Fertility, pregnancy and inflammatory bowel disease

- IBD pregnancies have the best outcome if planned for and if women conceive during remission
- Flares of IBD during pregnancy give a greater risk of harm to mother and baby than most IBD treatments
- Most IBD medications are safe to continue during pregnancy and breastfeeding, but it is important to discuss this with your doctor before pregnancy or as soon as you recognise you are pregnant
- Birth defects are NOT increased by IBD medications except for methotrexate
- Stopping your medication during pregnancy without specialist advice may harm your baby

Crohn's Disease (CD) and Ulcerative Colitis (UC) are the 2 most common forms of Inflammatory Bowel Disease (IBD), frequently affecting people who are contemplating having children. If you or your partner has IBD, you may be wondering about how this will affect your ability to have children, and how pregnancy will affect your IBD.

It is important to discuss these issues early, to help people consider all aspects, well before planning a pregnancy.

The good news is that the great majority of women and men with IBD have normal fertility, and women can expect a normal pregnancy and delivery, and development of a healthy baby.

Remember that a healthy mother is required for a healthy baby.

Pregnancy and Fertility in women WITHOUT IBD

Even in the general population, pregnancy does not progress normally in all cases. Problems or complications affecting the baby's health occur in about 15% of cases.

All pregnancies have a risk of 3 to 5% for birth defects, and at least 15% for miscarriages. Some medical conditions may increase these risks especially when they are not well controlled. Many pregnancies are unplanned, and this is why it is important to control your IBD well in the long term, and understand the implications of IBD on fertility and pregnancy before you are planning a family.

Pregnancy and Fertility in women WITH IBD

Part A: Fertility

Will I be able to conceive?

For Women

Ulcerative Colitis (UC)

If you have UC, your chances of conceiving are unaffected by the disease.

Even if you need to have a colectomy, fertility only appears to be reduced if you have undergone pouch surgery.

Reduced fertility appears to be much less of a problem when colectomy with an ileostomy / stoma – is done. This is an alternative to pouch surgery. Women who may need colectomy should discuss these issues early with their IBD Specialist and surgeon, as with planning good fertility and obstetric results can be achieved.

Crohn's Disease (CD)

If you have well controlled CD, your chances of conceiving are the same as the general population.

When you are having a flare of CD, your chances of conceiving are reduced. This is thought to be due to a number of possible mechanisms:

- Severe inflammation in the small intestine can sometimes affect the normal functioning of the ovaries and the fallopian tubes.
- Previous abdominal operations, especially if adhesions are present.
- Reduced levels of general health, including nutritional status.
- Reduced libido. Complications such as abscesses and fistulae in the pelvic and anal area, and general difficulties associated with living with IBD, such as fatigue, abdominal pain, diarrhoea, and a poor body image, can all contribute.

Special attention should be given to your general nutritional status. It is important to have adequate levels of folic acid, vitamin B12 and iron before pregnancy, since the need for these vitamins and micronutrients increases in early pregnancy. Folic acid is also required to reduce the risk of birth defects.

The good news is that if these issues are addressed and your CD is brought into a remission, your fertility and chance of a healthy baby are generally restored to normal.

For Men

There is no evidence that IBD affects male fertility.

However, for men as well as women, problems such as fatigue and poor body image can affect libido and sexual relationships and make it more difficult to conceive a child.

Abscesses and fistulae in the pelvic and anal regions may also cause some difficulties with erection and ejaculation.

Very rarely, men with IBD who have had a pouch operation, or have had both their colon and their rectum removed by surgery, may have difficulty having an erection. However, this problem is usually temporary or can be successfully treated with medication.

Can I improve my fertility?

For Women

It helps if you can get your IBD under control for at least 3 months before trying to conceive.

As your fertility may be being affected by factors other than your IBD, you may also find it helpful to follow some of the suggestions and tips usually given to couples wishing to conceive a child. For example:

- Try to eat a healthy and balanced diet. If this is difficult because of your IBD, you could discuss with your doctor taking some supplements to ensure you get all the nutrients needed. Normal stores of iron, zinc and vitamin B6 are particularly important for fertility in both men and women.
- For any woman, including those with IBD, it is important to take folic acid supplements 1 month prior to conception and for the first 12 weeks of pregnancy to reduce the risk of birth defects (neural tube defects). The usual recommendation for women without a family history or neural tube defects or medical complications is 05-1mg of folic acid daily unless your doctor has advised otherwise. For women with IBD who take sulfasalazine we recommend a higher dose of 2-5 mg of folic acid daily throughout your pregancy. This is because sulfasalazine can decrease the levels of folic acid in your body.
- Women can improve fertility by maintaining their weight in the normal healthy range, not smoking and avoiding alcohol during pregnancy.
- Regular moderate exercise of around 30 minutes a day can help by improving energy, improving libido, maximising your fitness and keeping your weight in check.

For Men

Men can increase their likelihood of producing plenty of healthy sperm by not smoking, keeping alcohol drinking within guideline limits (not more than 2 standard drinks per day), exercising moderately and avoiding stress.

Please read the following section on medication at conception as these apply to both men and women.

What if I am taking IBD drugs when I conceive?

It is not usually necessary to change the medicines you take for IBD before you try to conceive.

The only exceptions to this are:

1. **Sulfasalazine (Salazopyrin)**

   Sulfasalazine leads to reversible male infertility. This effect is temporary and fertility should return to normal levels within two to three months of stopping the medication.

   There are several good alternatives to sulfasalazine, such as mesalazine, olsalazine or balsalazide, which can usually be used instead. These have the same beneficial effects on IBD control but do not usually affect fertility.

2. Methotrexate

Methotrexate increases the risk of birth defects when taken by either men or women thus these drugs should be stopped after discussion with your IBD treatment team before planning pregnancy, and a safer alternative prescribed.

The most important way of improving your chances of having a healthy baby is to keep the disease under control before and during pregnancy. So if your current medication is working well and is NOT methotrexate, it is usually better not to change your medication

Will my pregnancy be normal?

If your IBD is in remission at the beginning of your pregnancy, your chances of delivering a healthy baby are almost the same as a woman without IBD.

If your disease is active at the beginning of the pregnancy, or you suffer flare-ups during pregnancy, there is a risk of the baby being affected. It is twice as likely that your baby will be premature and will have a low birth weight. This is still a small risk, and the baby is likely to be healthy.

In most cases, the risk of the baby being small or delivered early is related to the disease activity itself, rather than to the medicines you are taking. So, if you are pregnant and your IBD is active, it is best to visit your doctor as soon as possible to discuss how to get your IBD under control.

Should I keep taking my IBD medicines during pregnancy?

It is important to keep your IBD under control while you are pregnant. Active inflammatory diseases do more harm to your growing baby than most IBD medicines.

Many people are afraid to take medications during pregnancy, and this is understandable. This fear is often increased by the TGA classification of medication safety in pregnancy, which is often based on animal studies or theoretical concerns, and this classification system is unlikely to be used in Australia in the future.

The guide IBD doctors use to care for pregnant patients is that of expert agencies such as ECCO (European Crohn's and Colitis Organisation) which classifies medications as safe, probably safe or harmful based on post marketing studies on real patients, and expert experience with these drugs. It has been found that many IBD drugs are safer in real world experience than their "official" ratings, and ECCO guidelines take into account the fact that active disease during pregnancy is more dangerous than most of the medications.

How do IBD drug treatments affect pregnancy?

The majority of drug treatments for IBD are safer for your baby than active disease. However, there are some exceptions, as shown below.

If you are trying to start a family, or if you are already pregnant, do discuss this and your drug treatment with your doctor or IBD team as early as possible.

It is better to avoid disease flares while trying to conceive and while pregnant, so most doctors will recommend continuing with your medication, unless there are clear reasons not to. If the drugs you are on are not thought to be safe, there is usually a good alternative.

5ASAs

- Sulfasalazine (Salazopyrine)
- Mesalazine (Mezavant, Pentasa, Salofalk, Mesasal)
- Olsalazine (Dipentum)
- Balsalazide (Colazide)

5-ASAs have been taken by women during pregnancy for many years and are safe. Sulfasalazine has not been shown to affect fertility in women or to be linked to any birth defects if taken by women. There is very little transfer of these drugs across the placenta to the baby. They can be used as maintenance therapy and during a flare. If you are taking sulfasalazine you are advised to take folic acid supplements (5mg daily). Mesalazine, which is a 5ASA drug without the sulpha component, is also safe.

Methotrexate (eg Methoblastin®)

This immunosuppressive drug sometimes prescribed for IBD, should NOT be taken by either men or women when trying to conceive as there is a risk of birth defects. You should avoid pregnancy if either partner has taken methotrexate within the last three months – or as advised by your doctor. This medication causes birth defects and increases the risk of miscarriage. If you become pregnant whilst taking methotrexate, do not take any more doses and see your doctor urgently.

Corticosteroids

- Prednisolone, (Panafcortelone®, Predsolone®, Solone®)
- Budesonide (Enterocort®, Cortiment®, Budenofalk)
- Hydrocortisone (given intravenously in hospital)

These medicines may be used in pregnancy, but the need to use them indicates poorly controlled IBD and so, if you are on steroids long term (or frequently) you should discuss a better IBD management plan with your treatment team, ideally BEFORE you conceive. There are some

studies suggesting that first trimester use of corticosteroids may increase the risk of cleft lip and/or palate but other studies have not supported this finding. If there is a risk it is likely to be very small. The background risk of oral clefts in any pregnancy is 1-2 in 1000 births and this may be increased to 3-6 in 1000 with corticosteroid use.

Rectal steroid preparations (enemas and suppositories) may also be used right through pregnancy if required.

Thiopurines Azathioprine (eg Imuran®)

- 6-mercaptopurine (6MP) (eg Puri-Nethol®)

These are immunosuppressive drugs used to maintain IBD control if 5ASA drugs alone are insufficient and are prescribed for about 40% of people with IBD. The aim of these drugs is to make the body's immune system less responsive. This has the effect of reducing inflammation in IBD (as inflammation is part of the immune system's processes). However, a less-responsive immune system may make a person slightly more susceptible to infections, especially if you are not having regular blood test monitoring on these drugs.

These immunosuppressive drugs have not been shown to affect fertility or pregnancy, so doctors advise continuing with azathioprine or 6-MP, rather than risking a flare up of the IBD.

The clinical experience of pregnancy outcomes with these drugs is now very large, and it is clear that the risks of active IBD are greater than the risks of taking these drugs for both mother and baby.

Therefore, IBD doctors will advise the continued use of azathioprine and 6-MP during pregnancy, as it is deemed that there is more risk to the baby if the mother becomes unwell.

Allopurinol (Zyloprim®)

Some people need to take this medication with azathioprine or 6 MP. As yet we do not have enough information from studies to recommend continuing allopurinol during pregnancy, and it may be unsafe, so it is best to discuss this with your doctor prior to conception. Your doctor will likely stop the allopurinol and find another medication to treat your IBD during pregnancy, or continue azathioprine without allopurinol.

Biologics - Anti-TNFα Therapy

- Infliximab (Remicade®, Inflectra®)
- Adalimumab (Humira®)

These drugs affect the immune process and are used in CD, when other drugs have not worked.

As they are more costly, the PBS currently restricts them to people whose IBD is not controlled by 5ASA's and / or thiopurines and / or corticosteroids.

The clinical experience available so far across thousands of exposed pregnancies suggests that these drugs are safe to use in pregnancy.

The evidence currently available is that pregnancy outcomes for women, who are taking these drugs during pregnancy are similar to women with IBD not exposed to Anti-TNFs, and to the general population.

Infliximab and Adalimumab do cross the placenta into the baby during the last trimester. Infliximab has been detected in cord blood, and in infants up to 12 months of age, if exposed in the last trimester of pregnancy. For this reason, if the mother is not at high risk of a flare, some doctors avoid using infliximab and adalimumab during the last trimester.

If the newborn has been exposed to Anti-TNFs in the last trimester of pregnancy, LIVE vaccines should be avoided for at least the first 12 months of life, unless the baby has a blood test to document a zero level of the Anti-TNFα drug in his or her system.

Most vaccines scheduled for babies are not live; **Rotavirus is an important exception and should be withheld if Infliximab (Remicade, Inflectra) or Adalimumab (Humira) has been administered in the last trimester. Some "travel" vaccines are also "live" vaccines and should not be given to babies under 12 months of age if mother has been administered anti-TNF's in pregnancy.**

Vedolizumab

We do not have much experience with Vedolizumab (Entyvio®) yet. So far there have been no concerns about birth defects from animal data. It is best to discuss with your IBD Doctor as experience is growing as the drug is more widely used.

Cyclosporin

This is a very strong immunosuppressant drug which is rarely used now in IBD (only to prevent emergency Colectomy) and has a significant rate of serious side effects. However, it has not been associated with specific harm to an unborn baby. This treatment would not be suggested unless you had a very severe (acute) colitis not responding to intravenous steroids. Cyclosporin in this situation is given to try to avoid the need for emergency surgery to remove the bowel, in which case its use may be justified. This is a rare scenario and would be discussed with you prior to using this drug.

Antibiotics

- Amoxicillin
- Metronidazole
- Ciprofloxacin

These are often used in IBD to treat abscesses or perianal disease, which can be uncomfortable, especially during later stages of pregnancy. They appear relatively safe to use if needed. Studies have not shown an increased risk of negative pregnancy outcomes such as spontaneous abortion, prematurity, low birth weight or malformations.

Drugs for symptom relief of IBD in Pregnancy.

Antiemetics

Metaclopramide and Vitamin B6 have been reported to be safe.

Antidiarrhoeals

Loperamide is considered safe.

Cholestyramine is considered safe

Diphenoxylate (Lomotil): If this is needed, discuss with your doctor.

Pain relief

Paracetamol is acceptable for use as directed on the packaging, but discuss pain with your IBD doctor if you need regular analgesia, as it suggests your IBD may not be well controlled.

Paracetamol is the safest choice for mild to moderate pain, or a high temperature.

Codeine is considered safe, although often has a constipating effect. If taken in high, regular doses toward the end of pregnancy, discuss with your doctor.

What about nutritional therapy?

Some people with Crohn's take special liquid feeds called elemental or polymeric diets as treatment. These diets may be safely used during pregnancy to treat active disease or as a nutritional supplement. They should ALWAYS be supervised by a professional dietitian and discussed with your IBD treatment team. Exclusion diets are not recommended for pregnant women without medical supervision as they can put you and your baby at risk of nutrient deficiencies.

What investigations for my IBD can I have during pregnancy?

If your disease flares during pregnancy you may need further investigations. It is important to make your doctor aware of your pregnancy before any procedure, as it may be possible to delay it until after delivery. Generally flexible sigmoidoscopy, rectal biopsy, ultrasound, MRI (without gadolinium contrast), endoscopy and in some instances colonoscopy can be carried out during pregnancy. The safest time for these investigations is during the second trimester, but tests are sometimes needed more urgently to keep the mother healthy, and are relatively safe at other times. Investigations which involve x-rays and radiation should normally be avoided by pregnant women unless absolutely essential. This includes CT scans.

What about surgery while I am pregnant?

Surgery is very rarely indicated during pregnancy, but very occasionally there are situations when an operation is the only option. In these cases, the risk to the baby is less than if the operation is not performed.

How can I increase the likelihood of having a healthy baby?

You can increase the likelihood of having a healthy baby in a number of the following ways:

Maintaining remission

For women with IBD, the most important message is that if your disease is under control then the baby is more likely to be healthy. Therefore it is important to take your medicines as directed to ensure that you are as well as possible before conception. It is also important to consult your doctor at an early stage if you fail to gain weight as expected or think you have a flare of IBD.

Diet

For any woman during pregnancy a balanced and varied diet with sufficient calories, vitamins and minerals is important for the growth of their baby. Having IBD, the increased nutritional demands of pregnancy may mean you may need to supplement your diet, particularly if you are underweight or have active disease. It is best to seek the advice of a dietician.

If you are taking corticosteroids like prednisolone, calcium and vitamin D supplements are important to prevent bone loss: The recommendation is 1500 mg of calcium and 800 IU of Vitamin D daily.

If you have Crohn's Disease and have had surgery to remove the terminal ileum (the end of the small intestine), you may need regular injections of Vitamin B12 to prevent anaemia.

Iron deficiency is quite common in IBD and iron supplements are often necessary to meet the increased demands of pregnancy. Check with your specialist before taking any supplements.

Fish oil supplements are quite often used by people with IBD. Research shows that for women with IBD who may be at increased risk of preterm birth and miscarriage, these supplements are not harmful and may be of some benefit. Research is ongoing.

Exercise

Regular exercise can help to keep you healthy. Gentle exercises such as walking, yoga and swimming are recommended.

Smoking

It is important for any woman not to smoke during pregnancy, as smoking harms the baby and leads to low birth weight with a higher risk of deformity and miscarriage. It also increases risks of blood clots during pregnancy and other complications.

The risk is even greater for women with IBD as smoking increases the activity of Crohn's and increases the need for surgery and medication.

The effects of smoking with UC are inconclusive; it certainly causes the same direct damage to the baby as in any non-IBD pregnancy but it may also reduce the severity of UC disease activity. On balance it is widely accepted that the damage caused by smoking is far more than any possible reduction in disease activity.

Alcohol

Drinking excess alcohol during pregnancy can seriously harm your baby's development. It is best to avoid alcohol during pregnancy.

Will pregnancy make my IBD worse?

Pregnancy has little effect on either UC or Crohn's. Overall about one third of women will have a relapse while they are pregnant, and this is similar to non-pregnant women with IBD over that period of time. Women with UC are slightly more likely to flare than non pregnant women.

A recent European study of women with IBD found that the rate of relapse decreased in the years following pregnancy. This suggests that pregnancy may sometimes have a positive effect on the disease process.

If IBD becomes active during a pregnancy there is no evidence to suggest that it will do so again in future pregnancies.

Similarly, if a pregnancy occurs without an episode of IBD, this is no assurance that the disease will remain inactive in subsequent pregnancies.

What sort of delivery should I have?

The type of delivery is usually decided upon by the Obstetricians, whilst also taking into account IBD issues.

In most cases, a normal vaginal delivery is suitable.

A caesarean section is often recommended if you have

- active perianal Crohn's
- a pouch (ileal pouch anal anastomosis)

It is also worth considering that vaginal delivery avoids surgery and its possible risks, including an increased risk of clots in the legs and lungs (venous thromboembolism).

What about my ileostomy?

Most women with ileostomies have a normal pregnancy and vaginal delivery. Sometimes a caesarean section may be necessary. Occasionally a stoma can move during pregnancy and cause discomfort. It will usually return to normal after the delivery. You may also find there is an increase in output during the third trimester, but this will resolve after the birth.

What about my pouch?

If you have an ileoanal pouch you may find you pass stools more frequently and have reduced control of your bowel in the third trimester. This should return to normal after the delivery.

An ileoanal pouch is often considered an indication for caesarean section delivery, as potential damage to the anal sphincter during a difficult vaginal delivery may increase the chance of incontinence. This can be discussed with your obstetrician, however, and some women still choose a vaginal delivery.

I want to breastfeed. Will my medicines do any harm to the baby?

Breast milk is the normal food for your baby and breastfeeding has many benefits for both you and your baby, including promoting the development of a healthy immune system and possibly reducing the risk of a child developing IBD in later life.

Most medicines are safe to use while you are breastfeeding. The amount of medicine in your breast milk is usually small and not enough to cause any problems for your baby.

Be aware that the product information from drug companies about safety in breastfeeding may be overly cautious and is often different from current expert medical advice.

Many medicines used for IBD are safe in breastfeeding but it is best to check with the team involved in your care. You can also get advice about the safety of medicines in breastfeeding from the Medicines Information Service at the Women's and Children's Hospital, (08) 8161 7222.

Medications considered SAFE whilst Breastfeeding:

Corticosteroids: Based on a large amount of clinical experience, corticosteroids are considered by doctors to be safe whilst breast-feeding. Research has shown that only small amounts pass into the breast milk. If you are on 40mg or more a day, you can reduce the effects of corticosteroids on your baby by waiting to breastfeed until 4 hours after taking a dose.

5-ASAs & Thiopurines (Azathioprine & 6-MP): extremely small amounts of the active drug are present in breast milk and there is no evidence of harm in children of mothers who have breastfed on the drug. Thus the benefits of breast feeding are regarded as outweighing any risk. If you have any concerns you should discuss these with your doctor.

Biologics – The structure of these drugs means that they are not well absorbed in the gut, which is why they are given by injection. Even the tiny amount of drug in mature breastmilk reaching the infant gut is not well absorbed by the baby. This means breastfeeding is safe when taking either infliximab or adalimumab.

Antidiarrheals: Loperamide is safe to use in breastfeeding. Only small amounts pass into the breast milk and it is unlikely to affect the infant.

Antibiotics: Most antibiotics (such as penicillins) are safe to use whilst breastfeeding as only small amounts pass into the breast milk. It is best to check each antibiotic with your doctor or the WCH Medicines Information Service.

Cyclosporin: May be used in breastfeeding. Most studies have reported low levels in breast milk, but the infant should be monitored for immunosuppressive effects. This medication is rarely required and needs to be supervised by a doctor.

Medications considered NOT SAFE whilst breastfeeding:

Methotrexate and some antibiotics such as tetracyclines in long courses should be avoided whilst breastfeeding. Please discuss this with your doctor as there are usually safe alternatives to these medications which will allow you to breastfeed.

What are the chances of my child having IBD?

Whilst a parent with IBD is slightly more likely to have a child who develops IBD, there is approximately a 95% chance that the child will not develop IBD. If one parent has the disease, the chances of a child developing IBD at some point in their life is around 5%. This risk seems to be slightly higher with Crohn's than UC. If both parents have IBD the risk of a child developing IBD in their lifetime can increase to 35%, but again they are still twice as likely (65%) not to develop IBD ever. The causes of IBD are still incompletely understood and even with genetic predisposition, other additional factors are needed to trigger the disease.

Remember:

- **IBD pregnancies have the best outcome if planned for and if women conceive during remission**
- **Flares of IBD during pregnancy give a greater risk of harm to mother and baby than most IBD treatments**
- **Most IBD medications are safe to continue during pregnancy and breastfeeding, but it is important to discuss this with your doctor before pregnancy or as soon as you recognise you are pregnant**
- **Birth defects are NOT increased by IBD medications except for methotrexate**
- **Stopping your medication during pregnancy without expert advice may harm your baby**

So, when you are ready to plan a pregnancy, the most important thing you can do for your baby is to see your IBD specialist to ensure your disease is well controlled with safe medications.

Here is a list of online resources to help you get the right information about this important topic. The best sources of information about IBD medications in pregnancy are your IBD treatment team and the Medicines Information Service at the Women's and Children's Hospital.

If you have any questions or wish to discuss this further, please call your local IBD Service listed below.

Information for your GP

- Overall fertility and pregnancy outcomes are good in women with inflammatory bowel disease
- The greatest threat to pregnancy outcome is from active disease at conception and during pregnancy
- IBD medications are considered safe in pregnancy except for methotrexate, and should be continued unless an IBD specialist advises otherwise
- Specialist IBD units exist in the major teaching hospitals in South Australia, such as Flinders Medical Centre and the Royal Adelaide Hospital, and are always available and willing to provide advice to GPs and patients about the management of IBD during pregnancy (please see contact numbers above).
- When an IBD patient is planning conception, it is ideal to arrange consultation with his or her IBD physician as early as possible to ensure disease is well controlled with medications considered safe.
- Electronic prescribing programs used by GPs often prompt pop up warnings when IBD medications such as mesalazine as prescribed, citing concerns about these medications in pregnancy. These pop up warnings are based on outdated data which do not take into consideration the negative effect of disease activity during pregnancy. The FDA in the US has changed their pregnancy category system in recognition of this problem, in that categories A,B,C,D and X are now not used in product labelling. The TGA in Australia is also reconsidering this approach.
- Consensus statements based on extensive international data agree that most IBD medications are safe during conception and pregnancy (except for methotrexate), and that most medications should be continued. (ECCO guidelines and Toronto consensus statement)
- These guidelines are recognised as the standard of care in Australia and internationally, and are available to view at www.ecco-ibd.eu
- Please do not hesitate to contact the information sources below for further information and support in managing IBD patients.

For more information

Royal Adelaide Hospital IBD Service
Email: HealthRAHIBDNurse@sa.gov.au

Flinders Medical Centre IBD Service (08) 8204 3942

Medicines Information Service at the Women's and Children's Hospital, (08) 8161 7222.

The Queen Elizabeth Hospital IBD Service
(08) 8133 4081 or 0466 395 485

Lyell McEwin Hospital (08) 8182 9000

Interpreter

This document has been reviewed and endorsed by consumers.

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