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Preconceptional counseling in women with inflammatory bowel disease

Sandro Lanzon-Miller

INTRODUCTION

Inflammatory bowel disease (IBD) is a generic term which predominantly describes two chronic inflammatory bowel conditions, namely ulcerative colitis (UC) and Crohn's disease (CD). IBD is characterized by a bimodal pattern of presentation with the first peak occurring in younger patients between the ages of 15 and 45 years. As such, it coincides exactly with the reproductive age¹. The second peak occurs between 60 and 80 years of age. Ulcerative colitis and Crohn's disease can affect both males and females.

The presence of IBD, the degree of disease activity when conception is desired, the type(s) and quantity(ies) of medication used before or during the pregnancy, as well as any surgery used as part of the management of the condition, all can exert a profound effect on trying to conceive as well as pregnancy outcome. At the same time, pregnancy itself can affect the underlying bowel condition in the female.

UC is an inflammatory bowel condition affecting the large bowel and presenting with continuous inflammation, with or without superficial ulceration, of the mucosal lining. The rectum is nearly always involved in UC, and the inflammation may extend for a variable distance proximally. When the entire bowel is involved, the condition is called pancolitis as opposed to proctitis if the rectum only is involved. UC is common in the

north European population, with a prevalence of 100–200 and an incidence of 10–20 per 100,000 persons^{2,3}. Incidence varies amongst different ethnic groups; for example, Ashkenazi Jews have a higher incidence compared to non-Ashkenazi Jews. In some populations, such as the Japanese, the incidence is very low.

CD, in contrast to UC, can affect both small and large bowel. Moreover, the disease is often discontinuous with so-called skip lesions in which severely inflamed sections of bowel can be immediately adjacent to non-inflamed segments. The inflammatory process is both granulomatous and transmural, and can lead to stricture formation or fistulization between adjacent loops of bowel (entero–entero fistula), other organs such as the bladder (enterovesical fistula), the vagina (enterovaginal fistula) or the skin, especially the perineum can be affected. The inflammatory process can also cause inflammation and subsequent blockage of the fallopian tubes, a feature which may permanently affect fecundity. The incidence and prevalence of CD is approximately half that of UC, but whilst the statistics for UC are static, they are increasing for CD. Although many similarities are present with regard to the types of medication used to treat UC and CD, major differences are also present with important implications for conception and successful outcome. This is particularly true if surgical management has been part of the treatment armamentarium. Disease activity

and the severity of such activity relative to the time of conception also affect the chances of a successful outcome. Because the variables and their combination(s) that impact conception are numerous, it is important to use an individualized approach for each couple thinking about starting a family. Generally the female with IBD seeks counseling prior to contemplating conception, but occasionally a disease-free woman seeks help because the intended father of her child has some form of IBD and she or they are concerned that this may impact the decision or ability to conceive. In either case, it is important to recognize that patients with chronic conditions such as IBD often have experienced negative effects as regards their quality of life and have issues meriting discussion in advance of making such a life-changing decision^{4,5}. All too often, these concerns are unvoiced and health-care providers should provide ample opportunity for patients and their partners to vocalize their concerns in the context of a tactful and sensitive discussion.

MANAGING EXPECTATIONS – A BESPOKE CLIENT CENTERED TEAM BASED APPROACH

It is easily appreciated that what for anyone represents a potentially anxious time is even more so for patients with IBD who plan or manage to conceive. Simply put, such patients are worried about what will happen and have recurring questions including:

- Is it going to be difficult to become pregnant because of my medical condition?
- Is there a chance of my baby having IBD?
- Is it more likely that my baby will have a malformation?
- Is it possible that my medications will harm the baby?
- Is it alright to stop my medication before trying to conceive?

- Is it alright to take my medication during pregnancy?
- Is the condition more likely to flare up whilst I am pregnant?
- Is it alright to take stronger medications if I have a flare up?
- Is the surgery I had going to affect my chances of conceiving?
- Is my condition such that I can't deliver normally?
- Is it possible to breastfeed if I am taking these tablets?
- Is it going to be alright, doctor?

Given these circumstances, it follows that a team approach should be adopted from the earliest stages with the patient (and partner) central to any decision making. For this to occur, the patient must be confident that:

1. She can contact the team at any time – usually this means by phone in the first instance, with the knowledge that she can be seen rapidly in clinic if need be. To easily accomplish this, the patient must be provided with the number of a contact person who she has met before, is always available and the patient can trust. In the UK this is usually a nurse specialist working with the gastroenterologist. Another important role for the specialist nurse is to act as liaison facilitator enabling all parties to co-ordinate their efforts.
2. She can get the same consistent message from the various parties involved in her care rather than contradictory advice from random health-care workers peripheral to her care. This means that *for quality care only senior members of the health-care team should be involved*, because junior team members may lack the in-depth knowledge or not understand the intricacies and subtleties around the pregnant woman with a difficult and often unpredictable condition.

3. The obstetrician, medical gastroenterologist and surgical gastroenterologist are clear in their focus and signed up to the same management plan. Nothing causes as much stress as being on the receiving end of mixed messages.

ISSUES TO BE ADDRESSED DURING PRECONCEPTION COUNSELING

Lifestyle

In addition to the advice that would be provided to any woman contemplating conception, patients with IBD need to consider the following.

Smoking

Smoking cessation help should be offered to all women. Not only is smoking associated with intrauterine growth retardation and smaller babies, but also in patients with CD it is associated with a greater likelihood of relapse and slower treatment response.

Nutrition

Patients with IBD whose disease has been active often have some evidence of nutritional deficits in trace elements, iron stores or vitamins. This is especially true for those with CD. Therefore, early attention to this is especially important. Folic acid supplementation is routinely advised in all women, but is essential in patients with CD who may already be deficient and any IBD patient who has been on sulfasalazine which is a folic acid antagonist. Folic acid supplementation should be started in the preconception period, as the neural tube closes by the 28th day of pregnancy and supplementation begun after that day cannot be relied upon

to prevent neural tube defects (see Chapter 22).

Inheritance

Patients with IBD are usually quite aware of the genetic component to the condition, with UC and CD sufferers both reporting having first degree relatives with some IBD with a frequency ranging from 8 to 13.8%⁶⁻¹⁰. The degree of concordance is greater with CD rather than UC. Studies of monozygotic twins in north European countries show a concordance of 20–50%, whereas for dizygotic twins the figure is only 3–7%¹¹⁻¹⁴. The degree of concordance in UC is lower than that for CD. The fact that the concordance is not 100% in monozygotic twins supports the theory that genetics is just one of several components contributing to the etiology of IBD and that other factors which we do not fully understand also are present.

Most patients simply ask the question: 'What's the risk of us having a baby with ulcerative colitis or Crohn's disease?' This point needs to be discussed frankly with the patient and her partner. How the patient is counseled is important, as there is a tendency to focus on the negatives rather than the positives.

The risk of any offspring having some form of IBD depends on whether one or both parents suffer with the condition. Ethnicity is also a factor, as Jewish populations have a higher incidence of IBD than non-Jews. Yang's empirical study of the observed familial life time risks of developing IBD in a South Californian population revealed that the risks were 1.6% and 5.2% for non-Jews developing UC or CD, respectively^{15,16}. However, for Jews the risks were considerably higher being 4.5% and 7.8% for UC and CD, respectively. If both parents suffer with IBD, then the chances are considerably greater at 36%.

Because patients or couples need easily understandable facts and figures to take away

and think about, I generally phrase the risks as follows. If only one of the parents has IBD, the chance of having a child without IBD is approximately 95%. For Jewish patients, the ballpark figure for being disease free is 90%. If both parents have IBD, the chance of the offspring being IBD disease free all their life is only 65%.

Fertility and fecundity

Definition

Unfortunately, even amongst clinicians there exists an opacity with regards to the correct use of these terms which are often used interchangeably. This circumstance has not been helped by demographers who refer to the ability of having babies as fecundity and the rate at which women actually have children as fertility; biologists and clinicians, on the other hand, seem to use the terms the other way around, namely saying that fertility is the theoretical capacity to have offspring, whereas fecundity is the actual realization of this, i.e. producing live born. To understand the differences seen between patients with active IBD, especially CD, and those with inactive disease, the use of the biologists' definition of fecundity and effective fecundity is revealing. Wood states that fecundity reflects both a woman's ability to conceive and her ability to carry the pregnancy to full term¹⁷. This author goes on to itemize some factors affecting ability to conceive which are of direct relevance to the IBD patient. These include not only what is referred to as 'susceptibility factors' such as the age of onset of menarche and menopause, but also pathological sterility – a factor in CD where inflammation of the fallopian tubes from adjacent inflamed loops of bowel may cause blockage. There are also 'fecundability' issues which include, amongst other things, duration and number of ovulatory cycles, which again are

often affected by severe flare ups of IBD and fetal loss.

Voluntary childlessness and fear

Mountfield *et al.*, working with a group of Australian women with IBD, studied the issue of 'voluntary childlessness' by means of a detailed questionnaire¹⁸. Among respondents, 42.7% described a fear of infertility which was more marked in patients with CD compared to UC and more frequent in patients who had undergone surgery. Mountfield further reported that those who were voluntarily childless were so because of the following fears:

- Fear of congenital abnormalities – 18%
- Concerns about genetic risks – 15%
- Fears about teratogenicity of IBD medication – 30%
- Medical advice about avoiding conception – 35%.

Unfortunately, ill informed counseling by doctors appeared to have been a significant factor in the wish to remain childless in 35% of respondents and this observation underlines the importance of ensuring that preconception counseling is carried out by senior specialists who can not only ensure that the correct information is imparted, but also that the same message is relayed by all who constitute the team.

Fecundity in inactive inflammatory bowel disease

Most studies show that the fertility and fecundity of patients with uncomplicated UC and CD is the same as that of the general population¹⁹⁻²². Therefore, patients with inactive uncomplicated IBD can be reassured that their chance of conceiving is the same as if they did not have the condition.

Fecundity in active inflammatory bowel disease

In contrast to those with inactive disease, patients with IBD with active disease or who have had surgery experience decreased fecundity compared to the general population, a fact which has been demonstrated in several studies^{23–25}. The decrease is probably small and is seen mostly with active CD^{26–28}. The most likely explanation for this situation is the intimate contact of inflamed loops of bowel with the female reproductive organs causing their inflammation. This not only results in blockage of the fallopian tubes, but may also contribute to the dyspareunia reported by some patients; it also may influence the frequency of intercourse during active disease, especially if the CD affects the perineum or pelvic structures²⁹.

Inflammatory bowel disease surgery and fecundity

Olsen *et al.* compared the fecundity of patients before and after restorative proctocolectomy and ileal pouch–anal anastomosis (IPAA) with the fecundity of women in the general population²⁴. Whereas these investigators demonstrated a fecundity ratio of 1.0 preoperatively, following surgery it dropped dramatically to 0.2 ($p < 0.001$). Based on comparative studies between IPAA and ileo–rectal anastomosis in patients with familial adenomatous polyposis, this reduction in fecundity is likely to be associated with the IPAA operation itself, because it does not appear to occur with ileo–anal anastomosis. Perhaps the pelvic dissection associated with IPAA engenders more fibrosis and inflammatory response in the adjacent upper genital tract.

The marked reduction in fecundity following IPAA represents a pivotal point in the preconception counseling of female patients with UC. Based on this finding, the European Evidence Based Consensus on the Management of Ulcerative Colitis document suggests in statement

7K that: ‘in fertile female patients, the option of an ileo–rectal anastomosis should always be considered because fecundity is at risk after IPAA’^{30,31}.

In other words, if a patient with UC has very active colitis which warrants surgery, then rather than proceeding with IPAA which is normally considered the best operation, one could offer the patient, as a temporizing measure, an ileo–anal operation until such time that the patient completes her family, at which stage IPAA can be offered. However, as part of the counseling discussion, patients need to be made aware that because the rectum remains *in situ* following the ileo–rectal anastomosis, they will remain symptomatic. Under such circumstances, this approach is predicated on the degree of inflammation not being too severe.

An alternative that also may be offered to patients requiring surgery for active colitis is to propose a subtotal colectomy (leaving the rectum *in situ*) and formation of an ileostomy, again offering an IPAA at a later stage.

Some patients proceed with the IPAA and if they fail to conceive in the ensuing years decide to undergo *in vitro* fertilization (IVF), with the rate of IVF being greater than in the general population.

Patients with active CD also may have reduced fecundity^{26,31}. This may be related not only to the disease process itself with inflammation affecting the fallopian tube, but also to the effect of previous surgery with subsequent adhesions or alteration of pelvic anatomy itself, and also factors such as pain on intercourse, which is often markedly worse during disease flare up²⁷. This latter point needs to be sensitively explored in any preconceptional counseling session.

Effects of inflammatory bowel disease on the outcome of pregnancy

Most population based studies show a higher incidence of adverse outcomes for patients with IBD^{28,32,33}. Cornish *et al.* carried out a large

meta-analysis to assess the risk of adverse outcomes in pregnant women with IBD¹⁹. The 12 studies included some 3907 patients with IBD and 320,531 controls. The analysis confirmed significant increases in adverse outcomes as follows:

- Prematurity x 1.87 (95% CI 1.52–2.31)
- Low birth weight x 2 (95% CI 1.38–3.19)
- Cesarean rate x 1.5 (95% CI 1.26–1.79)
- Congenital abnormality x 2.37 (95% CI 1.47–3.82)

Interestingly, the finding of an increase in congenital abnormalities was not present in four out of the 12 studies, but only in the later and larger studies. Further, the increase was only present in the UC subset of patients ($p < 0.009$) and not found in CD ($p = 0.06$). Similar findings were also noted by Mahadevan *et al.* in a population based study³⁴. However, the question of whether UC was a predisposing factor for congenital abnormalities was looked at in another population based study³⁵. Norgard *et al.* noted a slight increase in some forms of selected abnormalities (e.g. limb deficiencies), but overall there was no increase in congenital abnormality compared to the general population.

In general, the adverse outcomes described above have been presumed to be associated with disease activity at the time of conception^{35,36}. Whilst this was not the case in the Mahadevan study, a most prudent approach suggests that it is best to try and conceive when the disease is under good control³⁷. All subsequent relapses need to be treated aggressively to bring the disease back under control.

Effects of pregnancy on inflammatory bowel disease

It is impossible to predict how the pregnancy will affect underlying IBD. The relapse rate is about 33%, the same as in the non-pregnant

state. Approximately one-third of patients will experience a worsening of their condition, one-third will remain the same and one-third will experience an improvement^{38,39}.

Effects of inflammatory bowel disease medication on conception and outcome

The effects of IBD drugs on conception and pregnancy often form the main focus of the patient's anxiety. During counseling it is important to understand the natural fears that patients have about drugs causing malformation. *It is equally important to get across the most important message that will need to be reiterated at every encounter, which is that the best outcome for the baby is for the mother to be as well as possible throughout the pregnancy and that virtually whatever is required to achieve this state must be done.* At the end of the discussion, patients must understand that it is a balance of achieving the benefit of treatment (or deterioration if the drug is withdrawn) against possible risks.

A simple and easily understandable analogy that I always use during counseling goes as follows. I describe the fetus as being akin to a space man inside a space capsule. The mother is the space capsule. The survival and well-being of the spaceman depends on the space capsule being in good working order. In the same manner, the best outcome for the fetus is for the mother to be in the very best of health that can be achieved.

Drugs and the fetus

IBD drugs that can be used pre/postconception

5-Aminosalicylic acid (mesalazine/mesalamine – FDA category B) In conventional doses, this agent is safe. Rahimi *et al.*'s meta-analysis did not reveal concerns about its use⁴⁰. They obtained the following odds ratios (OR) for the following endpoints: congenital abnormalities

OR 1.16, stillbirths OR 2.38, spontaneous abortion OR 1.14, preterm delivery OR 1.35 and low birth weight OR 0.93. Whilst the OR was 2.38 for stillbirths, there were very wide confidence intervals (95% CI 0.85–8.72) and so it was not significant. Historical concerns about sulfasalazine have not been borne out in population based, case–controlled studies⁴¹.

Corticosteroids (FDA category C) (prednisolone/budesonide/hydrocortisone) Steroids are commonly used in IBD in the treatment of an acute flare up and, as such, there is a pressing need to get the condition under control. It is in this context that a judgment must be made regarding their use. A prospective case–controlled study by Gur *et al.* of 311 women using systemic steroids in the first trimester concluded that glucocorticosteroids did not constitute a major teratogenic risk⁴². Additionally, this study did not find an increase in cleft palate which had been reported in other studies^{41,43}. Given these data, the use of steroids in a flare up is an appropriate therapy.

Thiopurines (FDA category D) (azathioprine (AZA), mercaptopurine) Many of the data on these agents are based on their extensive use in patients with organ transplant or rheumatological conditions such as systemic lupus erythematosus (SLE). Despite the FDA classification of category D, most case studies in both the transplantation setting and the IBD literature do not show a significant increase in congenital malformation^{44,45}. Based on the favorable human data, most gastroenterologists recommend the continuation of azathioprine, although it crosses into breast milk so that manufacturers caution against breastfeeding. The evidence for clinical harm, however, is poor.

Cyclosporine/ciclosporin (FDA category C) Cyclosporine can be used in severe colitis in an attempt to avert colectomy, which is associated with a high rate of fetal mortality⁴⁶. There

is no evidence that it exerts any statistically significant teratogenic effect, although some evidence suggests that it may be associated with prematurity and be more likely to cause maternal hypertension⁴⁷. Because it crosses into milk, breastfeeding is contraindicated.

Infliximab (FDA category B) Infliximab is a monoclonal anti-tumor necrosis factor (TNF) antibody used when a patient with IBD fails to respond to other therapies. Evidence from the Infliximab Safety Database, the TREAT registry, OTIS (Organisation of Teratology Information Specialists) and the postmarketing reports collected by the manufacturer which describe several hundred patient outcomes do not provide significant evidence of teratogenicity^{48,49}. In addition, Mahadevan reported a series of ten patients intentionally treated by regular infusions throughout their pregnancy which failed to show any teratogenic effects⁵⁰. Infliximab does not cross the placenta until about week 24 of gestation.

IBD drugs which must never be used in pre/postconception

Methotrexate (FDA category X) Methotrexate is a folic acid antagonist and interferes with DNA synthesis. It is both teratogenic and acts as an abortifant⁵¹. Because it remains detectable in tissue for a long time, both the intended father (if he has been on it) and the woman contemplating conception must come off it 6 months before pregnancy is attempted, and reliable contraception must be used during this washout period.

Thalidomide (FDA category X) Use of this known teratogen has been limited to complex patients who failed on other treatments. Thalidomide inhibits TNF by increasing degradation of TNF mRNA. The devastating fetal effects (phocomelia) of this agent are well documented. As with methotrexate, thalidomide

should be stopped by the IBD patient (including the intended father if he is on it, see below) for at least 1 month and preferably longer before contemplating attempting to conceive and reliable contraception must be used during this washout period.

Mode of delivery

The mode of delivery should be decided by normal obstetric criteria. With quiescent or mildly active disease, vaginal delivery remains the norm. This includes patients with either an ileostomy or a colostomy (ECCO statement 11E)⁵². However, counseling should also cover special situations where a planned cesarean section should actively be discussed. The two special circumstances are active perianal CD and UC patients with IPAA.

Delivery in women with perianal Crohn's disease

In a study by Ilnyckji *et al.*, out of 54 patients with IBD who delivered vaginally, 15 had perianal CD. Of these, four had active disease and all reported a deterioration in their condition following vaginal delivery⁵³. In contrast, in 11 patients with inactive CD, none reported deterioration. This finding supports the clinical practice of recommending a planned cesarean section in active perianal CD and allowing a trial of vaginal delivery in inactive CD, albeit with a low threshold for converting to cesarean section.

Delivery in women with ileal pouch–anal anastomosis

The general recommendation for IPAA patients is to have a cesarean delivery to avoid the risk of damage to the anal sphincter. Unlike other patients, the integrity of the anal sphincter is

all that IPAA patients have to keep them continent. This is the reason why we normally advise delivery by cesarean in IPAA patients. Despite this clinical truism, there is little evidence to support this recommendation⁵⁴. This dichotomy needs to be discussed with the patient at an early stage in her care, and the patient's decision should be recorded in the case notes for the obstetric care team to be aware of as the pregnancy progresses. If, after counseling, the patient still desires to attempt vaginal delivery, then the threshold to convert to cesarean should be low and no instrumentation should be attempted

Inflammatory bowel disease affecting the intended father

There is no evidence that IBD *per se* affects male fertility. However, surgery for IBD and medication used to treat the condition may have an effect on male fertility.

Surgery in the intended father Impotence, usually in the form of erectile dysfunction or retrograde ejaculation, following either proctocolectomy or IPAA surgery is a potential problem. A review of this topic by Lindsey and Mortensen quoted a risk of sexual dysfunction in the order of 1–3% after pelvic surgery, but these authors conceded that partial impotence or retrograde ejaculation may be twice as common when it is specifically sought by carefully structured questionnaire⁵⁵. They also made the suggestion that consideration be given to offering storage of semen prior to IPAA in order to avoid this potential problem. The importance of this proposal is that if the male partner of the woman is considering pregnancy suffers with UC and is likely to require pelvic surgery in the form of a IPAA, then counseling needs to address this issue. The options are either to try to postpone the pelvic surgery until such time as conception has been achieved or, if this is not practical, to

see whether storage of semen can be arranged. Should the man be unfortunate enough to be in that small percentage in whom impotence occurs, then there remains the fall back option of using the stored semen to enable assisted conception to occur

Medication in the intended father Whilst many of the drugs used in treating IBD in the male are of no known concern with regards to preconception issues, three need special consideration, namely, sulfasalazine because of its effect on fertility and, more worryingly, methotrexate and thalidomide because of their devastating effects on the fetus.

Sulfasalazine is a folic acid antagonist which can cause a dose related decrease in sperm motility and total sperm count. There is no evidence that it is teratogenic^{56,57}. This is not a problem with the other 5-aminosalicylic acids (5-ASAs). It is important to recognize that although sulfasalazine is a folic acid antagonist, these effects are not reversed by ingesting additional folic acid. On the other hand, consideration may need to be given to withdrawing the sulfasalazine in the male patient and substituting the newer 5-ASA compounds if there has been difficulty in getting the female partner pregnant.

Methotrexate is a dihydrofolate reductase inhibitor and interferes with DNA synthesis. This drug is used in patients with active or relapsing IBD, usually CD patients who are resistant or intolerant to azathioprine. Because methotrexate is both an abortifacient and teratogenic, it is crucial that the male partner stops using it at least 6 months before contemplating attempting to inseminate his partner and two reliable forms of contraception continue to be used during this 'washout period'.

Thalidomide is an anti-TNF inhibitor used in only a very small number of patients who have failed on to respond thiopurines or methotrexate. Because of its well known and devastating teratogenic effects (phocomelia) it is essential

that exactly the same precautions need to be undertaken as with methotrexate.

Because both methotrexate and thalidomide are only used in IBD patients who have had difficult or resistant IBD, a very careful consultation with the intended father's gastroenterologist needs to be undertaken because of the consequences of embarking on this course of action.

CONCLUSION

Preconceptional counseling of the patient with IBD needs to be accomplished by an experienced specialist in order to provide consistent evidence-based advice. Such advice must be sensitive, tailored to the individual circumstances and disease type, and balanced in all regards. The aims are multiple:

1. If at all possible, to conceive when the disease is under control;
2. Regardless of the degree of activity, all efforts need to be made to keep the disease under control;
3. All flare ups should be treated very actively. The majority of IBD medications used are safe in pregnancy.

The analogy of the fetus being like a spaceman inside the mother ship must be introduced from the start to underline that fact that a successful outcome depends on the mother being kept well and in a good state of health.

Finally, although there is a slight increase in adverse pregnancy outcomes in patients with IBD, the majority will, with good care, deliver healthy babies.

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