Pregnancy and inflammatory bowel disease

What to do with the medication?

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Inflammatory bowel disease (IBD) medications considered safe to use in pregnancy are the corticosteroids, sulfasalazines, 5-aminosalicylate preparations, thiopurines, antitumour necrosis factor agents and ciclosporin. The best pregnancy outcomes occur in women whose IBD is in remission at conception and remains so throughout the pregnancy. Most of these women will need to continue taking maintenance medication, and some will need extra treatment to control flares.

Remember

Fertility is usually normal

- The fertility of patients with inflammatory bowel disease (IBD) is normal, with the exception of a small number of patients who have had pelvic surgery (proctectomy, J pouch formation) or who do not ovulate due to low weight or malnutrition.
- There is no evidence that the oral contraceptive pill (OCP) affects IBD activity.
- Although it is possible that women with significant small bowel disease or enhanced transit times due to active disease may malabsorb the OCP, this is rare. Women with vomiting or severe diarrhoea for more than 24 hours should follow the missed pill instructions for the OCP they are taking.
- There is no evidence that IBD medications affect fertility in females. Higher levels of voluntary childlessness are seen in women with IBD, and may reflect unwarranted concerns, indicating the need for better education about IBD and pregnancy.[1]
- In males, methotrexate and sulfasalazine cause reversible oligospermia and reduced sperm motility. In men wishing to father a child:
  - sulfasalazine should be changed to a 5-aminosalicylate (5-ASA) preparation
  - methotrexate should be stopped four months before planned conception.

IBD activity affects pregnancy outcome

- The best pregnancy outcomes occur in women in whom IBD is in stable remission at the time of conception and then remains in remission throughout the pregnancy.
- If conception occurs at a time of quiescent disease, the risk of relapse is the same as in nonpregnant women. Disease activity can be assessed either endoscopically before conception or with faecal calprotectin testing before and during pregnancy. Most patients will need to continue taking maintenance medication to remain in remission, and a small number will need extra treatment introduced in pregnancy to control flares.
- Active IBD at conception is associated with ongoing activity throughout pregnancy. Active IBD during pregnancy increases rates of adverse pregnancy outcomes including intrauterine growth restriction, preterm birth and small weight for gestational age, and may also increase miscarriage rates.[2]

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Safe medications

- Corticosteroids, sulfasalazine, 5-ASAs (mesalazine, balsalazide, olsalazine), thiopurines (azathioprine and 6-mercaptopurine; off-label use for IBD) and antitumour necrosis factor (anti-TNF) agents (adalimumab, infliximab) are safe to use during pregnancy and when breastfeeding, with no increase in congenital abnormalities or adverse pregnancy outcomes.[3]
- Recent data from a large US registry cohort have suggested there is no link between use of intravenous hydrocortisone and prednisolone in the first trimester and increased rates of cleft palate.[4]
- Women using sulfasalazine, those with significant length ileal disease and those on low residue diets require increased folate supplementation (2 mg/day).
- Thiopurines cross the placenta. They have a TGA category D for use in pregnancy because of animal data suggesting teratogenicity at high IV doses. Large case-control and observational studies in renal transplant and IBD, and a meta-analysis show no increase in congenital anomalies or adverse pregnancy outcomes and they are considered safe in pregnancy and breastfeeding by the European Crohn's and Colitis Organisation (ECCO).[3] The TGA does not use observational human data in allocating categories. A small study of infants of exposed in utero to thiopurines (30 women) revealed transient mild anaemia postpartum in 60% of the infants, the clinical significance of which is uncertain.[5] Full blood testing post-delivery is not currently recommended.
- Anti-TNF agents are transferred across the placenta from gestational weeks 16 to 18 in increasing amounts, resulting in neonatal levels higher than maternal levels at birth. Despite this, no adverse outcomes or developmental issues have been reported. For women whose IBD is in remission, current international guidelines suggest stopping anti-TNF agents at week 30 to reduce transfer of the drug across the placenta as only small numbers of children have been followed to age 1 year and long-term safety has not been established. This is not associated with an increased risk of relapse.[6] Patients can restart the medication following delivery. Conversely, women with evidence of active disease (e.g. elevated faecal calprotectin level or symptoms prior to anti-TNF agent dosing) or who have not been in stable remission for long can continue anti-TNF antibodies throughout pregnancy as there is no current evidence of harm and continuation will reduce risk associated with active disease.[3,6]
- Recent data suggest infants exposed to both thiopurines and anti-TNF agents during pregnancy have a small increase in the risk of standard childhood infections during the first year of life. Mothers of infants exposed to combination therapy should be counselled that any signs of infection in these infants require prompt assessment by a doctor.[6]
- A meta-analysis of studies of ciclosporin therapy in organ transplantation suggests ciclosporin use in pregnancy is safe but blood pressure needs to be carefully monitored and a low dose (2 mg/kg) is suggested.[7] As ciclosporin is readily transferred in breast milk and may reach therapeutic levels in infants, breastfeeding is not recommended.
- There are no data on the use of the immunosuppressant tacrolimus in women with IBD who are pregnant. However, ciclosporin and tacrolimus are primarily used in the short term for salvage therapy in patients with acute severe colitis, and alternatives exist, such as infliximab.

Medications of concern

- In women, methotrexate is an abortifacient and potent teratogen, with maximum effect at gestational weeks 8 to 10. Women should be warned to avoid conception while taking methotrexate and to cease taking it four to six months before trying to become pregnant, with at least one menstrual cycle before conception. Breastfeeding is contraindicated as the drug is excreted in breast milk and accumulates in the fetus. There are no data linking male methotrexate use and birth defects. There are reports of reversible oligospermia in men taking methotrexate; however, most were also taking other immunosuppressive drugs. A practical approach is to offer sperm testing to men taking methotrexate whose partners are having difficulty conceiving, and/or consider sperm banking prior to commencement of the drug.
- Allopurinol is now used in conjunction with the thiopurines azathioprine and 6-mercaptopurine to reduce production of the liver-toxic thiopurine metabolite 6-methylmercaptopurine and enhance levels of the active thiopurine metabolite 6-tioguanine (thioguanine) nucleotide. Both allopurinol and mycophenolate disrupt purine synthesis. Despite a case series of 14 women who used allopurinol throughout pregnancy that suggested allopurinol is safe, there was one case of multiple malformations similar to mycophenolate embryopathy in a series of 31 babies exposed in the first trimester.[8,9] If possible, allopurinol use should be avoided during pregnancy, and alternative strategies to reverse shunting used, such as splitting the thiopurine dose to twice daily.
- The antibiotics metronidazole and ciprofloxacin are generally used in short-term courses in the treatment of IBD (off-label use). A large study of 922 women exposed in all trimesters to courses of metronidazole did not show any adverse outcomes.[10] However, its long-term use in pregnancy is not recommended because it is carcinogenic in large doses in rodents. It is excreted into breast milk, but its effects are unknown. Use of ciprofloxacin is not recommended in pregnancy as it affects growing cartilage. It is excreted into

breast milk in very low concentrations and is therefore likely to be safe during breastfeeding in short courses. Guidelines from ECCO recommend avoiding antibiotic use in the first trimester and during lactation.[3]

Mode of delivery

- The mode of delivery in women with IBD is dictated by obstetric needs except in those with perianal fistulating Crohn's disease or active rectal inflammation.
- In women with perianal fistulating Crohn's disease or active rectal inflammation, delivery by elective caesarean section should be considered because vaginal delivery predisposes to perianal laceration and anal sphincter trauma.

Assessment

- Discuss fertility early – many patients have significant concerns that are unwarranted, and pregnancy may be unplanned. Recent evidence from Australia shows a short group education session can be effective in improving reproductive knowledge.[11]
- Discuss knowledge and beliefs about risks of both IBD and medications on pregnancy outcomes.
- Establish how many children are desired and when, and whether the patient has strong wishes regarding the mode of delivery.

Management

- Reinforce the importance of IBD being in remission at conception and during pregnancy.
- Reinforce the safety of most IBD medications.
- Reinforce the ability to breastfeed while taking IBD medications.
- Communicate with both the midwife and the obstetrician early to ensure consistent messages are given to the patient. Women with past or current moderately severe IBD should be managed by a high-risk obstetric clinic or by an obstetrician, particularly if the disease is active.
- Infants exposed to corticosteroids, sulfasalazine, 5-ASAs and thiopurines can have the usual vaccination schedule. Those exposed to anti-TNF agents during pregnancy should not receive live vaccination until 12 months of age. In Australia, the only live vaccine prior to 12 months in the schedule is rotavirus. Catch-up vaccination is not required as children over 6 months of age are at lower risk of significant illness than neonates. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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