnancy. ***(EL 5, RG D)***

Recommendation:

Does disease activity in UC affect the course of pregnancy?

UC is a risk factor for premature delivery and low birth weight.

Pregnant UC patients should be considered as patients with risky pregnancies and kept under close obstetric follow-up. ***(EL 1a, RG A)***

The relationship between disease activity and obstetric complications is not clear, and more extensive prospective studies are needed in this respect. ***(EL 5, RG D)***

Data regarding the increased rates of congenital malformations in infants born of mothers with UC are contradictory. ***(EL 5, RG D)***

The rate of cesarean section is increased in subjects with UC; however, not at a statistically significant level. ***(EL 1a, RG A)***

Pouch dysfunction and anal incontinence might develop secondary to vaginal birth in subjects with a history of IPAA. ***(EL 5, RG D)***

The type of delivery should be determined taking into consideration the long-term risks of vaginal birth and in cooperation with a gastroenterologist, an obstetrician and the patient herself in UC subjects with a history of IPAA. ***(EL 5, RG D)***

REFERENCES

1. Willoughby CP, Truelove SC. UC and pregnancy. Gut 1980; 21: 469-74.
2. Miller JP. Inflammatory bowel disease in pregnancy: a review. J R Soc Med 1986; 79: 221-5.
3. Porter RJ, Stirrat GM. The effects of inflammatory bowel disease on pregnancy: a case controlled retrospective analysis. Br J Obstet Gynecol 1986; 93: 1124-31.
4. Nielsen OH, Andreasson B, Bondesen S, et al. Pregnancy in ulcerative colitis. Scand J Gastroenterol 1983; 18: 735-42.
5. Castiglione F, Pignata S, Morace F, et al. Effect of pregnancy on the clinical course of a cohort of women with inflammatory bowel disease. Ital J Gastroent 1996; 28: 199-204.
6. Levy N, Roisman I, Teodor I. Ulcerative colitis in pregnancy in Israel. Dis Colon Rectum 1981; 24: 351-4.
7. Biancone L, Michetti P, Travis S, et al. European evidence-based Consensus on the management of ulcerative colitis: Special situations. J Crohns Colitis 2008; 2: 63-92.
8. De Dombal FT, Watts JM, Watkinson G, et al. Ulcerative colitis and pregnancy. Lancet 1965; 2: 599-602.
9. Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. Gastroenterology 1990; 99: 987-994.
10. Mountifield R, Bampton P, Prosser R, et al. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. Inflamm Bowel Dis 2009; 15: 720-5.
11. Wikland M, Jansson I, Asztély M, et al. Gynaecological problems related to anatomical changes after conventional proctocolectomy and ileostomy. Int J Colorectal Dis 1990; 5: 49-52.
12. Waljee A, Waljee J, Morris AM, et al. Three-fold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut 2006; 55: 1575-80.
13. Oresland T, Palmblad S, Ellström M, et al. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. Int J Colorectal Dis 1994; 9: 77-81.
14. Hudson M, Flett G, Sinclair TS, et al. Fertility and pregnancy in inflammatory bowel disease. Int J Gynaecol Obstet 1997; 58: 229-37.
15. Abramson D, Jankelson IR, Milner LR. Pregnancy in idiopathic ulcerative colitis. Am J Obstet Gynecol 1951; 61: 121-9.
16. Riis L, Vind I, Politi P, et al. European Collaborative study group on Inflammatory Bowel Disease. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. Am J Gastroenterol 2006; 101: 1539-45.
17. Nelson JL, Hughes KA, Smith AG, et al. Maternal-fetal disparity in HLA class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. N Engl J Med 1993; 329: 500-1.
18. Kane S, Kisiel J, Shih L, et al. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. Am J Gastroenterol 2004; 99: 1523-6.
19. Katz JA, Pore G. Inflammatory bowel disease and pregnancy. Inflamm Bowel Dis 2001; 7: 146-57.
20. Malgarinos G, Gikas A, Delicha E, et al. Pregnancy and inflammatory bowel disease: a prospective case-control study. Rev Med Chir Soc Med Nat Iasi 2007; 111: 613-9.
21. Fonager K, Sørensen HT, Olsen J, et al. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. Am J Gastroenterol 1998; 93: 2426-30.
22. Kornfeld D, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. Am J Obstet Gynecol 1997; 177: 942-6.

23. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology 2007; 133: 1106-12.
24. Fedorkow DM, Persaud D, Nimrod CA. Inflammatory bowel disease: a controlled study of late pregnancy outcome. Am J Obstet Gynecol 1989; 160: 998-1001.
25. Norgard B, Hundberg HH, Jacobsen BA, et al. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007; 102: 1947-54.
26. Ilnyckyji A, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. Am J Gastroenterol 1999; 94: 3274-8.
27. Hahnloser D, Pemberton JH, Wolff BG, et al. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. Dis Colon Rectum 2004; 47: 1127-35.
28. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut 2007; 56: 830-7.
29. Bortoli A, Saibeni S, Tatarella M, et al.; Study Group for Inflammatory Bowel Diseases GSMII. Pregnancy before and after the diagnosis of inflammatory bowel diseases: retrospective case-control study. Gastroenterol Hepatol 2007; 22: 542-9.
30. Lin HC, Chiu CC, Chen SF, et al. Ulcerative colitis and pregnancy outcomes in an Asian population. Am J Gastroenterol 2010; 105: 387-94.
31. Reddy D, Murphy SJ, Kane SV, et al. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. Am J Gastroenterol 2008; 103: 1203-9.
32. Szepes S, Mlnar T, Fokas K, et al. Pregnancy outcomes in women with inflammatory bowel disease and the drug treatment. ECCO Congress 2010 Prague (Abstract).