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Pregnancy and IBD treatment: This challenging interplay from a patients' perspective

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Abstract

Introduction: Current data suggest that exacerbations of Inflammatory Bowel Disease (IBD) during pregnancy worsen perinatal outcomes. However, patients' perceptions regarding the interaction between pregnancy and IBD management are unexplored.
Aims: To (1) obtain pregnancy outcome data from local female IBD patients, and (2) to gain insight into patients' understanding of the interaction between IBD and pregnancy, and how this affects medication-taking behaviour.
Methods: Female IBD subjects aged 18–50 years were surveyed by questionnaire. This large retrospective study sought patient who reported pregnancy outcomes and examined the relationship between major adverse outcomes, IBD activity and treatment. Subjective data regarding patients' perceptions about IBD management and pregnancy were sought.
Results: 219 females were surveyed, 143 completing a questionnaire (68.1%). 342 pregnancies occurred, 298 of which outcome data were available. Overall IBD women reported adverse pregnancy outcome rates comparable to the local population. Major adverse outcomes were more frequent in the subgroup with severe disease during pregnancy (5 / 14 (35.7%)) than those with inactive disease (14 / 284 (4.9%)), (OR 6.8 (95% CI 1.7–26.3), $p=0.006$). Adjusting for disease severity, neither corticosteroid, azathioprine nor 5ASA affected pregnancy outcome. Most female patients (84%) reported (unwarranted) concerns about the effect of IBD medications on pregnancy, free text responses indicating that this was of greater concern than any effect of IBD exacerbation.
Conclusions: Unwarranted fear of adverse medication effect on pregnancy is highly prevalent in women with IBD, yet awareness of the harmful effect of IBD exacerbation during pregnancy is poor. This information gap between patients and their gastroenterologists warrants attention.

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1. Introduction

The interaction between Inflammatory Bowel Disease (IBD) and pregnancy is of great importance, as disease onset often coincides with peak reproductive years, one quarter of patients conceiving after their IBD diagnosis.[1,2]

Whilst pregnancy is not thought to affect the activity of Inflammatory Bowel Disease (IBD),[3–6] numerous studies suggest that exacerbations during pregnancy worsen pregnancy outcomes, particularly increasing the incidence of Low Birth Weight (LBW).[7–10] Therefore, good disease control and compliance with medication documented to maintain remission are paramount.

Most IBD medications are regarded as less deleterious to pregnancy outcome than the risk of disease exacerbation during pregnancy,[11–16] although a spectrum of potential teratogenicities is recognized. Sulphasalazine, corticosteroids [17] and probably 5ASA agents, for example, are not thought to confer an increased fetal morbidity or mortality amongst pregnant IBD patients, whilst Azathioprine and 6-Mercaptopurine (6MP) have produced a small increased risk in spontaneous abortion and fetal abnormalities in rats but in small studies have been found to be safe in humans.[13] Experience with the biologic agents is limited but preliminary data suggest the incidence of fetal abnormalities is not increased in patients taking Infliximab during pregnancy.[18] The main exception to the general safety of IBD medications in pregnancy is that of Methotrexate, which is widely known to be teratogenic.

Previous research addressing the interaction between pregnancy and IBD has primarily been population or hospital based and focused on birth outcomes from administrative databases of IBD patients. Few data address how women with IBD in the community view the interaction between IBD, its treatment, and their own experience of pregnancy. Individual women are ultimately responsible for decision making regarding their IBD management during this time, and physician advice is more likely to be adhered to if women feel their concerns are understood by their doctor.

This observational study therefore sought to ascertain local pregnancy outcome data amongst women with IBD. Importantly, it also explored female patients' beliefs about the interaction between pregnancy and IBD management, and examined how these perceptions affected medication-taking behaviour.

2. Aims

To (1a) obtain pregnancy outcome data from local female IBD patients and (b) identify risk factors for adverse outcomes such as IBD activity or medication use during pregnancy, and (2a) to gain insight into patients' perceptions of the interaction between IBD and pregnancy, and (b) how this affected women's medication-taking behaviour.

3. Methods

All contactable subjects 18–50 years of age from a hospital based IBD database were surveyed by postal questionnaire, with two telephone reminders one month after initial postage where no response was obtained. The questionnaire was entitled "*Quality of Life, Body Image, Sexual Function and Pregnancy in IBD: A survey of patients in their reproductive years.*" This large cross sectional study contained 4 parts, encompassing patients' perceptions of body image, sexuality, fertility and pregnancy in both genders. Data concerning body image, sexuality and family planning are reported elsewhere (Muller et al., DDW 2008, Mountifield et al. [19]). Here we report on pregnancy data from female subjects, covered in Part D of the survey. This information was gathered by retrospective report by subjects and unless responses were unclear or appeared inconsistent, they were not independently verified or re-confirmed with subjects. The survey was initially tested on a small number of IBD patients to verify the clarity of instructions and ease of question understanding.

Subjects were asked 61 questions in Part D of the questionnaire, requesting a variety of categorical answers interspersed with the opportunity for free text responses. Demographic and disease data were taken from Part A of the questionnaire, with information regarding disease activity during pregnancy obtained by patient recall and classified as severe or non-severe.

Females were asked how many times they had been pregnant, the outcome of each pregnancy (ie termination of pregnancy, miscarriage, stillbirth, healthy baby) and asked to give details about any adverse pregnancy outcomes they reported. The number of pregnancies occurring after pouch formation was reported, as well as patient recall of IBD severity during each pregnancy, and whether surgery or admission was required. Subjects reported which medications they took for IBD during each pregnancy, whether they changed their medications, and estimated how often they missed medication doses during pregnancy. For any changes that were self-initiated rather than being physician-led, women were asked to state the reasons for these self-management decisions. A free text area was provided and subjects encouraged to expand upon their answers giving details about their pregnancy experiences and thoughts regarding the interaction with IBD.

After reviewing patients' responses two investigators (RM and RP) divided reported adverse events into major and minor groups, whereby major included fetal malformations, low birth weight, pre-term labour or any permanent defect or problem requiring ongoing management (see Table 1). Problems classified as "minor or unrelated" included brief neonatal jaundice, labour and breast feeding difficulties and successfully treated Rhesus incompatibility.

Descriptive data are presented, comparisons made using contingency tables with Fisher's exact test. In all analyses a p value <0.05 was considered significant. Multiple logistic regression analyses were performed to test independence of disease severity and steroid use during pregnancy.

Ethics approval for the questionnaire was obtained via the Flinders Medical Centre Clinical Research Ethics Committee, with receipt of a completed questionnaire taken as signifying individual patients' consent. Each patient had given prior consent to be enrolled on the clinical/research IBD database.

Table 1 Self reported adverse pregnancy outcomes in IBD women overall, and subgroups taking no medication, those taking corticosteroids during pregnancy and those with severely active disease during pregnancy, compared with non IBD Australian population rates.

Adverse outcome type	All IBD women	No medication	Steroid exposure	Severe disease	Non-IBD population (%)
N (% reported pregnancy outcomes)					
Stillbirth	2 (0.7%)	1 (0.62%)	0 (0%)	1 (7.1%)	0.7 [a]
Preterm delivery	7 (2.3%)	3 (1.9%)	2 (6.1%)	2 (14.3%)	10.2 [a]
Developmental delay	1 (0.3%)	0 (0%)	1 (3%)	0 (0%)	1 [a]
Congenital abnormality	1 (0.3%)	1 (0.62%)	0 (0%)	0 (0%)	2.3 [a]
Miscarriage	7 (2.3%)	4 (2.5%)	2 (6.1%)	1 (7.1%)	15–20 [a]
Low birth weight/small for gestational age	2 (0.7%)	0 (0%)	1 (3%)	1 (7.1%)	7 [a]
Healthy baby or minor problems	278 (93.3%)	152 (94.4%)	27 (81.8%)	9 (64.3%)	–
Total	298	161	33	14	–

[a] Chan A, Scott J, Nguyen A-M, Sage L. Pregnancy outcome in South Australia 2006. Adelaide: Pregnancy Outcome Unit, South Australian Department of Health, 2007.

4. Results

4.1. Demographic and disease data

219 females were surveyed, 143 returning a completed questionnaire (68.1%). The mean age of female subjects was 35.5 years (range 20–50 years), 128 women having CD (59%), 86 UC (39%) and 5 Indeterminate Colitis (IC) (2%). 342 pregnancies occurred (183 in CD, 151 in UC and 8 in IC women,) 298 of which complete outcome data were reported (Fig. 1). Of the remaining 44 pregnancies, 40 (27 CD and 13 UC) were deliberately terminated for non medical reasons, and 4 pregnancies were ongoing at the time of survey.

4.1.1. Pregnancy outcome data

Of the 298 pregnancies not deliberately terminated, 154 were in CD women, 138 to women with UC and 6 with Indeterminate Colitis (IC). Two sets of twins were reported, one set born to a CD woman and the other to a woman with UC. The average fertility rate for women reporting at least one previous pregnancy was 1.78 births overall (1.67 for CD and 1.94 for UC.) The average fertility rate for all females surveyed in this cohort has been reported elsewhere (Mountifield et al.[19]) and was 1.18 births per woman. 4 patients reported surgery for pouch formation, (3UC, 1 CD), 2 of whom had completed pregnancy prior to surgery, and 2 of whom had never been pregnant.

Of the 298 pregnancies with known outcomes, 213 resulted in healthy neonates, and 85 "adverse outcomes" were reported by subjects (see figure above). After review of each "adverse outcome" it was deemed that 20 events were "major" (see Table 1 for breakdown of major events) and 65 "minor". Minor adverse outcomes included neonatal problems including transient jaundice, sleeping or feeding difficulties, reflux, eczema, Rhesus incompatibility and lactose intolerance. Although reporting of minor problems was encouraged and a large proportion of women reported these, our results were calculated using the frequency of major adverse pregnancy outcomes, detailed in Table 1.

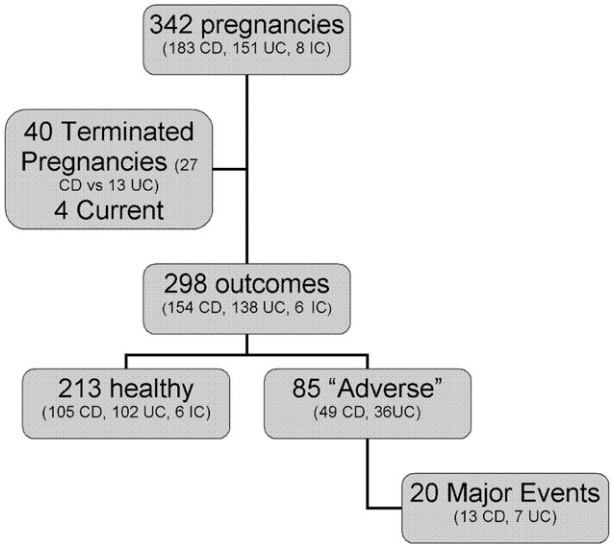

Figure 1 Reported pregnancy outcomes of female IBD respondents.

4.1.2. Risk factors for adverse pregnancy outcomes

Overall our IBD cohort reported a frequency of major adverse events similar to the local non IBD population (see Table 1). Subgroups of IBD women, however, appeared to have higher rates of major adverse outcomes compared with their IBD peers.

4.2. Disease activity during pregnancy

14 pregnancies were to women reporting severely active disease during pregnancy, 8 requiring hospital admission but none requiring surgery. In this severe group, 8 pregnancies were exposed to steroid. Of the 6 pregnancies not steroid exposed, ongoing active disease was treated using increased Azathioprine dosage in 2 patients, commencement of 6-Mercaptopurine in 1 patient, and a short Cyclosporine course in a further patient, whilst non steroid management method was not volunteered by the remaining 2 patients. Major

adverse outcomes were more frequent in those with severe disease during pregnancy (5 / 14 (35.7%) than those with mild or inactive disease (15 / 284 (5.3%), ($p=0.0009$) (Fig. 2) When adjusting for steroid use on logistic regression analysis, severe disease during pregnancy still had a significant negative effect on pregnancy outcomes, OR 6.8, (95% CI 1.7–26.3), $p=0.006$.

4.3. IBD medication exposure during pregnancy

Of the 298 pregnancy outcomes reported, medication data were incomplete for 61, leaving 237 pregnancies available for analysis with regard to medication exposure.

161 pregnancies were not exposed to any IBD medication. Major adverse effects were reported in 9 (5.6%) of these 161 pregnancies, with similar rates amongst CD and UC women (5.9% vs. 5.3%, $p=1.0$). Severe disease activity during pregnancy was much less common in these patients on no medications (2 / 161) than those on any IBD medications (12 / 136) during pregnancy (1.2% vs. 8.8%, $p=0.0041$).

33 pregnancies were exposed to oral or IV corticosteroids. Major adverse pregnancy outcomes were increased in the group receiving steroids compared to those pregnancies not exposed to steroid (6 / 33 (18.2%) vs. 14 / 253 (5.5%); $p=0.02$) (Fig. 3). Steroid exposed patients were more likely to have had severe as compared to mild or inactive disease activity during pregnancy in both CD (29.4% vs. 2.3%, $p=0.0006$) and UC (18.8% vs. 3.1%, 0.038). Not surprisingly, rates of steroid use were higher in those with severe, active disease during pregnancy (57.1 vs. 9.4%, $p=0.0001$). Interestingly, patients with severe disease activity during pregnancy had the same rate of major adverse effects whether they did (3 / 8) or did not (2 / 6) receive steroid therapy (37.5% vs. 33.3%, $p=1$). Multiple logistic regression analysis confirmed the confounding effect of disease severity on the relationship between steroid exposure during pregnancy and adverse outcomes. When adjusted for disease severity, there was no significant difference in major adverse outcomes in women receiving/ not receiving steroids during pregnancy OR = 2.2 (95% CI 0.7–7.5, $p=0.193$).

Azathioprine was only taken during 5 / 237 (2.1%) pregnancies, partly because 95.3% of patients reported non-severe disease. Additionally, 7 women who reported taking Azathioprine prior to pregnancy ceased this at conception, several suggesting in free text responses that this decision

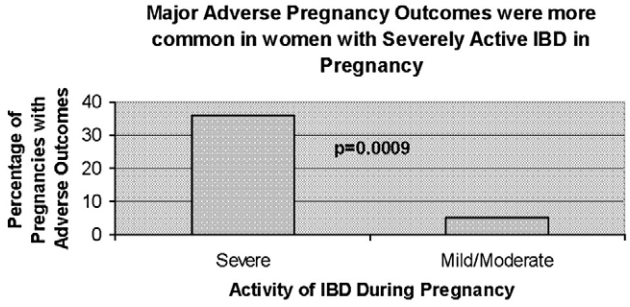

Figure 2 The relationship between severely active IBD during pregnancy and major adverse pregnancy outcomes.

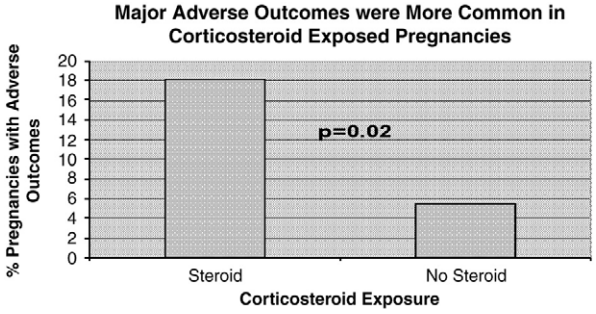

Figure 3 The relationship between corticosteroid exposed pregnancies and major adverse pregnancy outcomes.

was based on fear of adverse pregnancy outcomes. Forty-six pregnancies (19.4%) were exposed to 5ASA agents, in 18 CD and 28 UC women. No pregnancies were exposed to anti-TNF agents, likely due to lack of ready access to these agents in Australia at the time of the study (2005/06). Neither Azathioprine (40% vs. 13.3%, $p=0.14$) nor 5ASA agents (39% vs. 30.5%, $p=0.34$) altered the risk of major adverse pregnancy outcomes compared with those not exposed. Adverse pregnancy outcomes amongst patients ceasing azathioprine at or around conception were not significantly different in frequency to those continuing azathioprine throughout gestation, (3 / 7, 42.8% vs. 2 / 5. 40%, $p=1.0$). Similarly, no differences in adverse outcome frequency were seen amongst women ceasing 5ASA agents prior to conception (7 / 15, 47%) vs. those continuing medication during pregnancy (18 / 46, 39%, $p=0.76$).

4.3.1. Patients' beliefs about IBD and pregnancy outcomes, and medication compliance

In response to both direct questions and free text responses, a large proportion of subjects (84%) reported concerns that IBD medications would harm their pregnancy, whereas only 19% women reported concerns about the effect of active IBD on pregnancy. The overriding sentiment expressed by patients was that they would "rather put up with the disease symptoms than harm my baby with medications", indicating a lack of awareness about the known adverse effect of active disease on pregnancy outcomes, and also the pregnancy related risks associated with fluid and electrolyte disturbances, anaemia and the need for surgery in the setting of poorly controlled IBD.

With regard to specific negative pregnancy outcomes, women reported being most concerned with the "deforming" effects of medication, and the risk of "congenital defects", whereas more common adverse outcomes in IBD pregnancies such as Low Birth Weight and Premature Delivery were not the focus of free text responses.

4.3.2. The effect of patients' beliefs on medication-taking behaviour

The strong patient perception that IBD medications contribute to adverse pregnancy outcomes appeared to affect medication-taking behaviour in our subjects. Amongst women changing IBD medication whilst pregnant 7 / 25 (28%) did so without their doctors' knowledge. In most

cases changes involved reducing or ceasing medication. Corticosteroid and Azathioprine were the medications most frequently altered by women without medical supervision. Interestingly, free text responses indicated a tendency for patients to consider as required "rescue" steroid treatment for flares to be safer than ongoing prophylactic maintenance treatment during pregnancy, even amongst patients prescribed only 5ASA agents. Some patients reported the belief that "natural therapies" or "organic" products from a herbalist or other practitioner would be a "safer substitute" during pregnancy and thus ceased their conventional IBD medications in favour of this approach.

In many cases those women offering subjective responses reported their medication-taking behaviour being more strongly influenced by family, friends and the internet than their doctors. Pharmaceutical company Product Information was also cited as a source of compliance influencing information by several patients. Advice to "discuss this medication with your doctor in pregnancy" was reported by patients as ominous, and several did not follow this advice but subsequently decided upon medication cessation without supervision.

"Good" medication compliance "most of the time" was reported by 65.8% of subjects prior to pregnancy, and no overall improvement was reported during pregnancy.

5. Discussion

This study provides a unique insight into patients' understanding of the interaction between IBD, its treatment and pregnancy outcomes. The high response rate to our survey indicates the need amongst IBD women to address reproductive issues, and highlights the importance of physician-led discussion to identify barriers to treatment uptake.

In accord with other studies, our IBD women did not report major adverse pregnancy outcomes to be more frequent than in the general population. However, patients with severe disease or taking corticosteroids during pregnancy did report a significantly higher rate of adverse outcomes than those with mild to moderate disease or taking no medication, respectively. After controlling for disease severity, steroid exposure conferred no additional risk to pregnancy outcome, which is consistent with outcomes from other reported IBD populations.[11] It is important to note, however, the wide confidence intervals of this regression analysis as a result of the relatively small number of patients taking corticosteroids during pregnancy in this study. Interestingly, we could not demonstrate the expected higher rate of adverse pregnancy outcome frequency amongst those women ceasing Azathioprine and 5ASA agents prior to conception compared with those continuing during pregnancy. This is likely due to the small numbers of patients involved, and also the likelihood that patients advised to cease these agents had less severe disease than those advised to continue.

The novel revelation from our data, however, is that whilst an overwhelming (84%) proportion of women attributed adverse pregnancy outcomes to medications, particularly steroids, only a few (19%) recognized the known detrimental relationship between disease activity during pregnancy and adverse outcomes. Medication-taking behaviour (reducing or ceasing therapy) during pregnancy reflected this attitude. And, of concern, this reduction in therapy was undertaken by patients without prior consultation with their physician in a substantial proportion of cases (28%). A frequently expressed erroneous belief was the concept that a brief course of flare prompted medical treatment (often steroid) was better than more lengthy ongoing prophylactic treatment. This reflected the assumption by many patients that duration of medication exposure during pregnancy was more important than medication type and the presence or absence of active inflammation.

Interestingly, this potentially overzealous concern about medication use in pregnancy is not confined to IBD medication and IBD patients. A large survey addressing attitudes toward medication use to treat infectious disease in pregnancy showed that pregnant women had a very high level of concern about medication use, which was not influenced by reassuring advice from their own parents.[20] In IBD patients, fear-based medication noncompliance may precipitate flares, which in turn increase adverse pregnancy outcomes and reinforce this vicious cycle.

Inactive IBD during pregnancy confers a small increased risk of some adverse pregnancy outcomes, although numerous studies report similar risks to the general population.[21–25]

In CD a small increase in the risk of LBW and pre-term delivery has been reported,[26–30] especially in patients with ileal disease or previous surgery.[31] In UC women the rate of healthy delivery and healthy neonates is similar to the general population in some studies,[3,8,32] whilst others report a small increase in pre-term delivery and low birth weight infants.[33–35] An increased rate of spontaneous abortion has also been noted.[36]

The increased rate of adverse outcomes amongst our subjects with severely active disease during pregnancy was not surprising. Accumulating evidence suggests that IBD activity during conception and pregnancy is the most influential determinant of pregnancy outcome, although this is controversial. Whilst a large study of pregnant women with predominantly mild IBD found no association between disease activity and pregnancy outcome,[37] other data suggest that exacerbations during pregnancy are detrimental.[8–10] Numerous case control and cohort studies have reported an association between flares during pregnancy and pre-term delivery, low birth weight, and other adverse outcomes in both CD and UC.[7–10,23,30,38–41] Khosla et al.[9] demonstrated a miscarriage rate of 35% amongst IBD women with active disease at conception. A large nationwide Danish cohort study [42] found an increased risk of pre-term birth only in CD women with moderate to high disease activity during pregnancy, Baiocco et al. supporting the contention that the detrimental effect of disease activity is more pronounced in CD than UC.[8]

Our finding of increased adverse outcomes amongst women taking corticosteroid during pregnancy was likely confounded by the high proportion of women with severe disease in this group (24%). Many other studies report the same methodologic limitation in elucidating the relationship between IBD medication and pregnancy outcome. Corticosteroid therapy has been used extensively in pregnancy and has not been shown to cause fetal harm in IBD patients.[40] In a study of 531 women, 168 received extended duration steroid in pregnancy with no increase in prematurity, abortion,

stillbirth or developmental defects.[11] As prednisolone is extensively metabolized by the placenta it is considered safer than uncontrolled IBD during pregnancy.[43] 5ASA agents may very slightly increase adverse outcomes,[44] and azathioprine data are conflicting, some studies suggesting a small increased risk of fetal abnormalities [45] and others refuting this.[13] Although no long term data are available for the biologic agents, most reports thus far suggest they are relatively safe in pregnancy.[16,18,46,47]

The generalisability of our findings is encumbered by several limitations. Whilst we endeavoured to clarify the nature of reported adverse outcomes and distinguish between major and minor problems, data were based entirely upon self report without external verification. It is thus difficult to make comparisons with normal population data arising from administrative databases. The retrospective nature may have introduced recall bias in subject responses, and this may explain why numerous respondents selectively answered some questions but not others. Data regarding smoking rates in our population would also be advantageous as this has a considerable impact on perinatal outcomes.[48]

The importance of this study, however, is its identification of patients' attitudes and insights which create a barrier to treatment uptake in IBD. We have demonstrated no overall difference in risk of adverse pregnancy outcomes compared with the general population. Women with severe, active disease during pregnancy and those taking corticosteroids had increased adverse outcomes compared with other IBD women, although causality cannot be established in the case of steroid as this relationship is confounded by the effect of increased disease activity. Fear of medication teratogenicity is highly prevalent, whereas awareness of the deleterious effect of IBD exacerbation during pregnancy appears limited. These negative attitudes toward IBD medication promote patient initiated cessation during pregnancy, which may prove detrimental.

The gastroenterologist plays a pivotal role in providing early, evidence-based counselling to facilitate informed management decisions, and to emphasise the importance of disease control during conception and pregnancy. The views of individual women need to be acknowledged and the opportunity to ask questions was incorporated into the routine consultation, in order to optimise pregnancy outcomes in IBD patients.

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Otherwise no authors declare other conflict of interests with regard to this study.

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