

## LEADING ARTICLE

## Inflammatory bowel disease in pregnancy

E M Alstead, C Nelson-Piercy

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Women and men with inflammatory bowel disease (IBD) frequently express concerns about fertility and pregnancy. The evidence suggests that women with IBD can expect to have a normal pregnancy outcome provided they have inactive disease. They have an increased risk of having a small or premature baby but the majority will have a normal outcome of pregnancy. The commonly used drugs appear to be safe and well tolerated in pregnancy. There remains a need for further studies in this area to help in the difficult decisions about the management of IBD around the time of conception and during pregnancy.

## PREGNANCY OUTCOME

Several population based case control studies have not demonstrated an increased risk of spontaneous abortion, stillbirth, or neonatal death. There is a significant risk of preterm delivery (<37 weeks) and low birth weight (<2500 g) in mothers with IBD.<sup>9–13</sup> One study has also demonstrated that mothers with CD have an increased risk of giving birth to small for dates babies. In this study, congenital malformations were more commonly reported in babies of mothers with UC than CD or controls (7.9% v 3.4% v 1.7%).<sup>14</sup> Major abnormalities are generally reported in 2–3% of pregnancies: there is no clear explanation for the increase in congenital abnormalities in the children of mothers with UC.

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The likelihood of a flare up of IBD is probably unchanged during pregnancy and the puerperium.<sup>15</sup> If a woman conceives with active IBD, it is likely to remain active throughout the pregnancy. Approximately two thirds of women with active CD at the time of conception will continue to have active disease throughout the pregnancy. First trimester exacerbation has been associated with prematurity and multiple exacerbations with low birth weight.<sup>16</sup> Although it seems that disease activity is an important factor increasing the risk of both prematurity and low birth weight,<sup>16, 17</sup> there is probably an underlying risk for all women with IBD, the reasons for which are not clear.<sup>18</sup>

## DRUG TREATMENT

In view of the risk of preterm delivery and small babies with active IBD, the role of drugs in the maintenance of remission and the advisability of continuing them during pregnancy should be discussed at the earliest possible opportunity in all female patients. Most women's initial reaction is that they would not want to contemplate taking any sort of medication if they were planning conception or became pregnant. Therefore, an informed pre-pregnancy discussion, with the patient (and her partner if appropriate), facilitates a decision made in partnership with clinicians and the formulation of a management plan using the available data. The balance between continuing

## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disorder affecting young adults in the reproductive years. Women and men with IBD frequently express concerns about fertility and pregnancy. Some of these concerns are about the effect of the disease on their relationships and ability to have healthy children. Other major worries relate to the effects of medication which they may be advised to take either to prevent disease recurrence or to treat active disease.

## FERTILITY

Infertility affects 8–10% of healthy couples. Patients with IBD have fewer children than expected for the population<sup>1</sup> and this may in part be due to voluntary childlessness. Relationship difficulties, body image problems, fear of pregnancy, or inappropriate medical advice may all contribute to a decision not to have children.<sup>2</sup> Women who develop IBD before their first pregnancy have fewer children than population controls or women who develop IBD after they have had a child.<sup>3</sup> Women with ulcerative colitis (UC) have normal fertility, except after surgery.<sup>4, 5</sup>

Women with inactive Crohn's disease (CD) also have normal fertility although fertility is decreased with active disease. Control of disease activity appears to restore normal fertility.

Men are also concerned about their fertility. Sulphasalazine causes reversible semen abnormalities and infertility in 60% of men. This effect is reversed two months after withdrawing the drug.<sup>6</sup> 5-Aminosalicylate drugs (5-ASAs) do not have this effect. Azathioprine does not impair male fertility.<sup>7</sup> Concerns have been expressed from one small retrospective study about the possible teratogenicity of 6-mercaptopurine. There is no other precedent for this effect and the findings in this study could have occurred by chance.<sup>8</sup>

See end of article for authors' affiliations

Correspondence to:  
E M Alstead, Digestive  
Disease Research Centre,  
Bart's and the Royal  
London School of  
Medicine, Whitechapel,  
London E1 2AD, UK;  
e.m.alstead@mds.qmw.ac.uk

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**Abbreviations:** IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; 5-ASAs, 5-aminosalicylate drugs;

maintenance treatment and stopping it, which is likely to increase the chance of needing to treat an acute exacerbation, needs to be weighed up for each individual.

The drugs most commonly taken by patients with IBD who are pregnant are the 5-ASAs and sulphasalazine. The paper by Nørgård *et al* in this issue of *Gut*<sup>19</sup> provides the best available data on the use of 5-ASA preparations during pregnancy [see page 243]. Over a 10 year period, using a population based prescription registry, the Danish birth registry, and a hospital discharge registry for North Jutland county, the authors were able to identify all prescriptions for 5-ASAs in the three months prior to or during pregnancy (148) and all pregnant patients who did not have prescriptions (19 418), including those patients with a diagnosis of IBD who did not have prescriptions.

Logistic regression analysis demonstrated no significant increase in congenital abnormalities. An increased risk of stillbirth and premature birth was found in women with a diagnosis of UC. The data were controlled for the effects of age, parity, and smoking but not disease activity. From this study, as from many previous studies, it is not possible to infer that the adverse effect on pregnancy is due to the drug. Despite the fact that it is generally advised that it is safe to take sulphasalazine or 5-ASA preparations in pregnancy, many women choose to stop all medication prior to conception and it is therefore likely that those who receive prescriptions for 5-ASAs prior to or during pregnancy have active disease. 5-ASA drugs are related to sulphasalazine, which is now less commonly used in Western Europe and the USA. The sulphapyridine moiety in sulphasalazine is a folic acid antagonist, theoretically likely to cause neural tube defects as well as cardiovascular and urinary tract abnormalities and oral clefts.<sup>20</sup> In another large epidemiological study, published last year, Nørgård and colleagues<sup>21</sup> shown that there was no evidence of increased incidence of congenital anomalies in Hungarian women taking sulphasalazine during pregnancy.

“The Nørgård study confirms an association between the use of steroids and stillbirth”

Some women who suffer an exacerbation of IBD in pregnancy may need to take steroids. An association between steroid use and low birth weight has previously been demonstrated.<sup>16</sup> The Nørgård study confirms an association between the use of steroids and stillbirth. Steroids have not been associated with stillbirth when used for the treatment of other medical conditions and again, the adverse factor would appear to be disease activity. The only study looking specifically at the use of steroids to treat IBD in pregnancy did not find any association with complications of pregnancy.<sup>22</sup>

In women with more severe IBD, the use of second line agents during pregnancy may need to be considered. Generally, this will be continuation of azathioprine to maintain remission. Although there is extensive experience of the use of azathioprine in the treatment of transplant recipients and rheumatology patients, there have been only small retrospective studies in IBD of the use of azathioprine and 6-mercaptopurine during pregnancy.<sup>23 24</sup> Cyclosporin is not teratogenic and has been suggested to be safer than surgery in a pregnant woman with fulminant UC.<sup>25</sup> Starting cyclosporin in pregnancy is a different issue to that of continuing a drug such as azathioprine, upon which the patient is stabilised prior to pregnancy. As hypertension is a common side effect of cyclosporin therapy and fits have also been reported, the side effect profile of cyclosporin would suggest that it should be used with extreme caution, especially if started in late pregnancy.

In the post-marketing surveillance of infliximab used in the treatment of CD and rheumatoid arthritis, a number of pregnancies have been reported with no increase in adverse

events.<sup>26</sup> Unfractionated heparin has occasionally been used to treat refractory UC<sup>27</sup> and has been extensively used in the treatment of thromboembolic disease in pregnancy. Antibiotics, especially metronidazole and ciprofloxacin, have been reported to be safe in short courses in pregnancy.<sup>28 29</sup>

“Female and male patients starting methotrexate must be using a reliable form of contraception and should avoid conceiving for six months after stopping the drug”

Methotrexate, a folic acid antagonist, like sulphasalazine, is however highly mutagenic and teratogenic, causing neural tube and other defects. Female and male patients starting methotrexate must be using a reliable form of contraception and should avoid conceiving for six months after stopping the drug. Should conception occur in a woman unable to consider a termination, high dose folic acid treatment for the remainder of the pregnancy may slightly reduce the risks to the fetus.<sup>30</sup>

## SUMMARY

Women with IBD can expect to have a normal pregnancy outcome provided they have inactive disease. They have an increased risk of having a small or premature baby, in the order of about twice that for the general population. It is important to remember that this is still a small risk, and the majority of women with IBD will have a normal outcome of pregnancy. The evidence suggests that it is disease activity which is the main adverse factor predisposing to prematurity and low birth weight babies. The commonly used drugs, in particular the 5-ASAs and sulphasalazine, appear to be safe and well tolerated in pregnancy. The paper by Nørgård *et al* provides additional information which can be used to inform decisions made in partnership between clinicians and their patients. Steroids are also safe and should be used for exacerbations of active disease. The use of other agents is more controversial but women who need to remain on azathioprine or 6-mercaptopurine to maintain remission may decide to do so after full discussion with their clinician. There remains a need for further good studies in this area to help in the difficult decisions about the management of IBD around the time of conception and during pregnancy.

## Authors' affiliations

**E M Alstead**, Bart's and the London School of Medicine, and Whipps Cross University Hospital, London, UK  
**C Nelson-Piercy**, Guys and St Thomas's Hospital Trust, and Whipps Cross University Hospital, London, UK

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