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Mistakes in inflammatory bowel disease and reproduction and how to avoid them

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Inflammatory bowel disease (IBD) is a chronic relapsing gastrointestinal disease, often affecting young people during their fertile years. The chronic character of IBD means that lifelong medical treatment is often required. As such, it is not surprising that questions often arise about fertility and pregnancy in patients with IBD. The most important risk factor for adverse pregnancy outcomes in IBD patients is the presence of disease activity during pregnancy. Indeed, negative pregnancy outcomes (e.g. spontaneous abortion, preterm delivery and low birth weight) are associated with disease activity at the time of conception and during pregnancy.[1–4] The majority of pregnancies in women with quiescent IBD are uncomplicated. This demonstrates the importance of maintaining remission by continuing medication during pregnancy. Counselling patients before pregnancy on the effects of IBD drugs and disease activity on the child *in utero* is, therefore, of utmost importance. Although much is known about reproduction and IBD, misbeliefs regarding pregnancy and IBD still persist. Here, we present 10 major mistakes and misperceptions that are made when treating IBD patients who wish to reproduce. The list and discussion are evidence based and integrated in our clinical practice.

Mistake 1 Believing that IBD always negatively affects female fertility

Female fertility is not influenced by the presence of ulcerative colitis or Crohn's disease itself.[1,2] However, active disease has been associated with subfertility in female.[5] Possible reasons are inflammation of the colon that involves the fallopian tubes and ovaries, poor nutrition, depression, decreased libido and dyspareunia caused by perianal disease.[4]

Fertility is reduced in female ulcerative colitis patients who have undergone surgical resection with ileal pouch anal anastomosis (IPAA). Several studies have found that female patients who underwent IPAA had a threefold increased risk of subfertility compared with those who did not have surgical intervention.[6–8] The reason for subfertility after IPAA surgery is most likely destruction of fimbria, the increased rate of hydrosalpinx and tubal obstruction following pelvic surgery. Two small retrospective studies have shown that infertility rates are lower after laparoscopic IPAA surgery compared with open IPAA surgery,[9,10] which may be explained by reduced adhesion formation after laparoscopic surgery.

Overall, female patients with IBD have fewer children compared with the general population.[11,12] Incorrect beliefs and poor knowledge of IBD and pregnancy continue to contribute to the high rate of voluntary childlessness within the IBD population.[13,14]

Mistake 2 Believing that IBD always negatively affects male fertility

As is the case for female IBD patients, IBD itself does not lead to reduced fertility in male patients.[15] However, active disease has been associated with subfertility in male IBD patients. Possible reasons include poor nutrition, depression and decreased libido.[4]

The effect of IPAA on male fertility has not been studied. Male ulcerative colitis patients who undergo IPAA may experience erectile dysfunction and retrograde ejaculation; however, studies show no change or an even an improvement in sexual function after surgery.[16,17]

On the whole, male patients with IBD also have fewer children compared with the general population.[12]

Mistake 3 Thinking that all drugs prescribed for IBD negatively affect fertility in males and females

There are no studies that show a negative effect of IBD drugs on female fertility.[8] More data are available on subfertility and IBD medication use in male patients. We therefore describe current knowledge on the effect on male fertility of the IBD drugs that are most often prescribed.

Sulphasalazine causes a reversible, dose-related decrease in both sperm count and motility.[18,19] Sulphasalazine should therefore be switched to a different 5-ASA drug if the patient wishes to reproduce.

Corticosteroids can cause a reversible decrease in sperm motility and concentration; however, there seems to be no link between steroid use and infertility.[20,21]

Methotrexate causes oligospermia, which improves within a few months of stopping it.[22] Methotrexate is, however, teratogenic and contraindicated in both men and women wishing to procreate.[23] It has been advised that methotrexate should be stopped 4–6 months before conception.[24]

Azathioprine does not reduce semen quality and, therefore, does not affect fertility in male IBD patients.[25] A large prospective study including 115 pregnancies fathered by males using thiopurines (azathioprine or 6-mercaptopurine) during conception showed no statistically significant increase in the rate of major congenital anomalies.[26] In addition, a meta-analysis published in 2013 showed no association between congenital abnormalities and thiopurine use by the father at the time of conception.[27]

The effect of anti-tumour necrosis factor (TNF) drugs on male fertility has not been extensively examined. Infliximab seems to affect semen quality by reducing motility,[28] but the data are conflicting because men with spondylarthropathies who received anti-TNF therapy were found to have a tendancy for better sperm quality than those who did not.[29] There have been no studies on the effect of adalimumab on male fertility.

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Few studies have investigated the effect of male infliximab use during conception on the foetus, but the existing studies found no evidence that they increased the risk of adverse birth outcomes.[30-32] Therefore it is not recommended that male patients stop infliximab treatment before conception.

Mistake 4 Stopping azathioprine because of a pregnancy or the desire to become pregnant

In clinical practice, it is recommended that thiopurines should be continued during pregnancy because the risks of active disease most likely outweigh the risks associated with thiopurine use.

The immunomodulators azathioprine and 6-mercaptopurine are often used to treat moderate-to-severe IBD. In the past, studies have described adverse pregnancy outcomes with thiopurine use (e.g. an increased rate of spontaneous miscarriage, preterm delivery and low birthweight).[33,34] However, these studies failed to take into account disease activity during pregnancy, and it is known that a disease flare during pregnancy increases the risk of preterm delivery and low birthweight. More recent controlled studies showed no increased risk of adverse pregnancy outcomes in the case of thiopurine use during pregnancy.[35–38] During pregnancy, the active metabolite 6-thioguanine crosses the placenta, but the prodrugs azathioprine and 6-mercaptopurine do not.[39,40] A Dutch follow-up study was performed in children exposed to a thiopurine *in utero*, demonstrating normal growth and development up to 6 years of age.[41] Furthermore, the ongoing and prospective PIANO registry has not observed an increased risk of congenital anomalies or pregnancy complications among 337 pregnancies exposed to thiopurines.[42]

In case of longstanding remission using combination therapy with an anti-TNF agent, stopping the thiopurine before conception may be considered. However, the patient's medication history and disease severity should be taken into account.

Mistake 5 Stopping an anti-TNF agent because of a pregnancy or the desire to become pregnant

In clinical practice, it is recommended that anti-TNF agents should be continued during pregnancy as the risks of active disease probably outweigh the risks associated with anti-TNF use. The most extensively examined anti-TNF drugs are infliximab and adalimumab.

Infliximab and adalimumab are both IgG1 antibodies that can cross the placenta in the second and third trimesters.[43] Drug levels in infants exceed maternal anti-TNF levels and are dependent on the timing of anti-TNF cessation during pregnancy.[44–46] A systematic review has shown that anti-TNF therapy does not increase the risk of unfavourable pregnancy outcomes among women with IBD.[47] The long-term effects of *in utero* exposure to anti-TNF have not been extensively explored, although one study has shown normal health outcomes and first-year development in children exposed to anti-TNF agents compared with children born to non-IBD controls who were not exposed to anti-TNF agents.[46] In addition, preliminary results from two ongoing studies show normal growth and development in children exposed to anti-TNF agents *in utero* in the first years of life.[42,48] In the PIANO registry, it should be mentioned that combination therapy with immunomudulators did increase the risk of infections in offspring.

Clinicians should be aware that there are no long-term studies on the health outcomes of children exposed to anti-TNF *in utero*. More importantly, continuing anti-TNF during pregnancy may have consequences for the child's vaccination program because live vaccines should not be given to patients receiving an anti-TNF; live vaccinations should, therefore, be deferred until anti-TNF levels are undetectable in the child. Anti-TNF treatment may be stopped in pregnant patients who are in sustained remission. A prospective study, comprising 83 pregnancies exposed to an anti-TNF agent, showed that early discontinuation before gestational week 25 does not increase the risk of a disease flare and results in significantly lower levels of the anti-TNF agent in cord blood.[46]

Certolizumab pegol is a PEGylated Fab' fragment of a humanized anti-TNFα monoclonal antibody. This Fab' fragment crosses the placenta by passive diffusion and not by active transfer like infliximab and adalimumab. The drug levels reaching the foetus are, therefore, low. One study that analysed the pregnancy outcomes of intrauterine certolizumab pegol exposure suggests it does not have a harmful effect.[49]

Golimumab is a fully humanized monoclonal antibody that is very similar to adalimumab. There are limited data on pregnancy outcomes when golimumab is used during pregnancy, but the safety profile is probably similar to that of the other anti-TNF drugs.[35]

Mistake 6 Not treating a relapse during pregnancy

As it is known that active disease during pregnancy confers maternal and foetal risks, it is important to adequately treat a relapse during pregnancy. Similar rules apply to the induction of remission in pregnant IBD patients as in non-pregnant IBD patients and the choice of drug depends on the severity and the extensiveness of the IBD. Although data on anti-TNF initiation during pregnancy remain scarce,[50,51] starting an anti-TNF agent during pregnancy should be considered in the case of steroid-refractory disease. Starting thiopurines during pregnancy is not advised due to the relatively late disease response and the risk of potential side effects, such as bone-marrow suppression and pancreatitis.[35]

Mistake 7 Not performing a lower endoscopy because of pregnancy

Lower endoscopy should be performed during pregnancy when it is strongly indicated, regardless of the trimester. Inappropriate diagnostic work-up can lead to suboptimal treatment and a diagnostic delay will inevitably induce a therapeutic delay, so the risks of a lower endoscopy during pregnancy should be weighed against the expected benefits. The theoretical dangers of lower endoscopy during pregnancy have been hypothesized, such as spontaneous abortion, stillbirth and premature labour. The current ASGE guideline states that lower endoscopy should preferably be performed in the second trimester,[52] but a systematic review concluded that lower endoscopy poses a low risk for mother and child during any of the three trimesters of pregnancy.[53] Additionally, a prospective study comprising 42 pregnant women who underwent 47 lower endoscopies during pregnancy, showed no adverse outcome related to the endoscopy in any of the three trimesters.[54]

Mistake 8 Thinking that the preferred mode of delivery is the obstetrician's choice

The preferred mode of delivery should be made on an individual basis and a multidisciplinary approach. Data on long-term continence outcomes after vaginal delivery in female IBD patients are lacking. Advice from a gastroenterologist or colorectal surgeon should, therefore, be given to provide the obstetrician with a more balanced view on how present and future bowel function may be impacted by postpartum sphincter/pelvic-floor impairment.

A caesarean section is indicated in case of active perianal disease to avoid postpartum sphincter or pelvic-floor impairment.[8] An IPAA is a relative indication for a caesarean section. Several studies have debated the impact of a vaginal delivery on the functional outcome in terms of faecal continence in post-IPAA

women.[55–59] These studies showed conflicting results.

Overall, the preferred mode of delivery for female IBD patients should be a joint decision made by a multidisciplinary team, consisting of an obstetrician, gastroenterologist and possibly a gastrointestinal surgeon. Additionally, this decision should be made during elective follow-up visits and not at the last minute by the on-call obstetrician who may not be familiar with the patient's history and preferences.

Mistake 9 Assuming there is an increased risk of a relapse after delivery

In clinical practice there are still misbeliefs regarding the risk of a post-partum relapse among patients. However, patients should be counselled that there is no increased risk of disease flare after pregnancy.

One study showed that about one third of IBD patients experience a flare after delivery, which is no higher than the overall risk of a disease flare while not pregnant.[8] Other studies even show that pregnancy can have a beneficial effect on disease course. For instance, a small prospective study followed patients for 3 years before pregnancy and 4 years after pregnancy, demonstrating a decrease in relapses in the year after pregnancy compared with the years before pregnancy.[60]

Mothers who are breastfeeding can also be reassured that the risk of a disease flare is not increased by breastfeeding.[61] A population-based study showed that breastfeeding is not associated with an increased risk of disease flare and may even protect against IBD disease flares in the postpartum year.[62]

Mistake 10 Advising against breastfeeding while using a thiopurine and/or anti-TNF agent

Thiopurine agents (azathioprine and 6-mercaptopurine) are excreted in breast milk in miniscule amounts.[63] The major part is excreted in a mother's milk within the first 4 hours after drug intake. It could, therefore, be advised to avoid giving breast milk during the 4 hours after ingestion. A study of children exposed to azathioprine during pregnancy showed that there was no increased risk of infection in the 15 breastfed babies who were followed up to 4.7 years of age.[64] Also, the PIANO registry has shown no association between breastfeeding and infections or delayed achievement of developmental milestones in exposed children.[65]

Breastfeeding during treatment with infliximab and adalimumab also seems safe and should not be discouraged, considering the widespread and beneficial effects it has.[66] No adverse effects have been reported for the use of maternal biologic agents on breastfed infants. However, it should be noted that the data are still scarce. Infliximab and adalimumab are both excreted in low levels in breast milk[67,68] and it is unclear to what extent these drugs are orally absorbed by the infant. The PIANO registry showed no increased risk of infection or delay in development in infants exposed to infliximab or adalimumab through breast milk.[42] However, the long-term side effects of these drugs are unknown and additional studies are needed to confirm their long-term safety. Drug and antibody levels can be monitored in breast milk and infants, but the relevance of these measurements is unclear.[8]

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Your IBD briefing

Online courses

- 'Pregnancy and IBD' from ECCO [https://e-learning.ecco-ibd.eu/enrol/index.php?id=31].

Algorithms

- 'Pregnancy and IBD' from ECCO [http://www.e-guide.ecco-ibd.eu/algorithm/pregnancy-and-ibd].

UEG Basic Science Course

- 'IBD: models and methods' at UEG Basic Science Course 2015 [https://www.ueg.eu/education/conference-files/?conference=107].

UEG Week sessions

- 'Therapy update: IBD' at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1433&conference=109].
- 'Inflammatory bowel disease: Not all in the genes?' at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1424&conference=109].
- 'Small bowel imaging in Crohn's disease' at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1368&conference=109].
- 'Complications of Crohn's disease' at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1464&conference=109].
- 'IBD: What's new in 2014?' at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1284&conference=76].
- 'Environmental factors and IBD' at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1142&conference=76].
- 'Therapy update: Best use of biologics in IBD in 2014' at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1204&conference=76].
- 'IBD: New therapeutics for specific targets' at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1181&conference=76].
- 'Pregnancy and IBD' presentation from 'IBD course: Practical management of IBD patients' at UEG Week 2010 [https://www.ueg.eu/education/document/pregnancy-and-ibd/94290/].

Society conferences

- ECCO Congress [https://www.ecco-ibd.eu/index.php/congresses-events.html].
- 'IBD & Small Bowel Disease' at ESGE/ECCO Quality in Endoscopy 2013 [https://www.ueg.eu/education/conference-files/?conference=52].

Guidelines

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