Conception outcomes and opinions about pregnancy for men with inflammatory bowel disease

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Abstract

Background and aims: Patients with inflammatory bowel disease (IBD) who want to have children are anxious to receive medical treatment. The consensus regarding pregnancy has not been surveyed for male IBD patients. The present study was investigated opinions among male IBD patients about pregnancy, conception and neonatal outcomes for partners.

Methods: Subjects comprised 364 of 386 patients enrolled (94.3%). Subjects received a questionnaire regarding their opinions and thoughts about pregnancy. The course of partner’s conceptions and presence of neonatal malformations was also surveyed.

Results: The rate of live births for partners of male IBD patients was 91.6% (219/239). Most patients with CD (29/33; 88%) had their children after surgery had been performed. The rate of expressing hopes to have a child tended to be higher for patients with UC (93/128; 73%) than for patients with CD (61/97; 63%; p = 0.21). Furthermore, the rate of hesitation was significantly higher in CD patients (34/107; 32%) than in UC patients (38/188; 20%; p = 0.03). Patients considered that safety of medication (51%) and maintenance of remission (41%) was more important than receiving no treatment for IBD (19%) when planning to conceive. Mesalamine and infliximab were more favorable at conception than sulfasalazine and immunomodulators.

Conclusions: This is the first report to survey the thinking of male IBD patients regarding pregnancy. Most male IBD patients considered “maintaining remission” as important at conception. Our study provides important information for IBD patients and for the treating physician when planning to conceive.

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1. Introduction

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBDs). Since disease onset typically occurs between adolescence and young adulthood, most IBD patients experience marriage and having children. IBD patients and their families naturally want to know whether disease activity and drug exposures will affect fertility, pregnancy outcomes and the developing child. The effects of pregnancy on disease activity, pregnancy outcomes with IBD and the safety of medications for childbearing patients have been well investigated for female IBD patients, but less is known for male patients. In female UC patients, the fertility rate remains normal, but ileoanal pouch anastomosis is associated with reduced fertility.1 While pregnancy outcomes in female IBD patients resemble those in the general population, the frequencies of preterm birth, low body weight and small for gestational age births are increased in women with IBD.2–5 Risk categories for pregnancy have been assigned by the Food and Drug Administration. Sulfasalazine (SASP) and mesalamine are category B drugs, which indicate that animal reproduction studies have not demonstrated any risk to the fetus. Corticosteroids, antibiotics, cyclosporine (CsA) and tacrolimus are category C drugs. The use of thalidomide and methotrexate is contraindicated (category X) for pregnancy, while 6-mercaptopurine (6-MP)/azathioprine (AZA) is categorized as a grade D agent. This means that toxicities associated with fetal risk have been shown, but the benefits from use in pregnant women may be acceptable despite such risks. However, various studies have found no increased risk of malformation when 6-MP/AZA is used at conception.5–8

Medical treatment for men with IBD who want to conceive is less complicated than for women. SASP has been associated with infertility and 6-MP/AZA clearly impairs fertility in an animal model,9,10 although the evidence is conflicting in terms of the effects of these agents on male fertility.2 Some male IBD patients who hope to father children are thus anxious regarding the use of medical treatments. However, fertility, pregnancy outcomes of partners and influences on the fetus have not been well investigated for male IBD patients. Furthermore, no surveys have clarified the opinions, thinking and consensus regarding pregnancy in male IBD patients.

The aim of this study was to investigate opinions regarding pregnancy among male IBD patients. Conception and neonatal outcomes for partners of male IBD patients were also assessed in Japanese IBD patients.

2. Patients and methods

From August 2008 to December 2008, a total of 386 patients from the outpatient clinic of Keio University Hospital were asked to enroll in this study. We asked all male patients who were 20 to 59 years old who visited our hospital at that period. Of these, 364 patients (94.3%) (UC, n = 225; CD, n = 139) agreed to enroll in the study, while 22 patients (5.7%) refused. The mean age of enrolled patients was 38.2 years (range, 20–59 years; UC, 38.9 years; CD, 37.2 years). Mean duration of disease was 11.7 years (range, 1–25 years).

Subjects were given a questionnaire to answer (Table 1). The contents included age, type of disease (UC or CD), marital status, number of children, smoking habit, previous surgery for IBD, previous medical problems, and history of therapy for sterility. For patients whose partners had conceived, information was requested regarding the course of the partner’s conceptions (live birth, miscarriage, and elective abortion) and presence of congenital abnormalities. To assess relationships between conception outcomes and medication for IBD, use of all treatments for IBD at conception was queried. These included antibiotics, SASP, mesalamine, corticosteroids, elemental diet, 6-MP/AZA, CsA, infliximab (IFX) and surgery. Of the 5-ASA agents, only mesalamine has been used in Japan. Hospital records were also reviewed if there was any doubt about medical information. Records from 1979 to the present were available for review. Eleven results from questionnaires were inconsistent with the medical records, and data from medical records were used for those cases. To investigate whether fertility is affected by previous surgery, the number of conceptions by IBD patients before and after first surgery was assessed.

Since the partners of most patients had experienced multiple pregnancies, conception outcomes at each conception were investigated. For example, if a patient’s partner experienced miscarriage following the first conception and a normal pregnancy with the second conception, the patient was assigned to the miscarriage group for the first conception and the live birth group for the second conception. We defined a conception outcome as “live birth” if it resulted in a healthy baby.7

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Questionnaire contents.</th>
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<tbody>
<tr>
<td>1 General information</td>
<td>Height, bodyweight, age</td>
</tr>
<tr>
<td>Disease type (CD or UC)</td>
<td>Onset age of disease, Duration of disease</td>
</tr>
<tr>
<td>Number of previous hospitalizations</td>
<td>Status of marriage</td>
</tr>
<tr>
<td>Number of children</td>
<td>Previous/present smoking</td>
</tr>
<tr>
<td>History of surgery (IBD, others)</td>
<td>History of other disease</td>
</tr>
<tr>
<td>History of different</td>
<td>Experience of treatment for sterility</td>
</tr>
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</table>

2 Course of partners’ conception (live birth, miscarriage, elective abortion) |
3 Congenital malformation |
4 Medication for IBD |
5 Thoughts and opinions regarding conception and pregnancy |
Hope to having child |
Felt hesitation about having children |
Favorable/unfavorable treatments for IBD at the time of conception |
Condition under which the patient hopes to father children |
6 For partners |
Height, Body weight |
Previous/present smoking |
Previous/present drinking |
History of other disease |
Incidence of low body weight and preterm births were not investigated, since those pregnancy outcomes might depend on partner factors such as height, body weight, smoking and alcohol exposures, medication, and past medical history.

To assess patient thinking and opinions regarding pregnancy, the percentage of patients who hoped to father children was assessed and compared between UC and CD patients. Some patients might feel worried about having children while taking medical treatments or being ill. Subjects were therefore also asked whether they felt any hesitation about having a child. Favorable/unfavorable perceptions of medications with regard to conception/pregnancy (SASP, 5-ASA, corticosteroids, elemental diet, 6-MP/AZA, CsA, IFX) were surveyed. The condition (e.g., disease-free, medication-free, using IBD medications that are safe for conception) under which the patient hoped to father children was also asked.

Protocols in the present study were approved by the review board of the School of Medicine at Keio University. For statistical analyses, χ² tests (or Fisher’s exact test) and Mann–Whitney’s U test were used to compare proportions with Graphpad Prism 5 software (Graphpad Software).

3. Results

3.1. Conception outcome for partners of IBD patients

Subjects comprised 225 UC patients (62%) and 139 CD patients (38%). Patient characteristics are shown in Table 2. Surgery had been needed at least once in 16 UC patients (7.1%) and 82 CD patients (59.0%). While we included partner information regarding body weight, smoking and alcohol habits and medical history, few patients answered these questions. Almost one-quarter of patients provided height and body weights of partners.

A total of 239 conceptions for 136 patient partners (UC, n=225; CD, n=139) had been experienced. Conception and fetal outcomes are shown in Table 3. There were 171 conceptions for UC patients and 68 for CD patients. Mean age of patients at the time of conception was 32.5 years. The 239 conceptions for UC patients and 68 for CD patients. Mean age of patients at the time of conception was 32.5 years. The 239 conceptions resulted in 219 normal pregnancies (91.6%), 15 miscarriages (6.3%) and 3 elective terminations (1.3%). Conception outcome was unknown for in 1 CD patient and 1 UC patient. Three cases of congenital malformation (1.3%) were identified (palatal deformity, n=2; branchdactyly, n=1). For these 3 cases, the patient had maintained remission with SASP and 6-MP in 1 case and showed active disease despite use of 5-ASA enema and SASP in 1 case, while the third case occurred prior to disease onset. The incidence of malformation in patients using SASP (2/61, 3.2%) was not significantly higher (p=0.21) than that using 5-ASA (0/72, 0%). No patients discontinued IFX when conception was planned, since the patients did not wish to experience disease relapse. Three patients treated with IFX at conception had healthy children. Conception outcomes among partners of male IBD patients resembled those of the general population, although partner height, weight and general status were not compared between our study and the general population.

The number of children ranged from 1 to 3, with 58 patients reporting 1 child, 65 patients with 2 children and 15 patients with 3 children. No patients in this study had ≥4 children. The mean number of children was 1.20 among married CD patients and 1.37 among married UC patients.

The possibility has been raised that previous surgery may affect fertility in male patients with IBD. Only 1 of 16 UC patients (6.3%) who received surgery experienced conceptions, while 23 of 82 CD patients (28.3%) conceived. Fig. 1 indicates the number of conceptions before and after first surgeries for CD. The present study identified conception for only 3 patients prior to first surgery for CD, while 13 patients achieved conception within 5 years after operation. Most patients (87.9%) had their children after surgeries were performed (Fig. 1). Interestingly, 8 conceptions were observed even after second surgery. The ability to conceive thus remains even after surgery for CD.

3.2. Opinion regarding conception and medication use among men with IBD

A total of 225 patients in this study had no children. Among these, 154 male patients (68.4%) hoped to have a child in the future. The rate of expressing hopes to have a child tended to be higher for patients with UC (93/128; 72.7%) than for patients with CD (61/97; 62.9%; p=0.21) (Fig. 2). The great
majority (57/71; 80.2%) of younger IBD patients (<30 years old) hoped to have children. Therapies for sterility had been performed for 21 patients, including 10 CD patients (23%) and 11 UC patients (12%). The percentage of patients who had experienced therapies for sterility was significantly higher for CD than for UC (p = 0.03).

We assessed whether male IBD patients expressed hesitation regarding having children due to their disease. A total of 295 patients (81.0%) provided responses for those questions. Of these, 72 patients (24.4%) reported hesitation about having children at least once. Interestingly, the rate of hesitation was significantly higher in CD patients (34/107; 31.8%) than in UC patients (38/188; 20.2%; p = 0.03) (Fig. 2).

The opinions of IBD patients regarding pregnancy were also assessed. While 151 patients (41.4%) considered that “maintaining remission” was needed at conception, only 19.2% considered a “medication-free” state as necessary (Table 4). This percentage for “medication-free” state was lower than that among female IBD patients (our preliminary results; data not shown). The safety of medication for inducing/maintaining remission was the most critical issue for male IBD patients (187 patients; 51.4%). These opinions regarding pregnancy were similar between UC and CD patients (Table 4). To determine the thinking of patients regarding medication at conception, we included a question about which medications would be avoided if the patient was considering trying to father a child.

Acceptability of IBD treatment at the time of conception was assessed. Interestingly, 83 of 139 patients (59.7%) receiving SASP did not want to use this agent when attempting to conceive, while only 19.7% would avoid using mesalamine (Fig. 3). More than half of patients did not want to use steroids (74.5%) or 6-MP/AZA (51.1%) at conception, although steroid use has not been associated with infertility. While steroids and IM were considered unfavorable by most patients, 36 patients (27%) were receiving treatment with steroids (12%) or 6-MP/AZA (15%) when their partners became pregnant. CsA was also considered unfavorable for almost 60% of IBD patient. Elemental diet therapy and IFX were both considered relatively favorable (90.2% and 78.3%, respectively (Fig. 3). When patients conceived, only 8 patients (6%) were not using any medication for IBD. This rate was also lower than that in female patients (data not shown). Use of 5-ASA (55.6%) was more common than the use of SASP (25.6%) at the time of conception (Fig. 3). This result was consistent with the data from the questionnaire that SASP was considered more unfavorable than 5-ASA.

4. Discussion

Patient opinions regarding pregnancy in relation to IBD were surveyed in the present study. No previous studies appear to have examined unfavorable medications for pregnancy and conditions for conceiving. Most patients did not consider that a

![Figure 1](https://example.com/figure1.png)

Figure 1 Number of conceptions prior to and after first surgeries in men with Crohn’s disease.

![Figure 2](https://example.com/figure2.png)

Figure 2 The rate of IBD patients (UC: gray bar, CD: black bar) expressing hopes to have a child. The rate of hesitation to have a child due to disease was also assessed.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Survey regarding the condition under which the patient hoped to have children.</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Maintaining remission of disease</td>
<td>150 (40.9%)</td>
</tr>
<tr>
<td>Medication-free</td>
<td>70 (19.1%)</td>
</tr>
<tr>
<td>Use of safe medication</td>
<td>187 (51.1%)</td>
</tr>
</tbody>
</table>
medication-free state was necessary for conception. This opinion is different from that in female IBD patients. Male IBD patients might think that continued medication is a prerequisite for maintaining remission. In fact, only 6% of male IBD patients did not use any medication for IBD. Information regarding the safety of medication is thus indispensable for IBD patients wanting to have children, as they appear to consider the safety of medication as the most critical issue.

In our study, SASP was also considered unfavorable for almost 60% of IBD patient while only 19.7% would avoid using mesalamine when they hope to conceive. This result consisted with the data showing that SASP is associated with infertility and abnormalities in sperm number, motility.9,13 In general, we advised patients to switch SASP to mesalamine if they desired to conceive. Unexpectedly, almost 25% of IBD male patients continued with SASP in our study (Fig. 3). We have not assessed the reasons for continuing with SASP despite receiving information regarding infertility from physicians and/or other sources, such as the internet and articles on IBD. Mesalamine was not available until the middle 1990s in Japan, so most patients might have continued SASP to induce and maintain remission even though they wanted to have children. Our study also indicated that steroid was considered unfavorable by most patients although IFX was relatively acceptable when their partners became pregnant. The effect of steroid on male fertility and congenital abnormalities is not known. There is no evidence of an increase in congenital anomalies regarding steroid use.12,14 Corticosteroid can be used during conception period since disease activity may have a negative impact on fertility and semen quality.2 IFX is widely used for inducing and maintaining remission in CD.15–17 Three patients treated with IFX at conception had healthy children in our study. For men with IBD, IFX does not cause any increase in congenital malformation.18 although semen mortality and morphology are decreased.19 IFX can be continued to maintain remission and prevent development of antibodies to IFX even in IBD patients hoping to conceive.2

Fertility has not been well investigated among male IBD patients. Damage to the reproductive organs seems to be less than that in women with IBD. Narendranathan et al. surveyed the mean number of children among men with IBD. Compared to controls, numbers of children were lower with CD, but not with UC.20 Our study indicated that CD patients hesitated to have children due to their disease than UC patients. This opinion may be associated with lower number of children in CD patients.

Since previous report indicated that the mean number of pregnancies in the male CD patients was significantly lower than the number for controls and surgery in the pelvis can lead to issue with fertility,2 we hypothesized that surgery would lead to infertility issues in CD patients and the number of patients conceiving would be lower after surgery than at any other periods in their life. Unexpectedly, CD patients in the present study were able to have children even after surgery. Notably, the ability to have children does not appear to be adversely affected within several years after surgery. Removal of complicated lesions for male CD patients leads to a "disease-free" state in which children may be easier to conceive.

The present study is the first study concerning the number of children, conception and fetal malformation that has examined Asian men with IBD. Almost 90% of men with IBD can expect to father healthy children. Miscarriage, elective terminations and congenital abnormalities did not show any particularly high incidence. These results are consistent with the findings of Ludvigsson et al.21 However, some limitations exist to the investigation of adverse pregnancy outcomes in our study. First, our study was based on responses to a questionnaire. Recall bias may thus be present in this study. However, most cases could be confirmed by medical records. Recall bias may thus be present in this study. However, most cases could be confirmed by medical records. Second, conception and pregnancy outcomes would have been affected by female factors, such as height, body weight, smoking habit, medical history and gynecological factors. In our study, only 25% of patients answered the questions regarding height and body weight of patients. Another limitation was that patients may tend to conceal adverse conception outcomes or some patients may not have been aware of some pregnancy outcomes for their partners (e.g., miscarriage or abortion), compared to female IBD patients. However, our data indicated that 7% and 1% of

![Figure 3](https://academic.oup.com/ecco-jcc/article-abstract/4/2/183/375848)

**Figure 3** The percentage of patients receiving treatment for IBD at the time of partner conception (gray bar) and acceptable treatment for patients planning conception (black bar). SASP, salsalazine; 5-ASA, mesalamine; 6-MP, 6-mercaptopurine; AZA, azathioprine; CsA, cyclosporine A; IFX, infliximab.
patient partners experienced miscarriages and malformations, respectively. These are not particularly low rates and are comparable to those in the general population. We thus believe that most patients in the present study did not hide negative events regarding conception and pregnancy outcomes.

In conclusion, this is the first report to survey the opinion of male IBD patients regarding conception and pregnancy. Our study indicated that patients considered that safety of medication is most critical when planning to conceive. They also think that continued medication for maintenance of medication is most critical when planning to conceive. They also think that continued medication for maintenance of remission is more important than "medication-free". Thus, physician should give proper information regarding safety of IBD medication.

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The study sponsors had no involvement. SA and MN have equally contributed to this study. SA carried out the study and data analyses. MN designed at the main part of this study and drafted the manuscript. KA, YN and TT participated in the design of this study. TY, TH and YI helped to draft the manuscript. MW gave us special comments for this manuscript. The authors would like to express their thanks to Mr. Matt Morgan (Forte Inc., Tokyo, Japan) for manuscript revision in English.

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