Crohn's disease and ulcerative colitis during pregnancy and breastfeeding

**The information in this brochure is based on current scientific knowledge, but it does not necessarily have to match the information in the package leaflet verbatim.
Therefore, please consult your doctor if you have any questions regarding your medication.**

Publisher

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14th updated and
revised edition 2022

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Introduction

The inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis very often occur in young people, in a phase of life in which family planning plays an important role. Not only the men and women who suffer from IBD, but also their partners, are often unsure how diagnostic and therapeutic procedures such as colonoscopy, gastroscopy, radiology, surgery or drug therapies for IBD might affect the course and outcome of pregnancy.

The question also often arises as to whether the bowel disease can be affected by pregnancy, and whether certain precautions are necessary, e.g., with regard to the method of delivery. Could pregnancy exacerbate IBD or trigger an acute flare?

In many cases, there is also uncertainty as to whether IBD might reduce fertility and thus, whether pregnancy is even possible. Since a genetic predisposition is suspected to play a role in the development of IBD, this also raises numerous questions among those affected and their families.

Therefore, it is necessary and useful for patients and their families to have a detailed consultation with the attending physician before, during and after pregnancy and during breastfeeding, to discuss and allay often unfounded fears about pregnancy, and to recognize any possible risks and complications for mother and child as early as possible.

This short brochure is intended to provide some answers to frequently asked questions. It is based on current medical knowledge, taking into account the available scientific evidence.

It must be emphasized, however, that this brochure should not be regarded as a universal answer to all questions related to pregnancy and breastfeeding in IBD and, in particular, that it is no substitute for a personal consultation with the physician. In every pregnancy and in every patient with IBD, special individual situations can exist or arise that cannot be covered within a brochure.

It is also important to recognize that over time, recommendations and medical advice can change as a result of new medical evidence and experience. This applies not only to diagnostic methods but also, in particular, to medicinal and surgical treatments: On the one hand, new insights are gained from new drugs and new therapeutic and diagnostic techniques, and on the other, experience grows, the longer these drugs and techniques are used. Therefore, if anything is unclear, or if you have any doubts regarding your own personal situation, you should always discuss these issues with your attending physicians.

Prof. Dr. Axel Dignass and Dr. Sibylle Honus

"Can women and couples with inflammatory bowel disease (IBD) have children?"

The general answer to this question is "yes". However, there are some basic things that should be considered when planning a pregnancy. As we will discuss below, pregnancy should be planned in an inactive phase of the disease (remission), if possible. In this state, with a few exceptions, both male and female fertility are unaffected, and the course of pregnancy in women with IBD does not significantly differ from that of healthy women.

However, it is important to consider whether disease remission requires the use of drugs that might adversely affect a pregnancy. Patients wanting to have a baby should therefore consult their doctor as early as possible and if possible, seek the advice of experienced specialists.

“Do men and women with IBD have reduced fertility?”

Fertility in women with IBD

As a rule, the fertility of female patients with ulcerative colitis does not differ from that of healthy women. However, exceptions are common after extensive surgery. Until a few years ago, it was thought that the reduction of fertility observed after extensive surgery was only temporary. However, there are now many indications that women who have undergone total removal of the large bowel (proctocolectomy) and subsequent pouch creation with re-connection of the small bowel to the rectum (ileoanal pouch anastomosis) have a small but not negligible risk of persistent infertility. Various studies have shown that even 5 years after this operation, only about 40% of women of childbearing age who try to get pregnant in the natural way succeed in conceiving, in contrast to 90% of healthy women or women of reproductive age before IBD surgery. After artificial insemination (in vitro fertilization, IVF), however, these women can have a complication-free pregnancy and normal childbirth. In patients who want a baby but do not manage to get pregnant after IBD surgery, IVF should be considered, and competent professional medical advice sought as soon as possible.

It appears that modern laparoscopic surgical techniques can reduce the risk of persistent infertility. In women who want to conceive, it may be possible to form a temporary stoma or ileorectostomy, allowing construction of the ileoanal pouch system to be delayed until family planning is complete.

In less extensive surgery e.g., partial removal of the bowel or creation of an artificial bowel outlet (ileostomy), fertility is typically only somewhat reduced, and this reduction is usually only temporary. Often, fertility recovers to a normal level over a period of weeks to months. Overall, however, the fertility of women after surgery is probably somewhat diminished.

In women with Crohn's disease, the data are not quite so clear. Whereas fertility seems not to be impaired during the inactive phase of the disease, a temporary reduction in fertility has been observed during acute flares or after major surgery. This can make itself noticeable through a temporary absence of menstrual periods, a symptom commonly observed during times of increased weight loss due to the disease.

The reduction of fertility in phases of heightened inflammatory activity also seems to make sense from a biological point of view, since awaiting clinical improvment or remission tends to lead to a more positive course of pregnancy and avoids putting an unnecessary additional burden on the patient, as observed in pregnancies in flaring patients.

In female patients who have fully recovered from surgery and in whom disease activity has been stabilized, fertility does not appear to be substantially impaired, although individual studies have indicated fertility to be slightly reduced in women who have undergone surgery. As described above, this applies particularly to patients who have undergone complete removal of the large bowel by open, non-laparoscopic proctocolectomy.

It must also be emphasized that the inability to conceive may not necessarily be related to existing IBD, since even in completely healthy women, pregnancy will only occur in about 90% of women who have regular unprotected sexual intercourse.

Fertility in men with IBD

The fertility of men with IBD is generally not impaired. Abscesses and fistulas in the pelvic and anal regions can, however, lead to erection and ejaculation difficulties. Occasionally, such problems can also occur following extensive operations, especially ileoanal pouch surgery, but this is generally rare.

IBD therapy with salazosulfapyridine or sulfasalazine preparations is a special situation in this regard. These drugs can lead to temporary infertility in men, which resolves about 2 months after stopping the drug or switching to pure mesalazine or other pure 5-amino-salicylic acid (5-ASA) preparations. Temporary infertility during sulfasalazine treatment is caused by a reduced number of sperm cells, a reduction in seminal fluid and changes in the structure and mobility of the male sperm cells. These changes are observed in approximately 80% of men treated with this group of drugs. It is therefore advisable for men to switch to pure mesalazine or other 5-ASA preparations if they are currently wishing to father a child.

Restriction of sperm motility has also been discussed in association with the use of other medications, in particular infliximab, azathioprine and high-dose cyclosporine and tacrolimus. As yet, however, no clinical evidence of impairment of male fertility under these medications has been found, and thus no general recommendation can be made regarding changes of medication for men intending to father a child.

"Can IBD affect the course of pregnancy and the health of the child?"

The influence of Crohn's disease and ulcerative colitis on the course of pregnancy and infant health has been investigated in numerous studies. In general, it has been observed that about 85% of women with Crohn's disease or ulcerative colitis have an uncomplicated pregnancy. Birth defects (malformations) have only been observed in about 1% of patients with either Crohn's disease or ulcerative colitis. In general, the risk of miscarriage is not increased. These numbers are comparable to those seen in healthy women. It is important to realize that even in completely healthy women, pregnancy does not always progress normally: In about 15% of cases, there may be problems during pregnancy and/or complications affecting the baby.

Although the course of pregnancy in patients with IBD is generally not less favorable than in healthy women, various studies show that in patients with Crohn's disease or ulcerative colitis, higher inflammatory activity at the time of conception can adversely affect the course of pregnancy, leading to a significant increase in complications during pregnancy (Table 1).

When conception occurs during a phase of disease remission or low disease activity, pregnancy generally runs a normal course without increased risk of complications. If possible, therefore, pregnancies should be planned to occur during remission or phases of low inflammatory activity. In patients who have active IBD inflammation at the time of conception, the number of miscarriages, premature births and other pregnancy complications is significantly increased. If possible, findings that require treatment should be clarified prior to conception.

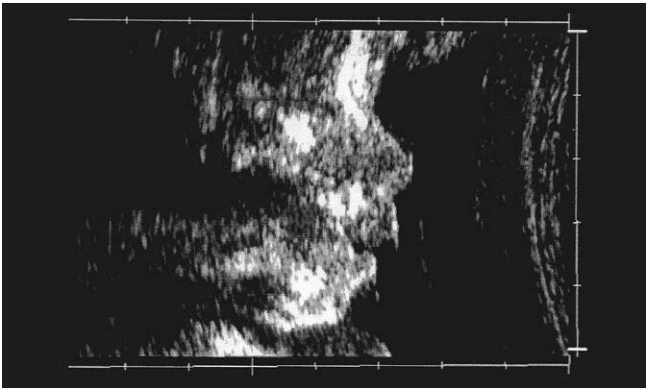
Outcomes of pregnancy in healthy women and in patients with IBD in relation to disease activity [shown as %]

Average percentages from European and American studies are shown.

	Normal	Birth defects	Premature births	Mis-carriages
General population	83	2	6	9
CD in remission	82 (71–93)	1 (0–6)	7	10 (3–27)
CD during flare	54	1	25	20
UC in remission	84 (76–97)	1 (0–3)	6	9 (1–16)
UC during flare	65	2	12	21

Table 1. CD = Crohn's disease; UC = ulcerative colitis.

If surgery will become necessary in the near future (e.g., scarred stenosis), this should be carried out before a planned pregnancy. Current medication should also be reviewed and any deficiencies corrected.



Ultrasound image showing the facial profile of a healthy baby girl in the 25th week of pregnancy.

"What examinations/ preparations should be carried out before a planned pregnancy?"

A general recommendation regarding examinations/ preparations that should be carried out before pregnancy cannot be given. This should be discussed with the attending doctor on a case-by-case basis. Complex procedures such as endoscopic or X-ray examinations are not always necessary.

However, in order to assess inflammatory activity and rule out nutritional deficiencies, a detailed medical consultation and lab tests, including a test for calprotectin in the stool, should usually take place before a planned pregnancy. Ultrasound examination of the abdomen and bowel by an experienced examiner can also be very informative.

In certain cases, additional measures may be necessary, such as endoscopy and X-ray examination of the small bowel, anti-inflammatory therapy, or additional supplementation of vitamins and minerals (e.g., vitamin B12, folic acid or iron). Taking folic acid before a planned conception and in the first weeks of pregnancy is particularly useful, as it can help prevent rare neural tube defects occurring during the development of the baby. Since the absorption and metabolism of folic acid may be additionally reduced during sulfasalazine/sulfapyridine therapy, folic acid should in this case be given prophylactically in sufficient doses before and during the entire pregnancy, or these drugs should be substituted by other 5-ASA preparations.

In patients with IBD (just as in healthy pregnant women), smoking during pregnancy is a risk factor for serious pregnancy complications including premature birth and miscarriage, and should therefore be avoided at all costs. Quitting smoking has a positive influence on the course of Crohn's disease.

"Can bowel surgery due to IBD affect the course of pregnancy?"

Overall, previous surgery does not seem to have any negative impact on the course of pregnancy. Even after extensive bowel surgery, e.g., colectomy with ileostomy formation, complication-free pregnancy is still possible. It is important to allow a sufficient period of time between surgery and conception, so that the wound healing processes are complete and there is no significant inflammatory disease activity.

As already described on page 9, women who have undergone complete removal of the bowel (proctocolectomy) with subsequent formation of a small bowel reservoir and reconnection of the small intestine to the rectum (ileoanal pouch anastomosis) are more likely to have permanently reduced fertility. Patients in this situation who want to have children should seek medical advice at an early stage and discuss the possibility of artificial insemination (IVF).

After colectomy (surgical removal of the large bowel), women should usually wait 6 months before planning a pregnancy, regardless of whether continence is surgically preserved or an artificial bowel outlet (stoma) has to be formed. Complications affecting the ileostomy, such as prolapse or blockage (occlusion), can occasionally arise during pregnancy. Following total colectomy with ileostomy, the frequency of miscarriages may also be increased.

In some cases, surgical intervention may even be necessary during an established pregnancy. While such surgery can occasionally cause premature birth or miscarriage, this is quite rare. However, even after extensive operations during pregnancy, e.g., total colectomy due to treatment-refractory ulcerative colitis or bowel obstruction in Crohn's disease, complication-free pregnancies have been observed.

"Can pregnancy negatively or positively influence the course of IBD?"

In the majority of patients, pregnancy has no influence on disease activity and maintenance of remission in IBD. In some cases, however, a clear improvement or worsening of the disease course of IBD has been seen (Tables 2 + 3). Among patients with Crohn's disease who conceive during the remission phase, only about 15% suffer an acute disease flare during pregnancy. This roughly corresponds to the normal course of Crohn's disease. In patients with Crohn's disease who already have inflammatory activity at the onset of pregnancy, about a third will continue to have disease activity throughout the pregnancy (Table 3). IBD flares occur more frequently in the first trimester of pregnancy and during the puerperium (postpartum period of adjustment/recovery of the mother after giving birth).

Influence of pregnancy on the inflammatory activity of Crohn's disease when conception occurs during a remission phase

Remission is maintained	~ 85%
Disease flare occurs	~ 15%
– in the 1st trimester	~ 13%
– in the 2nd trimester	< 1%
– in the 3rd trimester	< 1%
– during postpartum period	~ 2%

Table 2

Influence of pregnancy on the inflammatory activity of Crohn's disease when conception occurs during a phase of acute inflammation

Remission achieved	15%
Disease improvement	20%
Constant disease activity	30%
Worsening of disease	25%
Worsening of disease during postpartum period	10%

Table 3

Similarly, in patients with ulcerative colitis, disease activity is not significantly influenced by pregnancy. About one third of women with ulcerative colitis who conceive during a remission phase suffer an acute flare of ulcerative colitis (Table 4).

Influence of pregnancy on the inflammatory activity of ulcerative colitis when conception occurs during a remission phase

Remission is maintained	~ 70%
Disease flare occurs	~ 30%
– in the 1st trimester	~ 20%
– in the 2nd trimester	~ 7%
– in the 3rd trimester	< 1%
– during postpartum period	~ 3%

Table 4

This corresponds to the normal course of ulcerative colitis without an accompanying pregnancy. Flares most frequently occur during the first 6 months of pregnancy and during the postpartum period. If the onset of pregnancy occurs during an active phase of ulcerative colitis, the disease activity usually continues, as previously described for Crohn's disease (Table 5).

Influence of pregnancy on the inflammatory activity of ulcerative colitis when conception occurs during a phase of acute inflammation

Remission achieved	19%
Disease improvement	18%
Same disease activity	32%
Worsening of disease	31%
Worsening of disease duing postpartum period	possible

Table 5

The course of IBD can usually be favorably influenced by drug therapy, even during pregnancy, allowing patients to achieve a state of remission or low-level inflammation which can be maintained throughout pregnancy. In principle, it cannot be assumed that patients who experience a worsening of IBD during pregnancy will necessarily do so in the case of future pregnancies.

“Can IBD arise for the first time during pregnancy?“

Both ulcerative colitis and Crohn’s disease can become apparent for the first time during pregnancy. As a rule, the course of IBD is no more severe than in non-pregnant women. Occasionally, it is not possible to clearly differentiate between Crohn’s disease and ulcerative colitis, so that the diagnosis of indeterminate (unclassifiable) colitis is made. In most cases, however, this is of little relevance with regard to the current choice of therapy.

Special challenges may include the fear of diagnostic procedures such as endoscopy or x-ray exams (see also page 43).

"Can IBD be medically treated during pregnancy?

Many drugs or their breakdown products can pass through the placenta from the maternal circulation to that of the unborn child. It therefore seems self-evident that, in order to protect the unborn child from unnecessary risks, all drugs should be avoided, if possible, during and prior to a planned pregnancy. Drug therapy for pregnant women with IBD thus poses a particular problem that often gives rise to great uncertainty and numerous questions. For a start, it is important to note that the package information for almost all drugs advises against their use during pregnancy and states that they should only be taken if strictly necessary. The individual need for treatment can only be assessed on a case-by-case basis through medical consultation with experienced specialists. This statement reflects the necessity for a particularly high degree of safety. For most drugs, however, robust studies in pregnant women proving that they can be safely used during pregnancy are lacking, or there is evidence from animal experiments that shows risks to be increased during pregnancy. Even if there have been no reports of adverse effects of a particular drug on pregnant women or their babies, such a risk, no matter how small, cannot be completely ruled out.

It is therefore recommended to restrict drug intake during pregnancy only to medications that are really necessary. On the other hand, however, it is important to bear in mind that untreated or inadequately treated disease can pose a considerable risk to the course of pregnancy and the unborn child. It should be remembered, too, that even in completely healthy

women, only about 85% of all pregnancies remain complication-free.

Broadly speaking, the therapy of IBD during pregnancy is largely based on the same principles that apply to non-pregnant women. However, pregnant patients with IBD require regular cooperative medical care from a gastroenterologist (or internist with gastroenterology expertise) and a gynecologist, and some significant exceptions and peculiarities with regard to drug therapy must be taken into account.

"Are the typical IBD medications likely to pose risks for the child?"

Unfortunately, there is no general answer to this question. An individual consultation with the attending gynecologist and gastroenterologist/internist is therefore recommended. An overview of selected drugs for the treatment of IBD, and their use (in the usual dosage) during pregnancy and breastfeeding, is shown in Table 6. According to current data, the use of conventional steroids (e.g., prednisone, prednisolone, hydrocortisone, budesonide) and mesalazine or 5-ASA preparations in the usual doses to treat IBD before or during pregnancy appears not to increase the risks for the unborn child. However, for the reasons mentioned above, the information given in the package inserts of these drugs stresses that they should be taken during pregnancy only if strictly indicated. Patients who need therapy with 5-ASA or steroids (corticosteroids) to maintain remission should continue this therapy even after pregnancy is established because, as stated above, increased inflammatory activity of the bowel disease during pregnancy could represent a much greater risk for the fetus. If an acute flare of IBD occurs, these medications should be administered in doses sufficient to bring the acute inflammation under control as quickly as possible. Inadequately treated IBD harms both the mother and the baby more than drug therapy. If the dosage of drug therapy is inadequate, there may be no improvement or only insufficient improvement in disease activity.

Drug therapy of the father-to-be with the conventional pure 5-ASA or steroids (corticosteroids) has no negative effects on the course of pregnancy, according to the available data. As already mentioned, (see page 11), salazosulfapyridine/sulfasalazine therapy may cause a temporary reduction in male fertility, so that patients intending to father a child should be switched to a pure 5-ASA or mesalazine preparation.

Other drugs, such as antibiotics or immunomodulatory drugs (e.g., azathioprine or 6-mercaptopurine, methotrexate, cyclosporine A, tacrolimus, the anti-TNFα antibodies infliximab, adalimumab and golimumab, as well as the newer drugs vedolizumab and ustekinumab) should only be used when strictly necessary and after extensive consultation with an accomplished and experienced specialist (see also pages 27–38 in this brochure). With regard to the JAK inhibitor tofacitinib, the data on pregnancy and breastfeeding are not yet sufficient to allow reliable recommendations to be made.

Methotrexate, like the drug thalidomide, is contraindicated during pregnancy and prior to intended conception, and should be discontinued 6–9 months before a planned pregnancy, if possible. For safety reasons, use of methotrexate by male patients when intending to father a child is also not advised, although (in contrast to maternal use) no teratogenic effects of paternal use have been found to date.

The antibiotics metronidazole and ciprofloxacin, which are used in particular in fistulating Crohn's disease and pouchitis, requires especially careful consideration during pregnancy. Long-term therapy with these antibiotics is usually contraindicated. Since these are reserve drugs, an alternative, possibly more effective therapy may be considered after careful consultation with the attending doctor, if indicated. However, their use is possible and does not constitute a reason to terminate an unplanned pregnancy.

On the basis of the information currently available, various other drugs used to relieve symptoms of IBD can be taken without harmful effects to the child. This applies, for example, to the drug loperamide, which is used to alleviate severe diarrhea. Loperamide works mainly locally in the bowel and is only absorbed into the blood in small quantities. However, in a large observational study, a slightly increased risk of birth defects could not be ruled out when the drug was taken during early pregnancy. Therefore, the Summary of Product Characteristics (SmPC) for the drug advises against its use in this situation. However, no signs of a significantly increased risk of birth defects have been detected in animal experiments or in many years of general clinical use, so that ultimately, it is a question of weighing up possible risks and benefits. Continuous use during pregnancy is certainly not recommended.

Diarrhea may also be positively influenced by consumption of psyllium husks (Plantago ovata), for which no negative effects associated with its use during pregnancy have been described to date. Probiotics (e.g., E. coli Nissle, lactobacilli) can also be taken without any risk to the fetus, according to currently available information.

"Can the drugs azathioprine or 6-mercaptopurine be used before or during pregnancy?"

Recently, there have been considerable changes regarding the use of the immunomodulatory substances azathioprine and 6-mercaptopurine. Until a few years ago, it was believed that the use of these drugs before or during pregnancy was associated with a higher risk of side effects (miscarriages, birth defects, premature births). However, more recent findings resulting from the more common use of azathioprine and 6-mercaptopurine to treat other diseases besides IBD (e.g., organ transplants, rheumatoid arthritis) have shown that taking these drugs before or during pregnancy is not associated with an increased risk of pregnancy complications or birth defects. A large number of published reports now show that risks in patients with IBD are not increased by azathioprine or 6-mercaptopurine therapy.

However, it is not possible to rule out the possibility that a drug can influence the course of pregnancy. After a more thorough search of the literature, some case reports can also be found that show a slightly increased rate of pregnancy complications and miscarriages associated with the use of azathioprine or 6-mercaptopurine. However, due to the small number of cases, no statistical conclusions can be drawn, and other factors such as increased disease activity may also be responsible for these negative effects. In conclusion, therefore, not only can azathioprine and 6-mercaptopurine be used before and during a planned pregnancy, if medically necessary, but their use is recommended if the inflammatory activity cannot be controlled by other means.

The decision as to whether azathioprine should be discontinued when pregnancy is desired, or whether conception should be planned under continuation of azathioprine therapy, requires careful consideration of the advantages and disadvantages in consultation with the parents-to-be, who must be fully informed. This decision requires a high degree of responsibility and should be made in a joint discussion with the parents, their gynecologist and general practitioner, and specialists with gastroenterological expertise. Should conception occur during therapy with azathioprine or 6-mercaptopurine, this is not an indication for pregnancy termination.

Paternal use of azathioprine/6-mercaptopurine before a planned pregnancy is also not entirely uncontroversial. In this case, too, extensive experience from transplant medicine and from patients with rheumatic diseases or IBD indicates no increase in the risk of pregnancy complications or birth defects as a result of paternal treatment with azathioprine/6-mercaptopurine prior to or at the time of conception. As with women, there are individual case reports in the scientific literature that suggest paternal azathioprine or 6-mercaptopurine therapy may have a possible negative influence on pregnancy. But here, too, the number of cases is too small to allow statistical assessment.

General note on Table 6: Before using medication during pregnancy and breastfeeding, a critical review should be carried out with regard to the indication and use of medication. In principle, depending on the drug used, this applies to all phases of pregnancy and breastfeeding, since, due to a lack of study data, most drugs are not approved for pregnancy and breastfeeding, as is also pointed out in the respective Summary of Product Characteristics (SmPC). For certain combinations, additional monitoring examinations should be offered and performed. Also, for example, inoculation of the newborn child with live vaccines must be avoided or postponed (e.g., when anti-TNF antibodies have been used in late pregnancy). The information in Table 6 was taken from the package inserts and/or from www.embryotox.de; hence, statements may sometimes differ.

Use of selected drugs for the treatment of IBD (in the usual dosage) during pregnancy and breastfeeding

Medication	Pregnancy	Breastfeeding
mesalazine (5-ASA)	possible	possible
sulfasalazine	possible, folic acid supplementation recommended	possible
prednisolone/ prednisone	possible	possible
budesonide	possible	limited data, presumably possible
azathioprine/ 6-mercaptopurine	possible	possible (if possible, refrain from breast-feeding for 4 hours after drug intake)
methotrexate	contraindicated	contraindicated
cyclosporine A/ tacrolimus	possible, as a reserve drug	possible, careful assessment
infliximab	possible	possible
adalimumab	possible	possible
vedolizumab	limited data, possible	limited data, presumably possible
ustekinumab	limited data, possible	limited data, presumably possible
tofacitinib	contraindicated (but uncomplicated pregnancies have been reported)	contraindicated (insufficient data)
metronidazole	possible, limited therapy duration	possible, can cause diarrhea
ciprofloxacin	possible, as a reserve drug	possible, can cause diarrhea
probiotics	possible	possible
psyllium husks (Plantago ovata)	possible	possible

Table 6

In Germany, azathioprine may only be used during pregnancy after the attending physician has carefully weighed up the risks and benefits. However, according to current scientific evidence, the use of azathioprine is possible and appropriate in certain cases, following careful risk/benefit assessment by the attending physician. In recent years, we have overseen the treatment of a large number of women and men taking azathioprine before and during conception and pregnancy. In no case have we been informed of any fetal malformation or pregnancy complication in connection with this therapy.

If the doctor considers it appropriate to continue maternal azathioprine therapy during breastfeeding (off-label), blood tests of the infant may be required if complications are suspected. In addition, the pediatrician should be kept informed as to the mother's medications.

"Can methotrexate, tacrolimus or cyclosporine A be taken before or during pregnancy?"

The use of immunomodulatory drugs other than azathioprine and 6-mercaptopurine must be strictly appraised on a case-by-case basis.

Methotrexate should under no circumstances be used in patients wishing to have children and is strictly contraindicated in patients planning a pregnancy. Data from animal experiments show that the drug can cause damage to the genetic make-up (cellular DNA) and an increased incidence of birth defects and pregnancy complications (miscarriages, premature births). Higher doses of methotrexate are even used as a means of abortion. For this reason, we recommend that both men and women discontinue methotrexate therapy 6–9 months before attempting to conceive. If therapy with methotrexate is absolutely necessary, reliable methods of contraception must be used. However, it is no longer generally advised to abort if an unplanned pregnancy should occur during treatment with methotrexate, since complication-free pregnancies have also been described under treatment with methotrexate.

With regard to the use of cyclosporine A and tacrolimus, there are a number of case reports of patients with IBD or after organ transplantation describing uncomplicated pregnancies and indicating no increased incidence of birth defects in association with the use of these drugs. However, the existing data are by no means sufficient to issue a general recommendation

for the use or continuation of these medications during pregnancy. This decision should be taken only after detailed discussion between an experienced specialist and both parents, taking into account the previous course of the disease and the available scientific findings. Based on what is currently known, however, there is no indication for pregnancy termination if an unplanned pregnancy occurs during therapy with cyclosporine A or tacrolimus.

"Can infliximab, adalimumab, golimumab or other anti-TNFα antibodies be used before or during pregnancy?"

Based on current scientific knowledge, the use of infliximab and adalimumab does not appear to be associated with an increased incidence of birth defects or an increase in pregnancy complications. Data from animal experiments show that they cause no negative effects on the course of pregnancy and no increase in birth defects. Several thousand pregnancies have now been described in patients with rheumatological diseases or IBD using infliximab and adalimumab. Statistically, the available data show no increase in pregnancy complications or birth defects when male or female patients were treated with infliximab or adalimumab before or during pregnancy.

It is currently assumed that continuation of anti-TNFα antibody therapy during pregnancy is possible without increasing the risk of complications or birth defects.

Anti-TNFα drugs consist of antibodies that are known to be able to travel in increasing concentrations from the maternal blood via the placenta to the child from about the 2nd trimester of pregnancy. Stopping the medication in the last trimester has therefore been discussed, but is no longer generally advised. In a comparative study with around 80 pregnant women, it was shown that if disease activity/remission has remained stable until the last trimester, stopping treatment is not associated with an increased relapse rate in the last trimester. However, there were also no negative effects in those pregnant women who continued to receive

infliximab or adalimumab in the last trimester. If the drug is necessary for stable disease control, it is recommended to continue its use throughout the entire pregnancy.

A study published in 2016 with 80 mother-child pairs showed that in children of mothers treated with infliximab or adalimumab during pregnancy, antibodies were detectable in the child's blood up to 12 months after delivery. However, the children did not show a relevant increase in the risk of serious infections. Moreover, all children showed normal mental and physical development after 1 year. In this study, it was also found that continued administration of anti-TNFα antibodies after the 30th week of pregnancy was not associated with an increased rate of severe infections in newborn infants. Similarly, a more recent European study found that children whose mothers were treated with anti-TNFα antibodies during pregnancy showed no increased risk of serious infections. However, a slight increase in the rate of uncomplicated infections, or longer-term effects, e.g., on the developing immune system of the child, cannot yet be ruled out with certainty. In cases where anti-TNFα antibody therapies have been used during pregnancy, it is recommended live vaccinations of the infant be avoided or postponed until after the first 6 months of life whenever justifiable (in Germany, within the standard immunization schedule, this currently only applies to the vaccination against rotavirus).

At this point in time, it is not possible to make conclusive statements regarding the anti-TNFα antibody golimumab, as significantly fewer patients have been treated with this drug, and experience is therefore limited. However, experimental data indicate that the drug poses no increased risk.

For one of the anti-TNFα antibodies (certolizumab), experimental studies have shown that only a small amount of the substance is passed on to the child, an aspect that probably suggests a favorable safety profile. Certolizumab is currently only approved in Switzerland and the USA for the treatment of Crohn's disease. In Germany, at present, it can only be prescribed to treat rheumatological diseases.

In our view, if unintended pregnancy occurs under therapy with any of the currently available anti-TNFα antibodies, there is no reason for pregnancy termination.

"Can vedolizumab be used before or during pregnancy?"

Based on current data, the use of vedolizumab does not appear to be associated with an increased incidence of birth defects or pregnancy complications, since animal experiments have shown no negative effects on the course of pregnancy or the incidence of fetal malformation.

Likewise, observations from the marketing authorization studies and post-approval safety studies with vedolizumab have not, so far, shown any negative effects on the course of pregnancy or the newborn infant. However, the available data are less extensive than those gained from the anti-TNFα antibodies, describing only a limited number of women (or their partners) who were treated with vedolizumab before or during pregnancy. In a recently published European study of 250 pregnant women, approximately 80 women treated with vedolizumab before and during pregnancy were compared with women treated with anti-TNFα antibodies or mesalazine/steroid therapy. No increase in the rate of pregnancy complications or birth defects was detected.

In our view, there is currently no reason to terminate pregnancy if unintended pregnancy occurs during therapy with vedolizumab. Therapy with vedolizumab before and during pregnancy as well as during breastfeeding should be carried out in consultation with an experienced specialist. However, as current evidence is still limited, therapy should not be switched to vedolizumab before a planned pregnancy due to its supposedly favorable safety profile.

“Can ustekinumab be used before or during pregnancy?“

Ustekinumab was approved in 2016 for the treatment of Crohn’s disease, but not until 2019 for the treatment of ulcerative colitis. Previously, however, ustekinumab was already in use as a therapy for psoriasis, an inflammatory skin disease. Data from experiments in animals do not show any negative effects on the course of pregnancy, or any increase in birth defects. So far, data on human pregnancies are limited to reports of a few hundred women treated with ustekinumab for psoriasis or IBD before and during pregnancy, and there are only a few single case reports of women who received ustekinumab treatment for IBD throughout the entire pregnancy. Cases of paternal exposure are much scarcer still. Overall, however, the available data do not show a statistically increased risk of pregnancy complications or birth defects.

In our view, there is, at least for the moment, no reason for pregnancy termination if an unintended pregnancy occurs during therapy with vedolizumab. Therapy with ustekinumab during pregnancy (and while breastfeeding) should be carried out in close consultation with a gastroenterologist who has experience with ustekinu-mab therapy.

"Can tofacitinib be used before or during pregnancy?"

The JAK inhibitor tofacitinib was approved for the treatment of ulcerative colitis in Germany in 2018. Experimental data from animals in the approval studies showed an increase in the rate of birth defects (including skeletal malformation) when tofacitinib was administered. Due to a lack of clinical study data from patients, tofacitinib is currently contraindicated during pregnancy (and while breastfeeding). Reliable contraceptive methods should therefore be used during therapy with tofacitinib.

However, individual case reports of female patients with ulcerative colitis, rheumatoid arthritis or psoriasis who became pregnant under tofacitinib therapy have so far provided no indication of an increased rate of pregnancy complications or birth defects. However, the number of cases involved is very low and almost all patients discontinued the therapy after becoming aware that they were pregnant, so that no statements can currently be made about possible effects of the drug later on in pregnancy.

In our view, there is currently no reason to terminate pregnancy if an unintended pregnancy occurs under therapy with tofacitinib.

“Can steroid therapy be used in the final stages of pregnancy and while breastfeeding?“

In principle, it can be assumed that steroid drugs (e.g., prednisone, prednisolone, hydrocortisone, budesonide), in the dosages usually used to treat IBD, can be used without an increased risk of miscarriage or birth defects. Very high doses of systemic steroids in the final phase of pregnancy can, however, lead to reduced cortisol production in the adrenal gland of the fetus, which manifests as reduced cortisone levels in the newborn infant, causing apathy and inactivity. The newborn baby should therefore be closely monitored by a pediatrician if high doses of steroids are used in the final phase of pregnancy. Temporary steroid replacement therapy in the infant can bridge the time until the child’s adrenal gland is able to produce sufficient cortisone on its own.

Since steroids can also pass into the child’s body through breast milk, it is also possible, in principle, that the production of cortisol in the child’s adrenal gland may continue to be suppressed during breastfeeding. Here too, the infant should be closely monitored by a pediatrician. In both cases, however, permanent damage to the child’s body is unlikely. When steroid therapy of the mother is discontinued, the adrenal function of the infant normalizes, and with it the endogenous production of sufficient cortisol for the child.

"Is it necessary to discontinue 5-ASA therapy prior to delivery?"

In contrast to acetylsalicylic acid (aspirin), 5-aminosalicylic acid (5-ASA, mesalazine) does not inhibit the aggregation of platelets (thrombocytes) when given in therapeutic doses, and therefore has no effect on blood clotting.

Generally, therefore, it is not necessary to stop 5-ASA therapy before childbirth, especially since blood concentrations of 5-ASA are very low.

“Can use of the contraceptive pill trigger the onset of IBD?“

A number of studies have shown in the past that women who take birth control pills are slightly more likely to develop Crohn’s disease and slightly more likely to have acute flares of existing Crohn’s disease. However, other investigations have failed to confirm these results. No unfavorable effects of the contraceptive pill have been found in women with ulcerative colitis.

Observations from our own practice suggest that the overall risk of worsening or triggering an acute flare of IBD through use of the contraceptive pill is likely to be low. In general, therefore, we would have no reservations about use of the contraceptive pill in women with IBD.

However, it is important to note that the contraceptive effects of the pill can be reduced in certain cases due to impaired intestinal absorption in the presence of severe diarrhea. Protection against conception (contraception) may therefore be diminished, especially in contraceptive pills that have a lower hormone content (micropill). In this case, advice from the attending gynecologist should be sought.

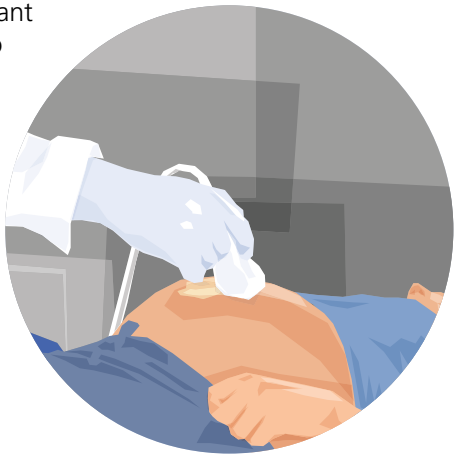
"Are there medical reasons that could necessitate abortion in patients with IBD?"

It is only very rarely, and perhaps never, necessary to abort a pregnancy because of IBD. Instead, IBD should be adequately treated and the patient should be closely monitored by their attending physicians.

“What diagnostic tests can be performed during pregnancy?”

Laboratory tests to monitor inflammation and detect early signs of nutrient deficiencies are useful and can be carried out as part of the gynecological and gastroenterological check-ups. Among these is the test to determine calprotectin, an inflammatory marker, in a stool sample.

Ultrasound examinations of the abdomen and bowel can be carried out at any time without endangering the mother or her baby, and can provide important information about the activity and extent of the disease. With appropriately experienced examiners, upper or lower endoscopy (including proctoscopy, sigmoidoscopy and even ileocolonoscopy) can also be performed without increasing the risk of pregnancy complications or premature birth. If bowel cleansing is necessary, cleansing solutions of the polyethylene glycol type should be used. When sigmoidoscopy is performed, one enema is usually sufficient. Pregnant patients can also be sedated using propofol without an increased risk.



However, invasive examinations (those that involve instruments entering the body) should only be carried out if they are absolutely necessary to guide therapy. Magnetic resonance imaging (MRI), which is thought to be harmless, can be useful in some cases too. In this case, if possible, the administration of contrast media containing gadolinium should be avoided.

Diagnostic X-ray examinations should be postponed until after delivery if possible, and otherwise reserved for emergency situations.

Capsule or double balloon endoscopy is usually not necessary during pregnancy. Double balloon endoscopy, in particular, should not be used, due to its very invasive character and the associated increased risk of premature labor.

“Are there any special considerations with regard to delivery?“

Vaginal delivery is generally the favored option, even in patients with IBD. It is also possible in patients with a stoma and in patients who have undergone bowel surgery with pouch formation (ileoanal pouch anastomosis). Occasionally, however, increased pressure caused by contractions during labor can lead to prolapse of the stoma or pouch problems. Thus, some gynecologists recommend delivery by cesarean section. In patients with a stoma, the method of childbirth should therefore be chosen in close consultation with the attending gynecologist.

Divergence from vaginal delivery may also be appropriate in patients with pronounced fistulizing disease around the anus and in the pelvis. In this case, cesarean section is more commonly preferred and appears more sensible. Again, the decision should be taken in close consultation between the pregnant woman and the attending gynecologist.

The extent to which perineal incision (episiotomy) may pose an increased risk for the development of perianal fistulas is controversial. Most reports published on this topic do not show a significantly increased risk for the development of perianal fistulas after perineal incision.

„Is it necessary to follow a special diet during a pregnancy with IBD?"

In principle, there is no need for women with IBD to follow a special diet. However, it is important to follow the usual recommendations for a balanced diet with sufficient intake of minerals and vitamins during pregnancy.

Frequently, for example, iron deficiency can develop. Iron deficiency or the resulting anemia can have very unfavorable effects on the course of pregnancy. Iron should therefore be supplemented in the form of iron capsules/tablets or drops or, in severe cases, after careful diagnostic and clinical evaluation, by intravenous administration of iron.

Special dietary recommendations must be taken into account in patients who have existing lactose intolerance, bile acid malabsorption or e.g., narrowing of the gastrointestinal tract (stenosis) as part of the underlying disease or due to a concomitant disorder. Patients with lactose intolerance may benefit from a lactose-free or low-lactose diet. Since this usually results in reduced calcium intake, additional calcium should be taken in the form of effervescent or chewable tablets. In the case of pre-existing bile acid malabsorption, the so-called MCT (medium-chain triglyceride) diet has often been found to have beneficial effects. Patients with narrowing (stenoses) of the gastrointestinal tract, as described above, benefit from a low-fiber diet, which should be continued during pregnancy.

“How high is the risk of children developing IBD if the parents suffer from Crohn’s disease or ulcerative colitis?“

The children of parents with IBD have a relatively low risk of developing Crohn’s disease or ulcerative colitis. IBD is not a hereditary disease in the strict sense. What is inherited, however, is a genetic predisposition to develop these diseases under certain circumstances. Familial clusters of IBD are occasionally observed.

It is not possible to exactly predict the individual risk of developing IBD if other family members are affected; this can only be estimated on the basis of empirical studies. According to these data, the relative risk of developing IBD fluctuates between 0% and 36%, depending on the degree of kinship to somebody who already has the disease (Table 7).

Estimated relative risk of developing IBD

Risk for children if one parent has IBD	1–7%
Risk for children if both parents have IBD	up to 36%
Risk for other siblings if one child has IBD	2–6%
Risk for parents if one child has IBD	1–5%

Table 7

The fact that children of parents with IBD have a slightly increased overall risk of getting IBD themselves is no reason to avoid having children: Improved medical therapies now allow IBD to be treated quite effectively, if diagnosed early, and the life expectancy of patients with IBD is not significantly different from that of healthy people.

“Can women with IBD breastfeed their babies?“

Women taking steroids and 5-ASA drugs can breastfeed their babies, as the amounts of these substances that enter the child’s body via breast milk are negligible and there are not known to be any negative effects on the infant. Just as in non-pregnant women, systemic steroids should be reduced as quickly as permitted by the clinical course of the disease. If high-dose steroid therapy becomes necessary, the baby should be monitored regularly by a pediatrician. If, for example, weaning occurs while the mother is taking high doses of steroids, there is a risk of temporary adrenal insufficiency in the infant. In this case, the infant may temporarily require steroid treatment under the supervision of a pediatrician.

The anti-TNFα antibodies infliximab and adalimumab are found in small amounts in breast milk, but since no negative effects have been found on breastfed children, breastfeeding is also possible under infliximab or adalimumab therapy. For other anti-TNFα antibodies, the data are more limited. Therefore, no recommendations can be made.

The antibodies vedolizumab and ustekinumab have only been detected in small amounts in breast milk and case reports have shown no negative effects on breastfed children. However, the number of cases is currently very small. Breastfeeding under therapy with vedolizumab or ustekinumab is presumed to be possible without risk to the child, but a general recommendation cannot (yet) be made due to the limited data available. Therefore, this should be discussed with the attending specialists on a case-by-case basis.

In animal studies of the JAK inhibitor tofacitinib, the drug was detected in the milk of lactating animals. As yet, no data are available from human mother-child pairs. The drug is therefore currently contraindicated in breastfeeding mothers.

The use of azathioprine, 6-mercaptopurine, cyclosporine A or tacrolimus can be considered during breastfeeding if clinically necessary.

It is generally assumed that maternal therapy with azathioprine, 6-mercaptopurine, tacrolimus or cyclosporine A during breastfeeding is possible without associated risks for the child. However, according to the Summary of Product Characteristics (SmPC), use of azathioprine is not recommended during breastfeeding. In this case, as already mentioned, it is necessary to assess the situation on a case-by-case basis, in close consultation with the attending specialists.

Since the highest concentrations of azathioprine are detected in breast milk within the first 4 hours after taking the drug, it would be possible to discard a portion of milk after taking the medication or to delay breastfeeding for 4 hours after taking it.

Overall, the available short-term follow-up data show no increased risk for the newborn child. However, since possible long-term consequences and negative effects on the infant cannot be reliably estimated, the indication should at least be critically reconsidered and discussed. Due to the inadequate detoxification capacity of the child's immature liver, it is not possible to predict what quantities of the above-mentioned drugs will remain in the child's body, especially in premature babies who are not fully developed. Therefore, especially in this situation, acute and long-term secondary effects cannot be entirely ruled out at the present time.

Under methotrexate therapy, however, breastfeeding should be avoided due to the possibility of severe negative consequences for the child.

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