

Care of Women with Chronic Inflammatory Bowel Disease (Chronic IBD) During Pregnancy

Recommendations of the Obstetrics and Prenatal Medicine Working Group of the DGGG

Betreuung von Frauen mit chronisch entzündlichen Darmerkrankungen (CED) in der Schwangerschaft

Empfehlungen der Arbeitsgemeinschaft für Geburtshilfe und Pränatalmedizin in der DGGG



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ABSTRACT

The incidence of chronic inflammatory bowel disease (chronic IBD) in persons of reproductive age is high. Chronic IBD does not typically lead to impaired fertility. Nevertheless, the percentage of women suffering from chronic IBD who have children is lower than that of the general population, due to self-imposed childlessness. Providing women with open, unbiased information and, if necessary, helping them to overcome baseless fears should therefore be an essential part of preconception counseling. With the exception of methotrexate, most standard drugs can and should be continued during pregnancy. If the pregnancy occurs during an inactive phase of disease, the rate of complications in pregnancy should, in principle, not be higher than normal. Nevertheless, pregnant women with chronic IBD are classed as high-risk pregnancies. Organ screening in accordance with DEGUM II criteria should be carried out in every case, and women must be monitored for the potential development of placental insufficiency. Any flare-ups which occur during pregnancy should be treated in full. Vaginal delivery can be considered if there is no perianal manifestation of disease; however, the individual risk must be carefully weighed up.

ZUSAMMENFASSUNG

Chronisch entzündliche Darmerkrankungen (CED) weisen eine hohe Inzidenz im reproduktionsfähigen Alter auf. Eine CED führt typischerweise nicht zu einer beeinträchtigten Fertilität, dennoch ist die Rate an Frauen mit Kindern aufgrund einer selbstauerlegten Kinderlosigkeit geringer als in der Gesamtpopulation. Ergebnisoffen zu informieren und ggfs. unbegründete Ängste abzubauen, sollte daher ein wesentlicher Bestandteil der präkonzeptionellen Beratung sein. Die gängigen Medikamente mit Ausnahme von Methotrexat können und sollen in der Schwangerschaft fortgeführt werden. Tritt

die Schwangerschaft in einer inaktiven Krankheitsphase ein, so ist prinzipiell nicht mit einer erhöhten Komplikationsrate in der Schwangerschaft zu rechnen. Dennoch gelten Frauen mit CED als Risikoschwangere. Es sollte in jedem Fall ein Organscreening nach DEGUM-II-Kriterien erfolgen sowie auf die evtl. Entwicklung einer Plazentainsuffizienz geachtet werden. Ein möglicher Schub in der Schwangerschaft sollte konsequent therapiert werden. Beim Fehlen einer perianalen Manifestation kann eine vaginale Entbindung angestrebt werden, dennoch ist eine individuelle Risikoabwägung erforderlich.

Forms of Chronic Inflammatory Bowel Disease

AGG STATEMENT

The two most important forms of chronic inflammatory bowel diseases in pregnancy are Crohn's disease and ulcerative colitis.

Chronic inflammatory bowel disease (chronic IBD) is the term used to describe immune-mediated chronic inflammation of the bowel. The two most important forms of chronic IBD are Crohn's disease and ulcerative colitis.

Crohn's disease is typically a non-continuous inflammation extending from the terminal ileum to a segmental colitis, which often spares the rectum. Many patients do develop perianal changes with fistula formation. Affected persons suffer from abdominal pain; abdominal resistance develops and stenosis of the small intestine is common. The incidence of disease is approximately 6.6/100 000; the mean age at onset of disease is 33 years. The definitive diagnosis is obtained using sonographic imaging and an ileocolonoscopy to provide evidence of discontinuous inflammation together with histological confirmation of granulomas [1].

Ulcerative colitis typically is a continuous inflammation emanating from the rectum. Affected persons may pass blood or mucus in their stools, although pain only occurs intermittently. Stenosis or fistula formation does not occur. The incidence is approximately 3–3.9/100 000. The highest age-specific incidence occurs between the ages of 16 and 25 years. The diagnosis of ulcerative colitis is based on the patient's history, ultrasound examinations, and endoscopic findings [2].

There are some transitional forms between the two types of chronic IBD. The following recommendations were agreed by the AGG. The recommendations are based on a search of the literature, and they aim to provide assistance to treating physicians during preconception counseling and when caring for affected patients.

Methods

A literature search of the PubMed database for the period from 1995 to January 2021 was carried out, using the search terms "chronic inflammatory bowel disease and pregnancy". Randomized clinical studies on this issue are lacking. Almost 200 publications were found during the literature search. The articles considered to be most relevant for the care of pregnant patients with chronic IBD were reviewed. They were taken as the basis for recommendations on the treatment of women with chronic inflammatory bowel disease in pregnancy, and voted on by the "Maternal Diseases" section of the Obstetrics and Prenatal Medicine Working Group of the DGGG (AGG).

Preconception Counseling

AGG RECOMMENDATION

Women with chronic inflammatory bowel disease should be offered preconception counseling.

AGG RECOMMENDATION

Clinical remission of disease should be aimed for prior to conception, as disease activity at the time of conception is correlated with an increased risk of premature birth and placental insufficiency.

AGG RECOMMENDATION

With the exception of methotrexate, medication to maintain remission or deal with a flare-up should, where indicated, be continued even if the woman wishes to have a child.

The fertility of women with Crohn's disease is not or only slightly lower [3]. Reduced fertility has only been reported for patients with active ulcerative colitis or who have undergone placement of an ileoanal pouch (IAP) [4]. Nevertheless, the percentage of affected persons who have children is lower than in the overall pop-

ulation. This voluntary childlessness has been reported for both women and men with chronic IBD [4]. Reported causes include fear of heritability, the risk of fetal malformations, and worries about the teratogenicity of the medication [5].

Although women with chronic IBD often receive long-term medical care, there appears to be a lot of uncertainty around family planning. These women are in urgent need of counseling and would particularly benefit from preconception counseling [6].

Discussions during counseling should include the discussion on how chronic IBD can affect the course of pregnancy and the impact pregnancy may have on chronic IBD.

Stable disease with the disease in remission does not affect the course of pregnancy, and pregnancy has no negative impact on disease activity. A European cohort study showed that the flare-up rate among women who were stable prior to conception is comparable with the rate reported for non-pregnant women. However, if conception occurs during an active disease phase, then 2/3 of women had increased flare-ups during the subsequent course of pregnancy and an higher risk of worsening disease after pregnancy [7].

Active disease during conception was also found to be correlated with an increased risk of miscarriage, premature birth, and a higher incidence of growth-restricted fetuses [8, 9].

A recent meta-analysis [10] showed a 2.42 times higher risk of premature birth (95% CI: 1.81–8.02), a 1.48 times higher risk of SGA (95% CI: 1.19–1.85), a 1.87 times higher risk of miscarriage (95% CI: 1.17–3.0), and a 2.27 times higher risk of intrauterine fetal death (95% CI: 1.03–5.04) in women who had active disease at the time of conception compared to women with inactive disease at conception.

The majority of women with chronic IBD take long-term medication which needs to be reviewed before becoming pregnant.

According to the recommendations of the European Crohn's and Colitis Organisation (ECCO) and the AWMF guideline on Crohn's disease [1, 11], women can continue to take their usual medication with the exception of methotrexate.

According to information from Embryotox, 5-ASA drugs, particularly mesalazine and sulfasalazine, have been investigated in detail and are considered to be generally very well tolerated. Glucocorticoids are permissible at all stages of pregnancy. Possible effects on the fetus depend on the glucocorticoid, the dosage, the duration of treatment, and the period of pregnancy. As local applications such as budesonide are not absorbed very well, they are considered harmless. If treatment consists of systemic application of a drug, it is important to bear in mind that fluorinated corticosteroids such as dexamethasone and betamethasone cross the placental barrier, while non-fluorinated preparations such as prednisone and prednisolone are largely enzymatically inactivated in the placenta. Systemic long-term medication with corticoids should be avoided where possible. In the rare cases requiring higher dose treatment over many weeks, fetal growth should be monitored by ultrasound. If treatment is continued up until the birth, it is important to be aware of the possibility of adrenal insufficiency in the neonate and to treat the infant accordingly. The mother may also develop relative adrenal insufficiency when giving birth, and steroid treatment should be adjusted peripartum if necessary. When planning the birth, it is important to already con-

► **Table 1** Overview of the most common medications used to treat chronic IBD and their safety during pregnancy.

Safe	Probably safe	Contraindicated
Oral 5-aminosalicylates	Infliximab	Methotrexate
Topical 5-aminosalicylates	Adalimumab	Thalidomide
Sulfasalazine/mesalazine	Certolizumab	6-Thioguanine (no data)
Azathioprine	Cyclosporine	
6-Mercaptopurine	Tacrolimus	
	Budesonide	
	Metronidazole	
	Ciprofloxacin	

sider how to adjust the steroid dosages in stress situations for any pregnant woman receiving long-term steroid therapy and to set up a substitution plan.

Azathioprine, followed by cyclosporine, is the most studied immunomodulator. TNF- α inhibitors are also acceptable if their use is imperative. However, the administration of TNF- α inhibitors in the second half of pregnancy should be limited to selected cases and must be justified. The antibiotic drugs metronidazole and ciprofloxacin can be used in pregnancy [12].

► **Table 1** lists the most common drugs used to treat chronic IBD and their safety levels in pregnancy (modified from [13]).

Data on the monoclonal IgG1 antibodies vedolizumab and ustekinumab in pregnancy is limited. Both drugs should therefore only be used during pregnancy after carefully weighing up the benefits and disadvantages in each individual case and after other treatment options have failed [12, 14].

Care During Pregnancy

AGG RECOMMENDATION

Pregnant women with chronic inflammatory bowel disease should be cared for by a gastroenterologist who is supported an interdisciplinary team.

AGG RECOMMENDATION

With the exception of methotrexate, treatment to maintain disease remission should not be discontinued in pregnancy.

AGG RECOMMENDATION

The diagnostic work-up should consist of carefully differentiated, sonography-based detailed examinations in accordance with DEGUM II criteria.

AGG RECOMMENDATION

Regular sonographic controls should be carried out (at least every 4 weeks) to confirm fetal growth.

AGG RECOMMENDATION

Flare-ups of chronic inflammatory bowel disease in pregnancy must be treated.

AGG RECOMMENDATION

From week 40 + 0 of gestation, the pregnant woman should be informed about the option of inducing labor.

The overall data on pregnancy risks is inconsistent. Some studies have reported a higher risk of premature birth in women with chronic IBD, particularly women who had active disease during pregnancy [15, 16]. In a meta-analysis carried out in 2007, the risk of premature birth for women with chronic IBD was 1.87 times higher (95% CI: 1.52–2.31, $p < 0.001$) [16]. A more recent meta-analysis came to a similar conclusion, reporting a 1.85 times higher risk of premature birth [18]. As the causes of premature birth (e.g., preterm labor, premature rupture of membranes or iatrogenic cause due to fetal growth restriction) were not differentiated in the studies, is it not possible to make any generalized statements on the etiology of these premature births.

The meta-analysis by O'Toole et al. found a 1.36 times higher risk of SGA (small for gestational age) fetuses (95% CI: 1.16–1.60), while the meta-analysis by Cornish even reported a 2 times higher risk of giving birth to an infant with a birth weight of < 2500 g. The analysis did not differentiate between fetal growth restriction (e.g., due to placental insufficiency) and constitutionally small fetuses with no pathological causes. The reason for the increased rate of smaller infants can therefore not be conclusively determined. In addition to the risk of placental insufficiency, the effects of anti-inflammatory drugs and the parent's constitution must also be weighed up.

The above-mentioned meta-analyses found an increased risk of malformations. The risk was calculated to be 1.3 and 2.3 times higher, although no serious malformations were reported. The meta-analysis by Cornish et al. only reported an increased risk of malformations for patients with ulcerative colitis. No increased risk was found for patients with Crohn's disease. The risk of intrauterine fetal death was marginally higher by a factor of 1.57 in the meta-analysis by Cornish et al.; this was not confirmed in the meta-analysis by O'Toole. However, both meta-analyses almost exclusively used only retrospective case series, meaning that the results must be interpreted with caution.

A prospective European study of 332 pregnant women with chronic IBD investigated the course of pregnancy in patients with chronic IBD compared to a matched control group [19]. According to this study, there was no difference in the rates of live births, miscarriages, intrauterine fetal deaths, premature births, SGA fe-

tuses, and cesarean sections. A maternal age of > 35 and smoking were risk factors for premature birth and associated with a higher rate of fetal malformations.

Patients should also be monitored for the development of gestational diabetes, as the incidence of gestational diabetes is higher in women with chronic IBD [20].

In summary, it is not possible to make a reliable statement about the course of pregnancy in women with chronic IBD, which is why any flare-ups in pregnancy must be treated. Pregnancies of women with chronic IBD are considered high-risk pregnancies. These women should be monitored by an interdisciplinary team who can advise the treating gastroenterologist. Organ screening in accordance with DEGUM II criteria should be carried out in every case, and particular attention should be paid over the course of the pregnancy to the possible development of fetal growth restriction. As the data on the risk of intrauterine fetal death is not clear, the pregnant woman should be informed about the option of having her labor induced at her calculated due date.

Mode of Delivery

AGG RECOMMENDATION

Pregnant women with ulcerative colitis and an ileoanal pouch should be advised to have a cesarean section.

AGG RECOMMENDATION

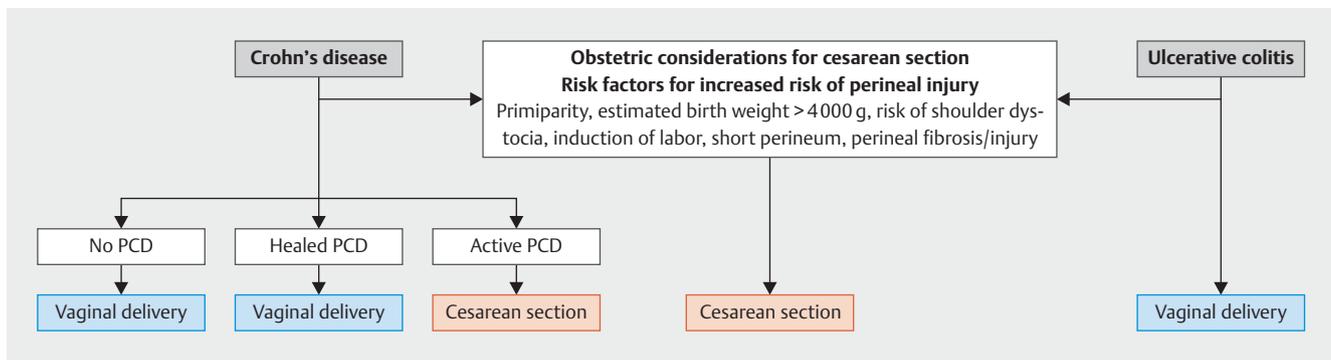
Pregnant women with active perianal Crohn's disease should be advised to have a cesarean section.

AGG RECOMMENDATION

Prophylactic episiotomy should not be carried out.

A recent retrospective study of 124 patients with chronic IBD found increased cesarean section rates, with 63.1% of women with ulcerative colitis and 40.7% of women with Crohn's disease having a cesarean section [21]. The highest cesarean section rates for women with Crohn's disease were found in women with active or inactive perianal disease. In the group of women with ulcerative colitis, the highest cesarean section rate was found in the group of women with an ileoanal pouch (IAP). The cesarean section rate in the meta-analysis by Cornish was 1.5 times higher for women with chronic IBD compared to the control group [17]. The differentiated analysis showed that the cesarean section rate was only significantly increased in the group of women with Crohn's disease, while the increase in women with ulcerative colitis was not significant. However, in the prospective study by Bortoli et al., the cesarean section rate was not higher in women with chronic IBD [19].

As large prospective studies are lacking, the question inevitably arises about the criteria that should be used by the physician



► **Fig. 1** Algorithm to determine the mode of delivery for patients with chronic IBD and a prior history of ileoanal anastomosis (PCD = perianal Crohn's disease) [22].

when considering the planned mode of delivery and discussing it with the expectant mother. In addition to the wishes of the mother, who typically will have a long history of disease, a number of different aspects need to be considered when determining the mode of delivery. Considerations which must be incorporated in the decision in every case include the type of disease, the disease activity, any prior abdominal surgery and the patient's obstetric history. Typically, patients are very worried about potential perianal injuries, wound healing disorders, fistula formation, pelvic floor injuries and possible subsequent incontinence [22].

The ECCO [18] recommends vaginal delivery in women with inactive or mild forms of disease and cesarean section for women with active perianal or rectal disease. In a systematic review, Foulon et al. were able to show that the overall cesarean section rate was higher for women with chronic IBD [24]. One of the reasons for this could be the fear of developing perianal disease and possibly incontinence after vaginal delivery.

However, it appears that worries about developing perianal manifestation of disease after vaginal delivery could be unfounded [24]. Even an episiotomy, vaginal-surgical delivery and birth injuries did not lead to a higher incidence of perianal manifestation in this group of patients. More episiotomies were carried out to prevent 3rd or 4th degree perineal tears. However, the benefit of carrying out a prophylactic episiotomy to avoid 3rd or 4th degree perineal tears is extremely dubious and prophylactic episiotomies should not be carried out [24]. As expected, the rate of cesarean sections in women with perianal manifestation of disease prepartum was significantly higher. In the group of women who aimed for vaginal delivery despite active perianal disease, there was a tendency for disease to get worse after vaginal delivery. The risk for women with healed perianal lesions should be carefully considered. Risks include parity, estimated fetal birth weight, perineal distance and consistency of the perineum.

Women with ulcerative colitis and an ileoanal pouch (IAP) represent a special group of women with IBD. One study reported an increased rate of sphincter defects with impairment of the pouch function, and these patients should be advised to have a cesarean section [26].

► **Fig. 1** shows a potential algorithm which can be used to determine the appropriate mode of delivery for patients with no ileoanal pouch [22, 24].

Postpartum Care

AGG RECOMMENDATION

The medication prescribed to treat chronic inflammatory bowel disease should be continued during lactation.

AGG RECOMMENDATION

Use of mesalazine and corticosteroids can be continued during the period of lactation after carefully weighing up the indications.

The benefits of breastfeeding for mother and child are undisputed. Maternal worries about the safety of medication during lactation means that women often stop regularly taking their medication. According to some reports, 60% of women with Crohn's disease decide to stop taking their medication because of concerns that the drugs could harm their child if the infant is being breastfed [27].

Most medications are compatible with breastfeeding. Less than 1% of the maternal plasma dosage of corticoids, thiopurines or anti-TNF preparations is transferred and these medications should therefore be classed as harmless [28]. In every case, the issue should be discussed by interdisciplinary team.

Conflict of Interest

The authors declare that they have no conflict of interest.

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