Conception and pregnancy outcome in women with inflammatory bowel disease: A multicentre study from Japan

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Abstract

Background: Neither conceptions and pregnancy outcomes nor the safety of medications for childbearing inflammatory bowel disease (IBD) patients has been investigated in Asia. The aim of this study is to analyse conception and pregnancy outcomes of Japanese female IBD patients.
Methods: We conducted a retrospective cohort study of pregnant IBD patients at 6 institutions. The incidences of abortion, Caesarean delivery, low birth weight (LBW) (<2500 g), and congenital malformation were analysed in these patients. Risk factors associated with adverse outcomes in IBD patients were also assessed.
Results: A total of 325 patients experienced 534 conceptions. Among these, 303 conceptions (57%) were observed during/after disease onset. Although conceptions and pregnancy outcomes after disease onset were comparable to the observed levels prior to disease onset in UC patients, the incidences of spontaneous abortion (OR 5.3; 95%CI 1.1–25.0) and Caesarean delivery (OR 4.8; 95%CI 1.5–15.0) were significantly higher in Crohn's disease (CD) patients whose conceptions occurred after disease onset compared to CD patients whose conceptions occurred before

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disease onset. The incidences of spontaneous abortion, LBW, and Caesarean delivery were higher in CD patients who had a history of surgery for perianal lesions than in those who did not have perianal lesions or who had ulcerative colitis (UC). In the IBD patients studied after disease onset, independent risk factors for spontaneous abortions included a history of previous treatment for sterility (OR 2.9; 95%CI 1.2–7.0). Independent risk factors for Caesarean operation (OR 4.1, 95% CI: 1.7–10.1) and LBW (OR 3.5, 95% CI: 1.3–9.1) included a history of bowel resection for the treatment of IBD. Congenital malformation was not associated with the factors of type of disease, smoking, and previous surgery.

Conclusion: In Japanese UC patients, conception and pregnancy outcomes after disease onset were comparable to the outcomes observed prior to disease onset, whereas CD appeared to be associated with adverse outcomes. Caesarean operation and LBW were more frequently observed in CD patients who had a history of surgery for perianal lesions and bowel resection.

1. Introduction

Onset of Crohn's disease (CD) and ulcerative colitis (UC) typically occurs during young adulthood, affecting individuals during their reproductive years. Having children is one of the most important events in an individual's life. IBD patients and their families naturally want to know whether disease activity and drug exposures will affect fertility, pregnancy outcomes and the developing child.

In female UC patients, fertility rates remain normal, but women with UC who have undergone ileal-pouch anal anastomosis experience reduced fertility.[1] For CD patients in remission, the infertility rates in female patients are almost equal to that in healthy controls,[2] whereas fertility may be decreased in patients with active CD.[3] The frequencies of preterm birth, low birth weight (LBW) and small for gestational age births are increased in women with IBD.[4–7] Recent meta-analysis has indicated that patients with IBD increased adverse outcomes compared to control groups.[8] The incidences of prematurity, Caesarean section and congenital abnormalities in IBD patients were 1.5–2.4 times higher than the incidences observed in controls. However, the meta-analysis did not account for disease activity and medical treatment.

It is important for physicians and IBD patients to know whether disease activity predicts adverse outcomes of conception and pregnancy. Previous studies have suggested that disease activity during conception or pregnancy is associated with foetal loss, low birth weight and preterm birth.[9–12] A more recent ECCO Consensus stated that it is advisable to strive for clinical remission of CD before conception.[13]

A recent study indicated that a non-Caucasian ethnicity is a predictor of an adverse pregnant outcome in women with IBD.[14] However, conceptions, pregnancy outcomes, and the safety of medications for childbearing IBD patients have not been well investigated in Asian countries. Reconfirmation of previous reports from western countries is important, because genetic backgrounds and environmental factors influencing IBD differ between Asian and western countries. Furthermore, there have been few recent studies comparing pregnant outcomes prior to diagnosis with those after diagnosis. The aim of this study was to analyse conception and pregnancy outcomes of Japanese female IBD patients. The patients' characteristics and incidences of adverse outcomes were compared prior to and after the onset of disease. Furthermore, risk factors associated with adverse outcomes were also assessed in the present study.

2. Methods

2.1. Study design and patient populations

This was a retrospective cohort study of pregnant patients with IBD at six large IBD centres in Japan (Keio University Hospital, Yokohama City University General Hospital, Social Insurance Centre General Hospital, Tokyo Medical and Dental University Hospital, Miyazaki University Hospital and Fukuoka University Chikushi Hospital). A total of 589 patients were asked to enrol in this study, and 11 patients refused to participate. Indeterminate colitis patients (n=6) were excluded from this study. Thus, we surveyed 572 female IBD patients (UC 325, CD247) from the six institutions and selected patients who experienced at least one conception (325 patients, 534 conceptions). The number of UC and CD patients who experienced conception was 245 and 80, respectively. The study population consisted of women who experienced conception between 1989 and 2008. The ages at the time of conception ranged from 17 to 46 years old.

2.2. Data acquisition

Subjects were given a questionnaire to answer. From the questionnaire, the following information regarding conception and pregnancy outcomes in IBD patients was collected: type of disease (UC or CD), marital status, number of children, smoking habits, age at each conception, history of surgery for IBD (bowel resections), history of surgery for perianal lesions, such as perianal fistula, abscesses and fissuring ulcerations in CD patients, history of gynaecological disease, previous medical problems, and history of therapy for infertility. Information was also requested regarding the outcome of the conceptions (live birth, spontaneous abortion or elective abortion), mode of delivery, birth weight and presence of congenital abnormalities. Gynaecological diseases included ovarian cysts, uterine fibroids and endometriosis. Ovarian cysts are detected and diagnosed by gynaecologist or ultrasonography. No patients experienced ovarian cancer or uterine cancer in this study. When women become pregnant in Japan, they receive the "*notebook for mother and children*" from the regional health centres. Thus, information regarding conception and the outcome of pregnancy could be obtained from these notebooks for this study. Information regarding pregnancy courses/outcomes and birth weight were usually filled out by physicians or nurses in the notebooks. To identify the course and outcome of their pregnancies, patients referred to the notebooks. Physicians in all institutions reviewed the patients' medical records to confirm the diagnosis of disease.

To investigate the effects of immunomodulators on the pregnancy outcome, we also surveyed whether patients received immunomodulators (Azathioprine (AZA), 6-mercaptopurine (6-MP) and infliximab) at the time of conception and/or during their pregnancies. Because health insurance does not cover the expenses associated with adalimumab and certolizumab in Japan, these treatments were not studied. Six cases were treated with 6-MP/AZA, and three cases received infliximab treatment at conception. We reviewed medical records for these cases and analysed the age at conception, continuation or discontinuation of

the immunomodulators when the patients became aware of the conception, conception outcomes, mode of deliveries and congenital malformation.

2.3. Data analysis and statistical methods

The incidences of adverse outcomes were analysed in this study. These outcomes included spontaneous abortion, therapeutic abortion, Caesarean delivery, preterm birth (<35 wk), low birth weight (<2500 g) and congenital malformation. Incidences before disease onset were compared within each disease group (UC and CD) with incidences that occurred after disease onset. Incidences between groups were also compared. We evaluated risk factors for each adverse outcome such as type of IBD (CD or UC), age at conception, history of gynaecological disease, history of treatment for sterility and history of surgery for IBD. Disease activities, medication at conception/each trimester could not be precisely obtained from the questionnaire and medical records. Thus, we excluded medication and disease activity as risk factors for adverse outcomes of pregnancy in this study.

The protocols in the present study were approved by the review board of each institution. For statistical analyses, t-tests, χ^2 tests, univariable and multivariable analyses were used to compare groups using SPSS version 18 (SPSS Corp., Tokyo, Japan).

3. Results

3.1. Comparison of conception and pregnancy outcomes before and after disease onset

In the present study, 325 patients (UC 245 and CD 80) experienced conception at least once, and 534 conceptions were observed (Table 1). The prevalence of previous surgeries was significantly higher in CD patients than in UC patients (56.2% vs. 6.5%, respectively), whereas the incidence of previous gynaecological disease was comparable between both groups. Among these conceptions, 303 conceptions (57%) were observed during/after disease onset. The rate of live births for UC and CD patients after disease onset was 82.9% and 81.1%, respectively (Table 2).
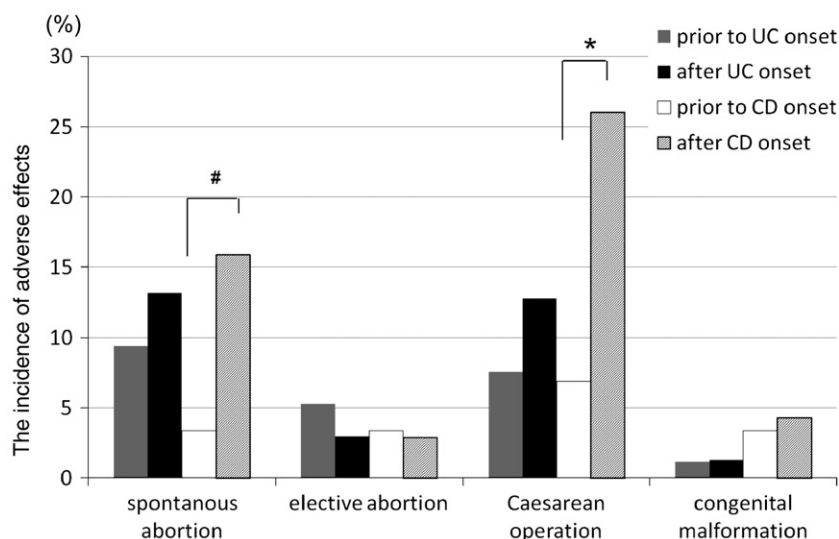
Table 1 Conception and pregnancy outcomes in patients with lBD.

	UC	CD
No. of patients	245	80
Duration of disease (year)	10.6+/−7.9	12.8+/−8.7
History of previous surgery (%)	16 (6.5%)	45 (56.2%)
History of previous gynaecological disease (%)	46 (18.8%)	19 (23.7%)
Average height at survey	158.2+/−5.3 (141−177)	157.1+/−6.1 (140−176)
Average weight at survey	50.7+/−7.3 (37−88)	49.6+/−9.3 (30−105)
No. of conceptions	406	127
Live births (%)	337 (83.0%)	110 (86.6%)
Spontaneous abortions (%)	47 (11.6%)	13 (10.2%)
Elective abortions (%)	16 (3.9%)	4 (3.1%)
Maternal deaths (%)	2 (0.5%)	0 (0%)
Low birth weight (%)	29 (7.1%)	19 (15.0%)
Caesarean operations (%)	43 (10.6%)	22 (17.3%)

Table 2 Conception and pregnancy outcome in patients during/after disease development.

	UC	CD	p value
No. of conceptions	234	69	
Live birth	194 (82.9%)	56 (81.2%)	0.828
Spontaneous abortion	31 (13.2%)	11 (15.9%)	
Therapeutic abortion	7 (3.0%)	2 (2.9%)	
During pregnancy at the survey	2 (0.9%)	0	
Caesarean operation	30 (12.8%)	18 (26.0%)	0.009
Mean birth weight (g)	3002+/−462 (1200−5000)	2843+/−747 (497−4270)	0.07
Low birth weight	15 (6.4%)	13 (18.8%)	0.004
Preterm birth (<35 wk)	5 (2.1%)	7 (10.1%)	0.048
Congenital malformation	3 (1.3%)	3 (4.3%)	0.13
Mean age at conception	30.5+/−4.6 (19−42)	28.7+/−4.4 (19−41)	0.006
Previous/current smoking at conceptions			
Yes	41 (17.1%)	12 (17.3%)	
No	187 (77.9%)	53 (76.8%)	0.92
Unknown	6	4	
History of previous treatment for infertility			
Yes	21 (9.0%)	14 (20.2%)	0.04
No	156 (66.7%)	48 (69.6%)	
Unknown	57	7	
History of gynaecological disease			
Yes	31 (13.2%)	14 (20.2%)	0.42
No	148 (63.2%)	50 (72.4%)	
Unknown	55	5	
Previous surgery for IBD	16 (6.8%)	44 (63.8%)	<0.001
Any medications for IBD during pregnancy			
Yes	69 (29.4%)	14 (20.3%)	0.14
No	144 (61.5%)	48 (69.6%)	
Unknown	21	7	

First, conception and pregnancy outcomes before and after disease onset were investigated and compared. As we expected, the mean age at conception in patients whose conceptions occurred after disease onset was significantly higher (UC 30.5+/−4.6 years and CD 28.7+/−4.4 years) than the ages of patients whose conceptions occurred before disease onset (UC 27.5+/−3.9 years and CD 27.6+/−3.9 years) in both UC and CD patients. In UC patients, the incidences of spontaneous abortion and elective abortion after the onset of disease were comparable to those with incidences before onset of disease (spontaneous abortion: OR 1.5, 95%CI 0.8−2.8, elective abortion: OR 0.6, 95%CI 0.2−1.5, respectively), as shown in Fig. 1. The incidence of Caesarean operation after UC onset (30/234, 13.2%) tended to be higher than the incidence prior to disease onset (13/170, 7.6%); however, there was no significant difference (Fig. 1: p=0.10, OR 1.8, 95%CI 0.9−3.5). In CD patients, the incidences of spontaneous abortion (p=0.02, OR 5.3, 95%CI 1.1−25.0) and Caesarean delivery (p=0.004, OR 4.8; 95%CI 1.5−15.0) were significantly higher in patients whose conceptions occurred after disease onset than before disease onset (Fig. 1). The incidence of elective abortions in post-CD patients was comparable to that in pre-CD patients. Our result also indicated that the rate of spontaneous abortions in CD patients after disease onset (15.9%) was not higher than the rates in UC patients (13.2%, see Fig. 1). Congenital malformations after disease onset were not more frequent in either

Figure 1   Conception and pregnancy outcomes in UC/CD patients. The incidences of adverse effects after disease onset were compared to incidences prior to disease onset. χ^2 tests were for statistical analysis used. #: $p \leq 0.05$, *: $p \leq 0.01$.

UC (OR 1.1, 95%CI 0.2–6.6) or CD patients (OR 1.2, 95%CI 0.2–7.9), as compared to congenital malformations before disease onset.

3.2. Comparison of conception and pregnancy outcome in UC patients and CD patients after disease onset

Next, we focused on conception and pregnancy outcomes for 303 conceptions in IBD patients whose conceptions occurred after disease onset. The incidence of spontaneous/elective abortions in UC patients was comparable to the incidences in CD patients (Table 2). With respect to fertility, 20.2% of CD patients (14/69) and 9.0% of UC patients (21/234) had a history of treatment for

infertility. In CD patients who had a history of bowel resections, 29% (13/45) experienced treatment for infertility. Although the mean age at conception in UC patients (30.5 years old) was higher (p=0.006) than in CD patients (28.6 years old), the incidence of Caesarean delivery in CD patients (18/69, 26.1%) was higher than in UC patients (30/234, 12.8%) (OR 2.4, 95%CI 1.2–4.8). The incidences of LBW and preterm birth in CD patients (18.8% and 10.1%, respectively) were also significantly higher than the incidences in UC patients (6.4% and 2.1%, respectively).

Next, we assessed whether perianal lesions affected conception and pregnancy outcomes in CD patients. The incidences of spontaneous abortion and LBW were higher in CD patients who had history of surgery for perianal lesions (abortion: 28%, LBW: 40%) than those who did not have history of surgery for perianal lesions
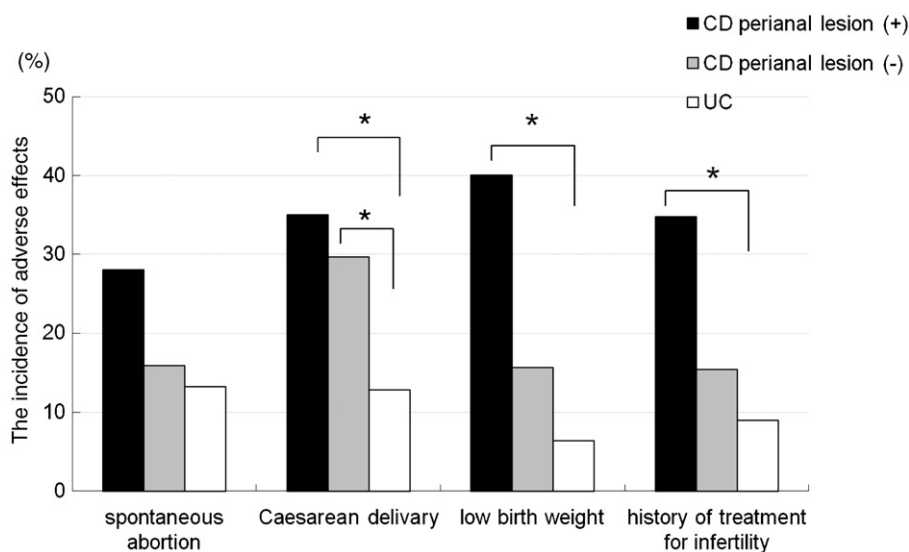
Figure 2   Conception, pregnancy outcomes and infertility in CD patients with (black bar) or without (grey bar) perianal lesions and UC patients (white bar). Patients with perianal lesions were defined by a history of surgery for perianal lesions before conceptions. The incidences of abortions, Caesarean operation, low body weight and history of treatments for infertility were compared between the 3 groups. χ^2 tests were used for statistical analysis. *: $p \leq 0.01$.

Table 3   Risk factors for adverse outcomes in IBD patients (univariable analysis).

	Spontaneous abortion		Caesarean operation		Low birth weight	
	p value	OR(95%CI)	p value	OR (95%CI)	p value	OR (95%CI)
Mother's height <150 cm	0.17	2.0 (0.73–5.60)	0.21	2.1 (0.63–7.28)	0.28	2.1 (0.53–8.36)
Mother's age at conception (>35 years old)	0.24	1.5 (0.75–3.10)	<0.001	3.9 (1.90–7.94)	0.54	1.4 (0.51–3.62)
Smoking	0.24	1.6 (0.74–3.20)	0.59	0.8 (0.32–1.90)	0.41	1.5 (0.58–3.78)
History of previous treatment for infertility	0.001	3.4 (1.56–7.57)	0.11	2.3 (0.81–6.41)	0.5	1.5 (0.46–4.84)
History of gynaecological disease	0.09	1.9 (0.90–4.15)	0.06	2.3 (0.95–5.56)	0.71	1.2 (0.43–3.54)
Previous surgery for IBD	0.32	1.4 (0.71–2.90)	0.005	2.7 (1.32–5.49)	0.002	3.5 (1.52–8.15)

(abortion: 15.9%, LBW: 15.6%), although these were not significantly different (p=0.23, 0.051, respectively). Notably, the incidences of abortion (p=0.053, OR 2.6 (95% CI 0.98–6.59)), Caesarean delivery (p=0.007, OR 3.7 (95% CI 1.35–9.91)), and LBW (p<0.001, OR 9.7 (95%CI 3.45–27.4)) were higher in CD patients with history of surgery for perianal lesions, when the incidences were compared between CD patients with perianal lesions and UC patients (Fig. 2). The incidence of abortion, Caesarean delivery and LBW was also higher in CD patients without a history of surgery for perianal lesions compared to UC patients (Fig. 2). However, these differences were not significantly different between the groups, except for the incidence of Caesarean delivery (29.7% in CD without perianal lesion, 12.8% in UC, p=0.008). In other words, the significance of the incidence of adverse outcomes was found between CD patients with perianal lesions and UC patients. Furthermore, 8 of 23 patients (35%) with a history of surgery for perianal lesions underwent treatments for infertility, while 15% of CD patients without perianal lesions and 9% of UC patients experienced infertility treatments (Fig. 2).

Six congenital malformations were observed in infants delivered after disease onset. Ventricular septal defect was found in two cases, sudden death due to heart failure occurred in one case, Hirschsprung's disease was present in one case, diencephalo-hypophyseal dysfunction occurred in one case and finger deformity (shortened fingers) was present in one case. Three cases were found in each group of patients, and the incidences were not significantly different in both groups (p=0.14, 95% CI 0.68–17.6).

3.3. The effect of immunomodulators and biologics on the pregnancy outcome

Pregnancy outcomes in patients who used immunomodulators at the time of conception were also analysed. Three patients were being treated with infliximab with 6-MP/AZA after becoming aware of each conception. All three patients continued infliximab therapies. Among these three patients, two patients discontinued AZA during

pregnancy, and one patient continued combination therapy with infliximab and 6-MP. None of the three patients delivered infants with any congenital malformation, although LBW (1945 g) was observed in one infant. Another three patients were treated with either 6-MP (n−1) or AZA (n=2) alone. After pregnancy was diagnosed, two patients withdrew from AZA treatment, and one patient continued 6-MP. These patients did not experience any adverse outcomes.

3.4. Risk factors for adverse conception and pregnancy outcomes in female IBD patients

Patients who had a history of previous treatment for infertility were more likely to have spontaneous abortions compared to patients who did not (Table 3, OR 3.4, 95% CI: 1.6–7.6). A history of bowel resection and the mother's age were similar between the two groups. A history of bowel resection for treatment of IBD and the mother's age at conception (>35 years old) were risk factors for having a Caesarean delivery (Table 3). Patients who had a history of previous gynaecological diseases were more likely to have a Caesarean delivery compared to patients without gynaecological diseases; however, these differences were not statistically significant (p=0.06, OR 2.3, 95% CI 0.95–5.56). A history of bowel resection for treatment of IBD (OR 3.5, 95% CI 1.52–8.15) was a risk factor for LBW (Table 3). No factor, such as age at conception (mean age at conception; adverse outcome (+) 29.8 years old, adverse outcome (−): 28.7 years old, respectively), disease type (CD vs. UC; OR 3.5 95% CI 0.69–17.60), history of bowel resection (OR 4.1, 95% CI 0.83–21.2) and history of smoking at conception (OR 1.1 95% CI 0.12–10.27) correlated with congenital malformation. The independent risk factors for spontaneous abortion in a multivariable analysis (Table 4) included previous treatment for sterility (p=0.02, OR 2.9, 95% CI: 1.2–7.0). A multivariable analysis also indicated that history of bowel resection for treatment of IBD was a risk factor for Caesarean delivery (p=0.002, OR 4.1, 95% CI: 1.7–10.1) and LBW (p=0.01, OR 3.5, 95% CI: 1.3–9.1).

Table 4   Risk factors for adverse outcomes in IBD patients (multivariable analysis).

	Spontaneous abortion		Caesarean operation		Low birth weight	
	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)
Mother's height <150 cm	0.13	2.3 (0.78–6.54)	0.09	3.2 (0.84–12.19)	0.19	2.6 (0.61–11.20)
Mother's age at conception (>35 years old)	0.32	1.5 (0.66–3.47)	0.13	2.0 (0.73–5.62)	1.00	1.0 (0.29–3.52)
Smoking	0.64	1.6 (0.25–9.71)	0.678	0.8 (0.32–1.90)	0.693	1.5 (0.58–3.78)
History of previous treatment for infertility	0.02	2.9 (1.18–7.04)	0.39	1.7 (0.51–5.56)	0.5	1.3 (0.35–4.83)
History of gynaecological disease	0.36	1.5 (0.64–3.39)	0.07	2.6 (0.94–7.14)	0.79	1.2 (0.37–3.77)
Previous surgery for IBD	0.74	1.2 (0.50–2.67)	0.002	4.1 (1.66–10.10)	0.01	3.5 (1.35–9.09)

4. Discussion

In the present study, conceptions and pregnancy outcomes were analysed in female, Japanese IBD patients. There have been few studies comparing pregnancy outcomes prior to and after diagnosis. Our study indicated that the incidences of spontaneous abortion and Caesarean delivery were significantly greater in CD patients whose conceptions occurred after disease onset, as compared to those that occurred before disease onset. Our results were consistent with the results from a recent European case–control study, indicating that women with CD had higher rates of preterm delivery and LBW after diagnosis compared to rates that occurred prior to diagnosis.[15]

In the present study, LBW and preterm birth were observed in 6.4% and 2.1%, respectively, of UC patients after the onset of disease. In the general population, previous reports indicate that the incidences of spontaneous abortion, LBW, and premature birth were almost 20%, 8%, 6%, respectively.[8] Thus, incidences of adverse outcomes (e.g., LBW and preterm birth) in UC patients were not significantly higher than healthy controls. However, results from our study indicated that the incidences of Caesarean delivery, premature birth and LBW in CD patients were significantly higher than those in UC patients. These results could be explained by several complications, such as the higher incidence of previous surgeries, perianal lesions, intra-abdominal abscess and fistulas in CD patients.

The incidence of congenital malformation is 1–4% in the normal population.[8,16] Our study indicated that the incidence of congenital malformation was comparable between the normal population and IBD patients during/after disease onset (UC 1.3%, CD 4.3%).

Results from our study showed that previous surgery for IBD, CD and mother's age at conception were risk factors for Caesarean delivery. Although information regarding the reasons for Caesarean delivery was not obtained in our study, obstetricians and/or physicians might prefer Caesarean delivery in patients with perianal lesions or previous surgery, as Caesarean delivery is recommended in patients with perianal disease or rectal involvement.[13] Other studies also indicated that the risk of incontinence and anal sphincter tears is less in Caesarean delivery than in vaginal delivery.[8,17–20] In contrast, recent studies have indicated that vaginal delivery does not lead to adverse outcomes if patients do not have any perianal lesions.[21] Caesarean delivery may not be necessary in patients with inactive perianal lesions.[16] In the clinical setting, obstetricians, gastroenterologists and patients should discuss the necessity for Caesarean delivery.

In the present study, fertility was not directly investigated. However, our study indicated that the history of treatment for infertility was more common in CD patients (20.2%) than in UC patients (9.0%) after disease onset. Active CD disease reduces fertility by various mechanisms such as abdominal adhesion and inflammation in the ovaries/ovarian tubes.[13,22–25] Patients who undergo surgery are at risk for impaired tubal function, resulting in a reduction in fertility.[13] These results suggest that fertility in CD patients with the non-penetrating type (Vienna Classification; B1) may be higher than those with the penetrating type because pelvic dissections, adhesions and potential scarring are reduced in patients with non-stricturing/penetrating CD.

Our study also showed that the incidences of adverse pregnant outcome and the history of treatment for infertility were higher in CD patients with history of surgery for perianal lesions. Previous study indicated that perianal lesions as well as younger patients and the initial requirement for steroids are predictors for disabling Crohn's disease.[26] The presence of perianal lesions is in relation to further hospitalisation, flare-up of disease and chronic symptoms. Patients with perianal lesions may experience dyspareunia and have inflammation in the pelvis. As a result, the incidences of infertility and adverse pregnant outcome are relatively high in this population.

When IBD patients are trying to conceive, do we have to stop the use of immunomodulators? Although previous animal studies have demonstrated that teratogenicity frequently occurred in mice exposed to AZA,[27] a more recent clinical review has indicated that these drugs are safe and well tolerated during pregnancy.[28] Discontinuing 6-MP/AZA might not be necessary in female IBD patients who hope to conceive, if those patients need 6-MP/AZA.[20] Nevertheless, most patients from our study can discontinue 6-MP/AZA when they plan to conceive or when they become aware of conception. In fact, although our survey of 578 patients indicated that almost 20% of female patients (134 patients) used 6-MP and/or AZA at least once (data not shown), only six patients used 6-MP/AZA at the time of conception and only two patients continued to do so during pregnancy. In our previous study, both female and male IBD patients who hope to have children prefer not to take 6-MP/AZA.[29] This result is similar to the results reported in a recent large community-based study indicating that relatively few patients were treated with immunomodulators (4%).[30] Although it is difficult to exactly evaluate the safety of immunomodulators, the benefit of medical treatment of quiescent disease may overcome the risks of adverse conception and pregnancy outcomes.

There are potential limitations of the present study. First, precise information regarding disease activities and medication in pregnant IBD patients was lacking in this study. Disease activities in some patients changed over the course of pregnancy. This is not easily dealt with. To analyse whether disease activities are related to adverse outcomes, disease activities at conceptions and during pregnancies should be checked prospectively. Thus, medical treatments and disease activities were excluded from our study to assess risk factors for adverse pregnant outcomes. Secondly, although we asked the patients to list all medications at the time of conception and during pregnancy, there was incomplete data on medication use during pregnancy. Our preliminary analysis regarding medications for patients showed that almost 30% of medical information from pregnant IBD patients was not consistent with those from medical records (data not shown). This inconsistency can be explained by recall bias and patients' adherences for medications during pregnancies. Therefore, we mainly focused on the relationship between use of immunomodulators/infliximab and adverse outcomes. Thirdly, our study was neither prospective study nor case–control study. Thus, the number of UC patients is more than CD patients in this study. Finally, pregnancy and conception outcomes were obtained from the patients' self-reports in the present study. However, the patients referred to their own records (*notebook for mother and children*) to reduce recall bias.

In summary, conception and pregnancy outcomes after disease onset was comparable to outcomes that occurred prior to disease onsets in UC patients. These adverse outcomes were more frequently observed in CD patients than in UC patients. The incidences of spontaneous abortion and Caesarean delivery were significantly greater in CD patients whose conceptions occurred after disease onsets than in those with conceptions that occurred before disease onsets. A history of surgery for perianal lesions and bowel resection was a risk factor for Caesarean delivery and LBW. Although our results regarding adverse outcomes are similar to previous studies, they could help physicians/patients in Japan and other Asian countries to know the outcomes of conceptions and pregnancy.

Acknowledgements

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