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PREGNANCY OUTCOMES OF WOMEN WITH INFLAMMATORY BOWEL DISEASE

Running head: Inflammatory Bowel Disease and Pregnancy

ABSTRACT: Background: Inflammatory bowel diseases (IBD) generally affect women of childbearing age. In this study we investigated the effects of IBD on pregnancy, pregnancy outcomes and on newborns by comparing with a healthy control group.

Methods: Data on the productive history were collected both in the question-and-answer format, and also from hospital records. The control group was made up of healthy volunteers of the same age group, who were living in the same region and who had a similar sociocultural structure. Control group data were also collected by asking questions on reproductive history in the question-and-answer format, and also from the obstetrical medical records.

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Results: The study was conducted on a total of 545 women, 219 of whom had ulcerative colitis (UC), 85 Crohn's disease (CD) and 241 healthy controls. The mean gestational age, birth weight and birth height of subjects in UC group was found to be significantly lower compared to the control group ($p < 0.05$). Preterm birth was more common in UC and CD group, compared to the control group ($p < 0.01$). No statistically significant difference was present between the groups with regard to abortion, and congenital anomalies. Cesarean section rate was higher in both UC and CD group than the control group ($p < 0.05$).

Conclusion: Gestation age, birth weight and height were low, whereas the preterm birth rate was higher in UC group. The rate of cesarean section was higher in both UC and CD groups, in those, who were diagnosed with disease during pregnancy, and also in women who became pregnant after disease diagnosis.

Key Words: Ulcerative colitis, Crohn's disease, pregnancy outcome

INTRODUCTION

Inflammatory bowel diseases (IBD) most commonly affect women of childbearing age (1). The effect of the disease on women's fertility and pregnancies is a subject of controversy (2). Many studies have been conducted, which investigate the effects of the chronic IBDs known as, ulcerative colitis (UC) and Crohn's disease (CD) on pregnant women (2-7). No negative effect of IBD on pregnancies has been reported in some of the studies, whereas other studies demonstrated an increase in the premature rate of birth and low birth weight in the newborns of women with IBD (2-12). Current literature indicates that patients with active or quiescent UC, except patients who have had an ileal pouch-anal anastomosis (IPAA), have normal fertility. Patients with active CD have increased infertility, perhaps due to the inflammatory process creating adhesions in the fallopian tubes or ovaries. Meanwhile CD patients with inactive disease have a normal fertility rate (13).

An increase in the rate of preterm birth in patients with IBD has been reported both in patients with pre-IBD and in post-IBD pregnancies (14). The inclusion of tumor necrosis factor-receptor 1 and tumor necrosis factor-receptor 2 by the genes, which may possibly be the cause of preterm birth, and also as a result of the role played, by these genes in the etiology of IBD, it has been considered as a possible cause for the relationship between IBD and preterm birth (15).

Our aim in this study was to investigate the effect of IBD (UC, CD) on pregnancy, in pregnant women with the disease, and the rate of preterm birth, weight of the newborn, birth height, birth weight and the rate of congenital anomalies, through comparison with a healthy control group.

MATERIALS AND METHODS

Study Subjects

Women with UC and CD, who were followed up at our clinic, were enrolled in the study. These patients were diagnosed with IBD according to international diagnostic criteria (16). Detailed reproductive histories of every patient were obtained by question-and-answer formatted questionnaire; and data from hospital record files were obtained.

Data from the obstetrician's files were obtained and the reproductive histories of the control group that was made up of women from the same region, women with similar socio-cultural characteristics, and of the same age group, were obtained through the collection of data by a questionnaire in the question-and-answer format. A total of 219 patients with UC, 85 with CD and 241 control subjects were assessed for analysis. The women's number of live births, gestational age (in weeks), and birth weight, and birth height, mode of delivery, stillbirth, and congenital anomalies were determined. Cigarette smoking habits during pregnancy were recorded. Pregnancies before and after the diagnosis of the disease in UC and CD groups, and newborn results were compared.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Definitive statistical methods (mean, standard deviation) were used for the evaluation of the study data, whereas the One-way Anova test was used to evaluate quantitative data, and the Tukey HSD test was used for the identification of group with a difference. The Kruskal Wallis test was used for the comparison between two groups of parameters with abnormal distribution, whereas the Mann Whitney U test was used to determine groups, which demonstrated differences. Comparison between groups for parameters, which demonstrated normal distribution, was performed using the Student t test. On the other hand comparison qualitative data was performed using the Chi-Square test. Results were in the 95% range and a $p < 0.05$ was evaluated as significant.

RESULTS

A total of 545 women within the age range of 28 and 78 were enrolled in the study. The mean age of the subjects was 40.70 ± 10.31 . The subjects were divided into three groups. The UC group was made up of 219 patients, 85 in the CD group, whereas the healthy control group was made up of 241 patents. No statistically si-

gnificant difference was found between the groups with regards to mean age at the time of delivery, in years ($p>0.05$). Pregnancies were ended up with live births in 187 patients in the UC group, 75 patients in the CD group, and in 220 mothers in the control group.

The mean gestational age of the control group was found to be statistically significantly higher compared to the UC group (Table 1). Statistically significant difference was found between the groups with regards to the birth weight of the infants ($p=0.014$). The mean birth weight of subjects in the UC group was found to be statistically significantly lower when compared to those in the CD group ($p=0.010$) (Table 1). The mean birth height of subjects in the UC group was found to be highly statistically significantly lower than those of the subjects in the CD group ($p=0.001$) and the control group ($p=0.001$). No statistically significant difference was present between the mean birth height of the infants in the control group and the CD group ($p=0.995$) (Table 1).

The incidence of gestation age of the patients in the UC group (50.2%) and CD (49.4%) group at or below the 37th week of gestation was statistically significantly higher compared to the control group (19.9%) ($p=0.001$). The incidence of birth weight between 2500 g and below, distribution rates of the mode of delivery, the incidences of abortions according to the groups, the rates of cigarette smoking and the incidences of congenital anomalies according to the groups were not different between the groups (Table 2).

The rate of diagnosis before pregnancy in the UC group was 79% (173 pregnancies), and 87.1% (74 pregnancies) in the CD group; there was no statistically significant difference between the two groups ($p>0.05$) (Table 3). Before diagnosis in the UC group, evaluation of those diagnosed during pregnancy and of newborns after disease diagnosis demonstrated that there was no statistically significant difference between the mean of gestation age, birth weight and birth height ($p>0.05$). However, there was statistically significantly higher difference when compared with the mode of delivery ($p=0.001$). The rates of cesarean section (C/S) in subjects who were diagnosed with the disease during pregnancy and in post-disease deliveries were 62.5 and 20% respectively (Table 4).

There was no subject, who was diagnosed with the disease during pregnancy, in the CD group. Comparison of those, who were diagnosed with disease before pregnancy and those diagnosed after pregnancy demonstrated that there was no statistically significant difference between the means of gestational age, birth weight, and birth height ($p>0.05$); however, a significant relationship was observed with the mode of delivery ($p=0.033$). The rate of C/S observed with delivery after disease diagnosis was (37.5%), whereas the rate of C/S observed before disease diagnosis was (10.4%) ($p=0.033$) (Table 5).

DISCUSSION

There is an increased risk of complications such as preterm birth and premature membrane rupture, associated with malnutrition, inflammation and drug use, in women with IBD (17). Inflammatory bowel disease often affects in the fertile age of these women (1). Many studies have been conducted, which investigate the effect of IBD on fertility, pregnancy and especially pregnancy outcomes (9,18,19). Fertility is known to be decreased significantly in IBD women with active CD, and post-pouch surgery (9,18-24). On the other hand, the effect of quiescent IBD of pregnancy outcomes and progress is minimal (18,25-27). Reports from previous studies conducted on women with IBD show that there is an increase in the risk of low birth weight (LBW) and preterm birth, and that the risk of cesarean section was high (3,4,9). In our study, the incidence of premature births (<37 weeks gestation) were significantly higher compared to the control group. Comparison of the UC and CD groups did not show any significant difference with regards to premature birth. In the literature, evaluation study conducted by Cornish et al.(8) between 1980 and 2006 on pregnancy and IBD, the incidence of premature births was reported in eight studies (2-6,11,28-30); they reported that the incidence of premature infants in patients with IBD, in the UC and CD groups were increased more than those of in the control group (2-6,11,28-30). Comparison of premature infants in the UC and CD groups in this study also demonstrated that there was no statistically significant difference between UC and CD groups with regards to premature infants (2,5,11,29,30).

In a study conducted by Baird et al., 177 patients with CD and 84 with UC were compared with the control group and preterm birth risk was increased in women with IBD (2). Various biologic factors play very important role in preterm births. They may include infectious, nutritional, immunological, and neurological factors. Some unidentified infectious agents may directly or indirectly predispose to preterm births in IBD. Nutritional and immunological factors, which have influences at the beginning of delivery in IBD, are factors which increase intestinal permeability (31). The formation of prostaglandins was higher in women with IBD, compared to the control group; this has an influence on premature initiation of the delivery, and plays a role in the preterm birth (32). Neurologic factors also have an influence in preterm birth. It is known that neurologic control of intestinal smooth muscle is impaired; the same mechanism has been shown to be effective on uterine smooth muscle (33). Women with IBD are advised to avoid the risk of prematurity, and especially undergo close monitorization during the last trimester (8), taking into consideration the effect of premature births on the physical, mental and social health of the infant (34-36).

Previous studies have demonstrated that LBW of infants born to mothers with IBD was higher when compared to the control group; however, the incidence was reported to be higher in infants born to mothers with CD (4,9,11,28). In a study con-

ducted by Kornfeld et al., the risk of LBW in offspring of mothers with inflammatory bowel disease was markedly increased. This condition was reported to be due to the nutritional status of the mother and child, and that malnutrition affected growth and development of the fetus (4). Norgard et al demonstrated that the risk of LBW and preterm birth of infants born to mother with IBD was not increased; however, the risk of preterm birth during pregnancy in those, who were hospitalized for the first time, was reported to be increased by three-folds (3). In a study conducted by Fonager et al, birth weights of newborns of CD women was reported to be low, whereas the risk of LBW and preterm birth was reported to be increased. They reported that this condition may be due to disease activity or to a possible malnutrition and essential nutrition loss during the critical phase of fetal growth (9). In this study, a statistically significant difference was found between the groups with regard to the birth weight. It was lower in UC group than that of in the CD group. No statistically significant difference was present between the mean birth weight of subjects in the control group, and those in the UC and CD groups. Low birth weights (LBW) of 2500 g and below did not demonstrate any statistically significant difference between the groups. Comparison of subjects, who were diagnosed with the disease before, during and after pregnancy in the UC group demonstrated that the birth weights of those, who were diagnosed with the disease during pregnancy were low; however, no statistically significant difference was observed. Cigarette smoking is one of the factors, which has an effect on the birth weight; cigarette smoking is associated with reduced growth of the fetus (37). In our study, no statistically significant difference was present between the groups with regard to this condition.

In our study we demonstrated that there was a statistically significant difference between groups in terms of heights of the newborns. The mean heights of newborns were significantly lower in the UC group compared to the CD group and the control group. No statistically significant difference was obtained between the CD and control groups in terms of heights of newborns.

In the Danish Cohort Study, Norgard et al reported that there was no increased risk of birth weight and intrauterine growth retardation in newborns before and after the disease diagnosis; however, there was an increased risk of preterm birth in patients diagnosed with the disease during pregnancy and gave birth within the 6 months from the initial hospitalization. In addition, they reported an increased risk of perinatal mortality and stillbirth in offspring of the patients with UC (3).

In comparative studies, Moser et al. (38) demonstrated that newborns of patients with CD had lower birth weights and the risk increased in patients with ileal CD, particularly and previous intestinal infection or those who continued to smoke during pregnancy. Furthermore, Molares et al. (39) concluded that there might be risk factors related to abnormal pregnancy outcome in patients with active CD with any reactivity during their conception or pregnancy.

In this study, we did not observe any statistically significant difference between the UC, CD and control groups with regards to the mode of delivery. However, we demonstrated a statistically significant difference in the mode of delivery in the UC group between pregnant women who were diagnosed with the disease before pregnancy, and those who were diagnosed with the disease during and after pregnancy. We demonstrated that the incidence of C/S was highest (62.5%) in subjects who were diagnosed with the disease during pregnancy. The decision of performing cesarean section in pregnant women with IBD is still a matter of debate (8,40). Some studies have demonstrated that the rates of incontinence and sphincter tear were lower in patients who underwent caesarean section, compared to those who preferred vaginal delivery, suggesting that caesarean section was the best delivery method in women with IBD (41,42). In another study, it was demonstrated that the anal sphincter tear which occurred during vaginal delivery did not affect continence, and reported that vaginal delivery reduced surgical procedure and adhesion formation in the high risk patient group (43). The indication for a C/S should be made by an obstetrician, and the opinion of the gastroenterologist should be obtained (44).

Evaluation of the incidence of C/S in our study demonstrated that the rate of C/S in pregnant women with CD was high in pregnancies after disease diagnosis ($p < 0.05$). There are also studies which have indicated that the incidence of C/S was higher in the CD group compared to the control group (5,29,30,38). Cesarean section should be recommended in CD patients with active perianal disease (45). In IBD patients with an ileoanal pouch studies have indicated that vaginal delivery after ileal pouch anal anastomosis (IPAA) is safe and not associated with long-term changes in pouch function (23,46,47). However, a study suggests that vaginal delivery increases the risk of sphincter muscle injury, which could have a long-term effect on pouch function (43). The choice for the mode of delivery after IPAA is still debatable (40).

The rate of spontaneous abortions was found to be 15.1% in the UC group, 10% in the CH group, and 8.3% in the healthy control group. As a result, there was no statistical difference in the rates of abortions. Previous studies have reported a higher rate of spontaneous abortions in patients with active CD (18,48).

In comparative studies of IBD and control groups, no statistically significant difference was defined in the rates of stillbirth between the groups (4,6,28,30). On the other hand, no difference was reported in the incidence of stillbirth in comparative studies involving the CD and control groups CD (2,5,9). Norgard et al. demonstrated in their study that there was an increase in the risk of stillbirths and perinatal mortality in women with UC (3). This risk was reported in previous studies involving the control group (4-7). Porter and Stirrat, and Schade et al. also reported that there was no increase in the risk of perinatal mortality in the newborns of women with UC (5,7). Morales et al. reported in their study that there was a significant increase in fetal loss during conception, in patients with active CD (39).

In our study, there was no statistically significant difference between the groups with regard to incidence of congenital anomalies. Some studies could not demonstrate any difference between the IBD and control group with regard to congenital anomalies (6,11,28,30); however, some studies reported that the incidence of congenital anomalies in the UC group was higher when compared with those of in the control group (11,30). On the other hand, there was no statistically significant difference between the CD group and the control group with regard to the incidence of congenital anomalies (11,30,38).

In an extensive comparative study conducted by Mahadevan et al. in Northern California, the conception, pregnancy and newborn outcomes of 461 pregnant women with IBD and 463 pregnant women without IBD were compared and investigated. They reported that the incidence of cesarean section in pregnant women with IBD was high, whereas the incidence of therapeutic abortions and congenital anomalies was similar in both groups. In this study, it was also reported that the rate of adverse conception, adverse pregnancy, and pregnancy complication was more in women without IBD, and that there was no statistically significant difference between the groups with regard to adverse newborn outcome. They concluded that there was an increased risk in pregnant women with IBD, and this was found to be independent of disease activity and the medication used (49).

Patients with IBD most commonly become pregnant before the disease diagnosis; the incidence of pregnancy in patients who become pregnant after the disease diagnosis was reported as 25% (9,18,19). In this study, the mean pregnancy age of the subjects was 25.25 ± 4.63 in the UC group, 25.72 ± 4.73 in the CD group and 25.75 ± 5.20 in the healthy control group. The mean age of diagnosis in the UC group was 32.39 ± 9.34 , and in the CD group the mean age of diagnosis was 32.83 ± 8.67 . The pregnancy rate after disease diagnosis was determined as 16.9% for UC, and 12.9% for CD. Most Turkish women with IBD became pregnant before disease diagnosis, and very few pregnancies were planned since the number of children after disease diagnosis was found to be sufficient.

In conclusion, the incidence risk of premature infants in women with IBD was more than that of in the general population; most women who became pregnant during the disease diagnosis preferred C/S, no increase was also observed in those with congenital anomalies, compared with the general population. The nutritional status of patients with IBD should closely be monitored, and it is important that they should be followed-up by both the obstetrician and gastroenterologist, as high risk pregnancies.

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TABLES

Table 1: Results of the study population and outcome of pregnancy

	Ulcerative colitis Mean \pm SD	Crohn's disease Mean \pm SD	Control Mean \pm SD	p
Age at disease diagnosis	32.39 \pm 9.34	32.83 \pm 8.67		0.825
Mean age at the time of delivery (years)	25.25 \pm 4.63	25.72 \pm 4.73	25.75 \pm 5.20	0.516
Gestation age (wks)	33.93 \pm 9.97	35.14 \pm 8.34	36.33 \pm 8.48	0.019
Birth weight (g)	3144.12 \pm 502.22	3356.67 \pm 526.42	3211.52 \pm 555.72	0.014
Height (cm)	49.46 \pm 2.23	50.54 \pm 1.74	50.57 \pm 2.39	0.001

Table 2: Detailed distribution of data from pregnancy results

		Ulcerative colitis n (%)	Crohn's disease n (%)	Control n (%)	p
Gestational age (wks)	≤ 37	110 (50.2%)	42 (49.4%)	48 (19.9%)	0.001
	> 37	109 (49.8%)	43 (50.6%)	193 (80.1%)	
Birth weight (g)	≤ 2500	14 (7.5%)	5 (6.7%)	20 (9.1%)	0.744
	> 2500	173 (92.5%)	70 (93.3%)	200 (90.9%)	
Mode of delivery	Normal	162 (87.1%)	65 (86.7%)	190 (86.0%)	0.946
	C/S	24 (12.9%)	10 (13.3%)	31 (14.0%)	
Abortion	Present	33 (15.1%)	10 (11.8%)	20 (8.3%)	0.076
	Absent	186 (84.9%)	75 (88.2%)	221 (91.7%)	
Cigarette smoking	Present	8 (10.0%)	3 (10.3%)	12 (10.7%)	0.987
	Absent	72 (90.0%)	26 (88.7%)	100 (89.3%)	
Congenital Anomaly	Present	6 (3.2%)	4 (5.4%)	9 (5.4%)	0.560
	Absent	180 (96.8%)	70 (94.6%)	158 (94.6%)	

Table 3: Disease diagnosis in the ulcerative colitis and Crohn's disease groups according to pregnancy

		Ulcerative colitis n (%)	Crohn's disease n (%)	p
*Disease status	Before	173 (79.0%)	74 (87.1%)	0,101
	After	37 (16.9%)	11 (12.9%)	
	During pregnancy	9 (4.1%)	0 (0.0%)	

Table 4: Evaluation of disease condition in the Ulcerative colitis group

Ulcerative colitis	Disease Condition			p
	Before pregnancy Mean \pm SD	After pregnancy Mean \pm SD	During pregnancy Mean \pm SD	
Gestational age	34.23 \pm 10.02	32.30 \pm 10.60	34.89 \pm 5.75	0.542
Birth weight (gm)	3140.88 \pm 517.35	3206.45 \pm 444.36	2962.50 \pm 424.05	0.468
Height (cm)	49.56 \pm 2.13	49.16 \pm 2.79	48.87 \pm 1.64	0.499
Delivery	Normal n (%)	24 (80.0%)	3 (37.5%)	0.001
	C/S (n (%))	6 (20.0%)	5 (62.5%)	

C/S: Cesarean section

Table 5: Evaluation of disease condition in the Crohn's disease group

Crohn's disease	Disease condition		p	
	Before Mean \pm SD	After Mean \pm SD		
+ Gestational age	35.85 \pm 7.47	30.36 \pm 12.19	0.174	
+ Birth weight (gm)	3353.73 \pm 517.15	3381.25 \pm 638.04	0.890	
+ Height (cm)	50.46 \pm 1.73	51.25 \pm 1.75	0.229	
Delivery	Normal n(%)	60 (89.6%)	5 (62.5%)	0.033*
	C/S (n(%))	7 (10.4%)	3 (37.5%)	

C/S: Cesarean section