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Review article: the management of Crohn's disease and ulcerative colitis during pregnancy and lactation

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SUMMARY

Background
Inflammatory bowel diseases (IBD) commonly affect young patients in the reproductive phase of their lives. The chronic and relapsing nature of IBD and the potential need for medical or surgical interventions raise concerns about family planning issues.

Aim
To review the current knowledge on IBD management in pregnant and nursing IBD patients.

Methods
A PubMed literature search was performed using the search terms 'reproduction' and 'inflammatory bowel disease' and using the headers and main subjects of each section of this article as search terms.

Results
Male and female fertility are not impaired in the majority of IBD patients. In IBD patients with quiescent disease pregnancy outcomes are not impaired in comparison to the general population, however, an increased incidence of pregnancy complications is observed in active IBD patients. As methotrexate (MTX) has been demonstrated to be teratogenic, the use of MTX is contraindicated in patients, who wish to conceive, throughout pregnancy and when nursing. However, normal pregnancies following MTX treatment at conception and later have been reported. Most of the other currently approved IBD medications are not associated with adverse pregnancy outcomes and may be used to maintain quiescent disease or to induce a rapid remission in patients with flares and active disease. Breastfeeding in IBD patients is possible and recommended.

Conclusions
The overall outcome of pregnancies in IBD patients is favourable and not different to healthy controls, thus patients with IBD should not be discouraged from having children.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the most common subforms of the inflammatory bowel diseases (IBD). These diseases are chronic inflammatory illnesses potentially affecting wide parts of the digestive tract, sometimes accompanied by extraintestinal manifestations, and marked by episodes of inflammatory disease activity and remission. UC and CD commonly affect young patients in the reproductive phase of their lives. The chronic and relapsing nature of these diseases and the potential need of a medical therapy or surgical interventions raise questions concerning all fields of reproduction in both sexes. The influence of the diseases on pregnancy and vice versa is a major concern to patients in the phase of family planning. The fear of adverse effects of the medication on the unborn child in pregnancy and later when breastfeeding, the fear of complications after the different modes of delivery, the perception to suffer from a hereditary disease and other beliefs, reasonable and or not, may result in intended childlessness. The treatment of IBD patients from conception to birth is challenging and accompanied by uncertainties for patients and physicians, because the level of evidence of the treatment recommendations in this field is usually low. The aim of this article is to critically review the existing literature and to up-date the latest guideline recommendations.

METHODS

A PubMed literature search war performed using the MESH (medical subject headings) terms 'reproduction' and 'inflammatory bowel disease'. To generate a complete survey of all relevant articles more specific PubMed searches were performed using the headers and the main subjects of each section of this article as search terms. A special focus of interest was set on the time period between 2010 and June 2013. An additional source of relevant literature was generated by reviewing the reference lists from identified articles and from the current guidelines. The search was limited to articles published in English. The information extracted from literature was condensed to applicable recommendations and completed by our own clinical experience.

FERTILITY

Fertility in IBD

As male and female fertility are potentially influenced by different mechanisms for physiological and anatomical reasons and the wish to conceive is based on a variety of rational and irrational motivations it is important to distinguish between intended and unintended childlessness in CD and UC. The patient's (mis-) perception of the nature and the course of the underlying disease, its inheritance, side effects of medications and other interventions potentially contribute to an intended childlessness.[1]

Women and men diagnosed with CD or UC without signs of active disease, disease specific medication and without a medical history of surgical interventions are generally as fertile as the general population.[2, 3] However, patients suffering from UC and CD tend to have fewer children than the control populations.[4] In contrast to UC, active CD is reported to have a negative influence on fertility rates.[2, 5] The reasons for subfertility in CD include different mechanisms as impairment of the fallopian tubes, ovarian dysfunction, as well as dyspareunia as a consequence of a perianal or pelvic disease manifestation.[6, 7] In addition, severe disease activity and/or malnutrition/anorexia may result in secondary amaenorrhea and infertility.[2, 3, 6]

The standard medication including mesalazine, sulfasalazine and corticosteroids do not have any known negative influence on fertility in female CD and UC patients.[8] The immunomodulators azathioprine and mercaptopurine are generally considered safe for the use in the time period of conception and during pregnancy.[9–11] Methotrexate (MTX) is generally contraindicated in patients wishing to conceive and has to be stopped at least three, better 6–9 months prior to a planned conception in female and male patients.[12–14] In UC, proctocolectomy followed by ileal pouch anal anastomosis reduces fertility significantly.[15–18]

Male patients with IBD treated with sulfasalazine exhibit an impairment of fertility which improves after switching to mesalazine.[8] Thiopurines started at least 3 months prior to conception are not associated with a significantly elevated risk for unsuccessful pregnancies and fertility impairment in male patients.[19] The influence of frequently used IBD medications on female and male fertility is also summarised in Table 5 at the end of this review.

PREGNANCY

Natural course of pregnancy in IBD patients and expected outcome of mothers

Pregnancies in IBD will develop normally in about 80% of patients[20] (Table 1). A meta-analysis including 12 studies with 3907 female IBD patients found elevated odds ratios for preterm delivery in IBD (OR 1.87, 95%

Table 1 | Pregnancy outcome in IBD patients according to disease activity[22]

	Normal course (%)	Congenital abnormalities (%)	Pre-term birth (%)	Spontaneous abortion (%)
Background population	83	2	6	9
CD, in remission	82	1	7	10
CD, active disease	54	1	25	20
UC, in remission	84	1	6	9
UC, active disease	65	2	12	21

CI: 1.52–2.31), low birth weight in CD (OR 2.82, 95% CI: 1.42–5.60) and congenital malformations in UC (OR 3.88, 95% CI: 1.14–10.67).[21] These data are contrasted by a large study from 2007[22] and a prospective case–control study from 2011,[23] which found no differences in spontaneous abortion, preterm delivery, congenital malformations and low birth weight. However, most studies did not consider disease activity and in the latter studies from 2007 and 2011 most patients were in a stable remission thus possibly biasing data and leading to contrary results.

Available data regarding the influence of disease activity on pregnancy outcome are inconsistent. On the one hand significantly elevated rates of preterm delivery, low birth weight and congenital malformation have been reported when conception occurred in a period of active disease.[24, 25] Especially maternal weight gain of less than 12 kg in pregnancy was associated with adverse pregnancy outcomes,[26] indicating an active and not manageable disease. On the other hand comparing outcomes of 70 pregnancies (24 CD, 46 UC) before manifestation of IBD to 97 pregnancies (36 CD, 61 UC) after manifestation of IBD in the same women revealed no differences in pre-term birth, low birth weight and congenital malformations, even in cases of higher disease activity (10 active CD, 37 active UC).[27] Whether and to what degree disease activity of IBD influences pregnancy outcomes remains unclear. Nevertheless, normal pregnancy outcomes even in patients with active disease might be a result of recent advances in medical therapy, compensating the negative influence of disease activity on pregnancy outcome and underlining the necessity for an aggressive treatment of flares in pregnancy instead of accepting active disease. In addition, female IBD patients wishing to become pregnant should be advised to plan pregnancy in a phase of stable remission, if possible.

Course of IBD during and after pregnancy

The course of IBD during pregnancy depends on disease activity at conception. If women conceive during a stable remission of IBD, about 70% will stay in remission and about 30% will experience an acute flare, which corresponds to a usual course of IBD in a 9-month period in nonpregnant IBD patients.[28–31]

In contrast, two of three women conceiving during an acute flare of IBD will suffer from a persistent flare and two-thirds of these will experience worsening of disease activity.[22, 32, 33]

From a more global point of view, pregnancies seem to have a beneficial effect on the further course of IBD, as the rate of acute flares decreases after pregnancy in both CD and UC.[34, 35] As many women stop smoking during pregnancy, it remains unclear whether this beneficial effect is caused by smoking cessation, especially in CD.

In consequence, female IBD patients wishing to conceive should be encouraged in their decision, but conception should be planned at stable remission, whenever possible.

Diagnostic approaches in pregnancy

The criteria for diagnosis in IBD do not change during pregnancy, although there are some specific characteristics for diagnosing IBD disease activity assessment during pregnancy.

Different mechanisms like haemodilution, the anabolic metabolism, as well as changes in hepatic and renal clearance result in physiological changes of laboratory parameters. Table 2 summarises the most important changes during pregnancy.

Table 2 | Changes of laboratory parameters in the pregnant IBD patient

Parameter	Change
Albumin	Reduction in up to 1 g/dL
Haemoglobin	Reduction in up to 1 g/dL; possible aggravation and severe anaemia due to disturbed intestinal iron resorption
Erythrocyte sedimentation rate	Acceleration by factor 2–3
Leucocytes	Physiological leukocytosis of up to 15 000 μL

The ultrasound examination of the abdomen is the method of choice in pregnant women (Table 3). However, growth of foetus and uterus limit the applicability of this method in the later course of pregnancy. If findings are inconclusive or relevant parts of the abdomen cannot be examined appropriately, the use of alternative imaging methods will be essential.

Radiation limits the use of computed tomography to individual cases, which have to be chosen wisely (Table 3). Regarding magnetic resonance imaging (MRI), contrast media (mostly gadolinium-based) and the technique itself raise safety concerns for the offspring (Table 3). Experimentally derived data from animal studies showed elevated rates of congenital malformations, when animals were exposed to strong electromagnetic fields.[36–38] However, these results have not been reproduced in human cells.[39–41] The risk of acoustic damage to the foetus does not seem to be relevant,[42] furthermore in the fluid filled stomach of a volunteer a reduction in sound intensity from 120 to 90 dB was detected, falling below the critical threshold of 120 dB.[43] Safety data on gadolinium use in pregnancy are inconsistent. Several animal studies revealed growth retardation and higher rates of congenital malformations, though the dose of gadolinium was two to seven times higher than usual doses in human studies,[44] in contrast this disadvantage was not seen in other animal studies.[45–49] Beyond animal studies, there are only few data on the use of gadolinium in pregnant women. However, published studies of foetal Gadolinium exposure in the first[50] and second as well as third trimester[51–54] did not report adverse events.

In summary MRI should be performed in the second and third trimester without the use of a gadolinium-based contrast media, if possible. If necessary, Gadolinium-enhanced MRI should be considered in individual cases, if the potential benefit outweighs the potential risk for the foetus.

Endoscopy

Gastroscopy, sigmoidoscopy and colonoscopy (Table 3) with a distinct indication, performed by a well-experienced examiner, adhering to recommendations on patient position, sedation and monitoring, are assumed to be safe, especially in the second trimester.[6, 55] With the beginning of the second trimester patients should be positioned in a left lateral position with continuously monitoring of oxygen saturation. Examiners conducting gastroscopy should be aware of a higher risk for aspiration, as lower oesophageal sphincter may be insufficient, especially in the second trimester.[56] Flexible sigmoidoscopy should be preferred instead of colonoscopy, if possible, because less compromising bowel cleansing protocols (e.g. enemas) are sufficient, and the procedure time and length of sedation are usually shorter. Generally, polyethylene glycol based bowel preparation solutions are recommended although safety data for the use in pregnant patients do not exist.[57, 58] The monitoring of foetal vital signs should be considered.

All patients should be offered sedation during endoscopic procedures. We recommend use of propofol in the lowest effective dose, which is classified category B by Food and Drug Administration (FDA). It rapidly passes placental barrier, foetal blood levels reach about 70% of maternal blood levels.[59] Human studies found no differences regarding APGAR-Score and post-partal neurological status for the use of propofol (at doses of 2–

Table 3 | Safety of diagnostic approaches in pregnancy

Diagnostic approach	Safety in pregnancy	Comment
Ultrasound	Safe	Method of choice; often limited applicability in later in pregnancy
MRI	Possible in second and third trimester	Inconsistent data on gadolinium-use, thus MRI preferably without gadolinium; gadolinium use needs case-by-case decision
CT and X-ray	Not recommended	Limited by radiation; case-by-case decision in maternal life threatening situation (with MRI/ultrasound not available or inconclusive)
Endoscopy, general considerations	Needs distinct indication, well-experienced examiner, patient in left lateral position, continuous patient monitoring	
Gastroscopy	Possible	Elevated risk of aspiration (especially in second trimester)
Flexible sigmoidoscopy	Safe	Shorter procedure and sedation time compared to colonoscopy
Colonoscopy	Possible	
Propofol sedation	Possible	Use lowest effective dose

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2.8 mg/kg) compared to thiopental in Caesarean section.[60] Sedation for endoscopy usually requires a bolus of propofol, followed by repetitive boli of 5–10 mg every 2–3 min. Propofol doses commonly used for sedation for gastrointestinal endoscopy are lower than in anaesthetic induction protocols and propofol is assumed safe during pregnancy[61] and lactation.[62]

Reports of congenital malformations (heart defects, lip-jaw-palate clefts and inguinal hernia) after consumption of benzodiazepines in the first trimester[63] have raised safety concerns, even though later studies could not find adverse events.[64, 65] However, with propofol as a safe and widely used narcotic we recommend to avoid the use of benzodiazepine derivates during pregnancy.

THERAPY

Many patients wishing to conceive fear severe adverse side effects for their offspring or fertility and reported this fear to be the main reason for non-adherence to the prescribed medication.[66, 67] This highlights the importance of a detailed consultation and information of patients.

Therapy strategies during pregnancy and lactation are generally not different to those recommended in non-pregnant patients.[68, 69] The indication for initiation or continuation of a medical therapy is based on disease activity, location of manifestation and course of disease. There is no significantly increased risk for miscarriage and malformation under standard therapy including corticosteroids and mesalazine. The risk for pre-term birth and small for gestational age neonates under this medication is increased. Neither the diagnosis of IBD nor the adequate medical therapy are medical indications for abortion.[33, 70–74]

The basic principles of the medical IBD therapy before and during pregnancy are: (i) An acute flare has to be treated prompt and effectively. (ii) An effective therapy should not be discontinued, if not contraindicated. (iii) The individual course of disease and the medical history have to be considered when planning medical therapy. (iv) A medical therapy for maintenance of remission has to be discussed with the patient regarding all risks and benefits. (v) If possible, the medication with the minimal risk for mother and child should be chosen. (vi) The optimal time point of conception is in stable disease.

Finding the appropriate medical therapy during pregnancy may be complicated by the fact that almost all available medications have no explicit approval for the treatment of IBD during pregnancy from the official authorities. The 1979 established pregnancy risk categories by the American FDA (see Table 4) as well as recommendations by the European Crohn's and Colitis Organization (ECCO) may serve as guidance. In general, most of the established drugs for IBD therapy, with exception of MTX and thalidomide which are strongly contraindicated in pregnancy, are regarded as low risk.

Drugs

The use of frequently administered IBD medications during pregnancy is summarised in Table 5.

Aminosalicylates. Aminosalicylates are indicated to treat mild-to-moderate UC and for maintenance of remission. The efficacy of aminosalicylates in the treatment of CD is limited. Aminosalicylates including sulfasalazine are generally considered safe during pregnancy. A meta-analysis with a total of 642 pregnant IBD patients exposed to aminosalicylates found no statistically significant risks for congenital malformations, stillbirth, spontaneous abortion, preterm delivery or low birth weight.[75] As sulfasalazine acts as a folic acid antagonist,

Table 4 | FDA pregnancy categories

Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
Category B	Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women
Category C	Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category D	There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X	Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

Table 5 | Influence and use of frequently used IBD medications on female and male fertility, pregnancy outcome and lactation

Drug (FDA pregnancy category)	Influence on...		Use during pregnancy	Use during lactation
	Male fertility	Female fertility		
Mesalazine (oral: B; rectal C)	No influence[8]	No influence[8]	Possible[75]	Possible[146–150]
Sulfasalazine (B)	Possible influence (fully reversible after ending)[197, 198]	No influence[8]	Possible,[75] folic acid supplementation recommended[76]	Possible[155–159]
Prednisolone (C)	Unclear	No influence[8]	Possible[6]; risk of lip-jaw-palate clefts unclear[79–82]	Possible, only minor amounts detectable in breast milk and no significant risk[163]
Oral Budesonide (C)	No data	No data	Possible[88]	Unclear, but no significant side effects expected
Thiopurines (MP, Azathioprine) (D)	No influence[19]	No influence[9–11]	Possible[10, 11, 70, 91, 92]	Possible[165–169]
Infliximab (B)	Probably no influence[199–201]	Unclear	Possible,[10, 11, 70, 91, 92] Stop in last trimester recommended	Unclear, but no significant side effects expected
Adalimumab (B)	No data	Unclear	Possible,[11, 108, 110–112] Stop in last trimester recommended	Unclear, but no significant side effects expected
Golimumab (B)	No data	No data	Possible, however only animal data available[115]; Stop in last trimester recommended	No data
Methotrexate (X)	Unclear, discontinuation recommended	Contraindicated	Contraindicated[72, 97]	Contraindicated[171]
Ciclosporin(C)	Unclear	Unclear	Possible, rescue therapy in steroid-refractory UC	Possible [178–185]
Tacrolimus (C)	Unclear	Unclear	Possible, case-by-case decision for rescue therapy in steroid-refractory UC	Possible[178–185]
Ciprofloxacin (C)			Possible, only if no alternative antibiotic therapy is availabe	Possible, caution because of potential risk of diarrhoea/colitis in infants[187–189]
Metronidazole (B)			Possible	

an additional supplementation of 2 mg folic acid per day is recommended to diminish possible adverse effects of folic acid antagonists.[76]

Corticosteroids and budesonide. Steroids are drugs of choice for an acute flare and classified as safe in pregnancy according to actual ECCO guidelines.[6] They easily pass placental barrier, but especially prednisone and prednisolone are largely inactivated by placental 11 beta-hydroxylase.

Several animal studies consistently reported an increased incidence of cleft lip and palate after steroid medication in pregnancy,[77, 78] whereas data from human studies are inconsistent.[79–82] However a low risk for lip-jaw-palate clefts, especially after use of steroids in the first trimester, cannot be excluded and should be discussed with the patient. In our opinion the risk by an uncontrolled acute flare seems to be higher than the potential harm from steroid use.

Adrenal suppression and insufficiency are possible adverse events in patients treated by steroids. Neonatal adrenal suppression after maternal steroid therapy in pregnancy has been reported in case reports.[83–86] Only one case of neonatal adrenal suppression after steroid consumption in a pregnant IBD patient has been reported.[87] In this case, the mother had received a fixed dose of 32 mg methylprednisolone in combination with daily hydrocortisone enema (100 mg) for 1 month. In

conclusion, neonatal adrenal suppression or insufficiency seems to be a rare complication, but should be kept in mind, especially after high-dose steroid use in the late third trimester.

Budesonide is recommended for treatment of mildly active localised ileocaecal CD.[69] Actually, there is only a retrospective study with eight CD patients receiving oral budesonide (6–9 mg/day) during pregnancy[88] no adverse pregnancy outcomes have been reported.

Two studies examined the use of a special galenic formulation [extended release, multi matrix (MMX)] of budesonide in UC. MMX Budesonide was safe and moderately effective in the treatment of mild-to-moderate UC,[89, 90] but no data for its use during pregnancy is available.

Thiopurines. Thiopurines are indicated for the treatment of chronic disease activity in UC and CD with steroid dependent or refractory course of disease. Over the last decades, the clinical experience with the use of azathioprine and mercaptopurine during pregnancy has become great. Studies with several hundreds of pregnant patients receiving thiopurines did not find higher rates of abortion, congenital malformations and pre-term birth compared to non-exposed pregnancies[10, 11, 70, 91, 92] and stand in contrast to studies with lower case numbers reporting higher rates of pre-term delivery, malformations and low birth weight.[93, 94] Interestingly, in 2013 Casanova *et al.* reported a significant lower rate of neonatal complications after exposure to thiopurines during pregnancy compared to non-exposed neonates.[11] Data from a prospective multicenter follow-up study did not find negative influence on long-term development or immune function of children, who were exposed intrauterine to maternal thiopurine therapy.[95]

Thiopurines should be considered as safe in pregnancy. A worldwide survey reported that 89% of IBD experts continue azathioprine therapy during pregnancy in CD.[96]

Methotrexate. Methotrexate is considered teratogenic and mutagenic, consequently contraindicated in pregnancy.[72, 97] Patients on MTX have to be advised to use an effective method for contraception. In case of conception MTX has to be stopped urgently and folic acid supplementation in high doses is needed. A therapeutic abortion is not generally indicated, but detailed information about the teratogenic potential of MTX is required and patients should be offered an ultrasound malformation screening. Due to intracellular modification MTX has a long-lasting action and should have been terminated for about 3 months when planning pregnancy.

Calcineurin inhibitors. The use of calcineurin inhibitors might be considered in the treatment (induction and maintenance of remission) of severe UC. Most data on tacrolimus and ciclosporin use in pregnancy are derived from transplantation medicine. Since 1991, more than 2000 pregnancies after organ transplantation have been registered in Swedish National Transplantation Pregnancy Registry, most patients had kidney transplantation (76%) and were treated with tacrolimus or ciclosporin in combination with steroids.[98] With exception of mycophenolate mofetil, there was no increased incidence of congenital malformations compared to general population.

In addition, a prospective study with 37 women after liver transplantation, treated with tacrolimus and steroids found no elevated rates of congenital malformation compared to general population.[99] In conclusion, neither ciclosporin nor tacrolimus seem to have a relevant teratogenic potential.

Many studies described higher rates of pre-eclampsia, pre-term birth, low birth weight and small for gestational age. It is unclear, whether these adverse events are caused by disease itself or are a result of medication. Comparing 908 births before and 152 births after organ transplantation in the same women, rates of pre-eclampsia (22%), pre-term birth (46%), low birth weight (41%) and small for gestational age (16%) did not differ,[100] possibly indicating the underlying disease as main reason for these adverse events.

European Crohn's and Colitis Organization guidelines for UC discuss the use of calcineurin inhibitors as rescue therapy for steroid-refractory UC with evidence level 1b for ciclosporin and evidence level 4 for tacrolimus.[68] A retrospective study with eight pregnant UC patients[28] and a small case–control study with a subgroup of five women receiving ciclosporin[29] report high effectiveness for induction of remission in severe, steroid-refractory UC in pregnancy.

Successful use of tacrolimus for steroid-refractory UC in pregnancy has only been reported in form of a case report so far.[101]

In general, data and evidence levels regarding calcineurin inhibitors in CD are limited to uncontrolled studies or case reports, thus ECCO guidelines for CD discuss the use of tacrolimus and ciclosporin only on a case by case basis, data on use of calcineurin inhibitors in pregnant CD patients are still missing.

Biologicals. Biologicals are indicated for induction and maintenance of remission in moderate to severe CD and UC. Infliximab (IgG1), adalimumab (IgG1), golimumab (IgG1) and certolizumab (Fab Fragment) as anti-TNF-alpha antibodies and natalizumab (IgG4) as anti-Integrin antibody are available biologicals for IBD therapy. However, only Infliximab (IFX) and adalimumab (ADA) have approval for IBD therapy in Europe.

Class G immunoglobulins pass placental barrier by active transport, which significantly increases from week 13 of gestation and reaches its maximum in third trimester.[102–105] Within Immunglobulin G subclasses 1–4, IgG1 has the highest diaplacental transportation rate, followed by IgG4, IgG3 and finally IgG2.[105] Consequently, it was hypothesised, that neonatal concentrations of IFX and ADA would exceed maternal blood levels, whereas certolizumab (CZP) as fab fragment should have lower neonatal blood concentrations. Mahadevan *et al.* reported median neonatal cord levels for IFX of 160%, ADA 153% and CZP 3.9% compared to maternal blood levels after exposure to IFX ($n = 11$), ADA ($n = 10$) and CZP ($n = 10$) in all three trimesters. IFX and ADA could be detected in the infants for as long as 6 months.[106]

Greatest experience for the use of biologicals in IBD exists for IFX,[11, 107, 108] especially from TREAT registry.[109] These data suggest no elevated rates for congenital malformations.

Data on ADA use in pregnant IBD patients is limited to case reports[110–112] and studies with low case numbers,[11, 108] no adverse events in comparison to non-exposed pregnancies were reported.

Golimumab has shown to be efficient to induce and maintain remission in TNF-alpha naïve patients with UC.[113, 114] Use of golimumab in pregnancy is limited to animal studies in cynomolgus macaques,[115] no adverse events were observed. Like IFX and ADA golimumab is transported across the placenta, leading to foetal blood concentrations of about 50% compared to maternal blood levels, thus treatment should be stopped in the last trimester, like in IFX and ADA use.

Risks and benefits of the use of golimumab during pregnancy and lactation are assumed to be similar to those of the other monoclonal antibodies against TNF-alpha. However, as there is no clinical data so far, we recommend using IFX or ADA instead.

Certolizumab has approval for IBD therapy only in Switzerland and US and was classified by FDA as category B. So far, only a small study with 10 pregnant CD patients, who received CZP in all trimesters, is published.[106] Congenital malformations and adverse events were not found.

Because of increasing diaplacental transfer for IFX and ADA with a maximum in the third trimester, therapy with these biologicals is often terminated with the beginning of the third trimester. There is no evidence from studies for this recommendation, nevertheless in our personal opinion IFX and ADA should be paused with the beginning the third trimester, if the patient is in a stable remission, as persisting antibody levels in the newborn may result in potential immunosuppression in the newborn or impact the development of the immune system during childhood. In case of an acute flare scheduled biological therapy may be re-initiated as recommended by the London position statement on biological therapy in IBD.[116] It is particularly important that neonatologists are made aware if the mother has received anti-TNF in the last trimester as BCG vaccination of the newborn must be avoided in such cases.

Vedolizumab has been recently approved for the treatment of CD and UC not responding to conventional treatment. No data for the use of Vedolizumab during pregnancy is currently available, thus, no recommendations can be made. Natalizumab has no approval for IBD therapy in Europe. Studies or case reports of successful use in pregnant IBD patients are lacking so far. Most data concerning safety of natalizumab in pregnancy come from patients suffering from multiple sclerosis, one study with 35 women, who accidently conceived and gave birth to 28 babies, reported beside one case of hexadactyly no significant congenital malformations or neonatal complications.[117]

Antibiotics. Antibiotics are indicated for the treatment of perianal CD and to treat infectious complications in UC and CD, as well as pouchitis after ileo-pouch anal anastomosis (IPAA). The most intensively studied and widely used antibiotics in IBD are fluoroquinolones and nitroimidazoles. The majority of the alternative types of antibiotics is of minor relevance for the treatment of IBD and is generally used in case of intolerance to the standard treatment with fluoroquinolones and nitroimidazoles. The specific recommendations and restrictions concerning the use during pregnancy and lactation have to be considered thoroughly.

A meta-analysis and a prospective controlled trial evaluating the risk for birth defects, stillbirths, pre-term births and low birth weight following exposure to quinolones in the first trimester of pregnancy could not find an increased risk for complications.[118, 119] In contrast to these findings animal experiments detected an increased risk for cartilage damages after fluoroquinolone use during pregnancy.[120, 121]

Overall, fluoroquinolones should only be used during pregnancy if no alternative antibiotic with a more favourable risk to benefit ratio is available. Two large meta-analyses examining the safety of metronidazole as the most frequently used representative from the group of nitroimidazoles in pregnancy found no increased teratogenic risk.[122, 123] The use of metronidazole during all trimesters of pregnancy appears to be safe.

Rifaximine may be helpful in the treatment of chronic pouchitis and is recommended by ECCO guidelines.[124] Data concerning rifaximine use in pregnancy are still missing. Intestinal resorption of rifaximine is described below 1%; however, in patients with bowel inflammation low blood levels of rifaximine (<10 ng/mL) have been reported by the manufacturer. Resorption may be higher in case of high inflammatory activity in pouchitis and rifaximine treatment should be avoided in these cases.

Probiotics. While there is not enough evidence for effectiveness of probiotics in the therapy of CD up to date,[69] probiotics are effective in therapy of UC, with evidence for *Escherichia coli* Nissle and VSL#3. *Escherichia coli* Nissle is effective in maintenance of remission in UC and is suggested as alternative to 5-ASA.[68] The probiotic mixture VSL#3 has a positive additional effect on disease activity in patients with relapsing, mild-to-moderate UC, who are under treatment with 5-ASA and/or immunosuppressants.[125] Furthermore, it has been shown to be effective in the prevention of pouchitis[126] and in the maintenance of antibiotic induced remission of pouchitis.[126, 127]

As probiotics are part of physiological intestinal flora, *E. coli* Nissle and VSL#3 are not assumed to have any negative influence on pregnancy outcome.

Proton pump inhibitors. Proton pump inhibitors (PPI) are used for the treatment of CD manifestations of the upper gastrointestinal tract and, more frequently, as supportive or concomitant therapy. The use of PPI during pregnancy and lactation has been studied intensively. In a cohort study including 5082 live births exposed to PPI between 1996 and 2008, maternal PPI treatment was not associated increased risk of birth defects.[128] The use of PPI during pregnancy seems to be safe with the greatest experience for omeprazole, which is regarded the preferred medication.

In 2012 Andersen *et al.* reported an increased risk for asthma in children, who were prenatally exposed to acid-suppressive drugs (including PPI and histamin2-receptor antagonists,[129]), however it is not clear, if this is a class-effect of the used drugs or a bias by maternal comorbidities, as an increased risk was reported even for PPI use after pregnancy.

Bile acid sequestrators. Cholestyramine is indicated to treat bile acid malabsorption, especially after ileocecal resection in CD. In addition, it has been used to treat intrahepatic cholestasis of pregnancy as well as hypercholesterolaemia. A study examining the effectiveness of cholestyramine in intrahepatic cholestasis showed adverse effects of this medication during pregnancy.[130] Severe foetal intracranial haemorrhage during cholestyramine treatment has been described.[131] All bile acid sequestrates potentially inhibit the uptake of food components, medication and vitamins (also vitamin K). The use of cholestyramine during pregnancy cannot be recommended. In the rare case of the absence of any alternative medical therapy risks and benefits of a cholestyramine therapy have to be thoroughly discussed with the patients. Colesevelam and Colestipol are also not absorbable and will not enter the bloodstream after oral ingestion. Their use has not been investigated in pregnant women. Animal studies have not shown a significant teratogenic potential.[132, 133] The recommendations concerning the use of colesevelam and colestipol during pregnancy are similar to cholestyramine.

Metoclopramide, loperamide and simethicone. Metoclopramide, loperamide and simethicone are widely used medications playing an important role in the symptom orientated supportive IBD therapy.

Metoclopramide is often used during pregnancy because of its potent prokinetic and antiemetic potential. Two recently published register-based large cohort studies revealed no evidence for an increased risk of malformation of other pregnancy complications.[134, 135] Nevertheless, the use of metoclopramide should be recommended with caution because it crosses the placental barrier and reaches significant foetal plasma concentrations.[136]

The effect of loperamide on pregnancy outcome has been examined in retrospective cohort studies. One study included 89 pregnant women with exposure to loperamide and has shown no increased risk of major malformations.[137] Another Swedish study suggested a possible moderate increased risk for hypospadia, placenta previa, large for gestational age and Caesarean section.[138] In most cases acute diarrhoea does not require the use of anti-diarrhoeal medication. If really necessary, the risk of short-term loperamide therapy during pregnancy appears

to be acceptable. Long-term loperamide therapy should only be recommended if no applicable alternative medication is available.

Simethicone is a widely used medication to treat gas-related abdominal discomfort. The agent is not absorbed after oral ingestion making adverse effects during pregnancy extremely unlikely. Controlled studies investigating the use of simethicone during pregnancy are not available.

Ingredients and additives in drugs. All available drugs consist of more than the pharmaceutical active component. It is important to notice that not only the active pharmaceutical agent potentially causes adverse effects but also the other ingredients and additives. Phthalates for example are used in a variety of consumer products. These agents were found to cause reproductive and developmental toxicity in animal studies.[139] One study reported high urinary concentrations of phthalate metabolites under mesalazine therapy in one female patient.[140] The phthalate is part of the galenic coating for the delayed-release in a certain mesalazine formulation. The relevance of these findings remains unclear, larger studies are needed. The risks caused by these and other additives are difficult to assess. Generally, these risks seem acceptable when using well-standardised medication with approval of the major authorities (FDA, EMA).

MANAGEMENT OF COMPLICATIONS AND SURGERY

In general, therapy of intestinal stenosis, abscess or ileus in pregnancy is based on the same principles as in non-pregnant IBD patients and operation is indicated in most patients. Patients with a strong indication for abdominal surgery, like intraperitoneal sepsis, should undergo operation urgently, as severe illness seems be the greater risk for mother and foetus. This approach has been adopted from data on acute appendicitis. Nonperforated appendicitis in pregnancy is associated with maternal and foetal mortality of 0%, whereas perforation of appendicitis increases mortality for mother (17%) and foetus (43%).[141] In a retrospective study with 77 pregnant women with non-obstetric abdominal surgery with a clear indication (acute appendicitis, gall-bladder disease, adnexal mass) a maternal and foetal mortality of 0% was reported and authors concluded that necessary surgery in pregnancy is safe and that the severity of the underlying disease is the main risk factor for maternal and foetal outcome.[142] Because of higher rates of pre-term labour in the third trimester and spontaneous abortion in the first trimester authors recommend to perform surgical interventions in the second trimester, if possible.[142]

DELIVERY

The mode of delivery should generally be chosen according to obstetric recommendations. However, in some situations in IBD Caesarean section should be considered. In case of active perianal or rectal disease Caesarean section is recommended by ECCO.[6] If in doubt about perianal or rectal disease activity, a rectoscopy should be performed.

After restorative proctocolectomy with IPAA, patients are highly dependent on intact anal sphincter, consequently Caesarean section is advised, as the risk of sphincter injury seems to be increased after vaginal delivery.[143] In contrast, the possibility for necessary proctocolectomy with IPAA in the future should not lead to a general indication for Caesarean section in female UC patients, in our opinion.

In mothers with CD, absence of perianal or rectal affection allows vaginal delivery without elevated risk for post-partal flare,[144] but episiotomy should be avoided, if justifiable from the obstetric point of view, as perianal affection may be triggered by this intervention.[145]

In summary, there are few gastroenterological indications for Caesarean section, but decision about delivery mode should be taken by obstetrician, gastroenterologist and colorectal surgeon together. In IBD patients, threshold for Caesarean section should be set to a low level in cases of obstetric concerns. However, performing Caesarean section only on patient's wish in absence of medical indication has to been seen critical, as birth by Caesarean section is associated with moderately higher rates of IBD onset in childhood.[146]

BREASTFEEDING

Breastfeeding in IBD

Breastfeeding is generally considered to be the ideal form of nutrition with positive effects on various aspects of health of mother and child.[147] It is not associated with a worsening of the course of disease or the development of acute flares in IBD.[148] A systematic review examining the effect of breastfeeding on the development of IBD in children could find a possible protective effect on early onset IBD.[149] The cessation of an effective therapy should be avoided if possible. The use of possible IBD medications during breastfeeding is summarised in Table 5. While a meta-analysis supports this hypothesis of a positive effect,[149] other studies could not find an

association between breastfeeding and the risk of suffering from IBD.[150, 151] Even more controversially, there are reports from studies including appropriate numbers of patients that indicate an increased IBD risk associated with breastfeeding.[152, 153] Altogether, the role of breastfeeding as a risk factor of IBD remains unclear.

Breastfeeding and medication

Indeed, the proportion of breastfeeding mothers among IBD patients is smaller than in the general population.[154] A central concern in the decision against breastfeeding is the fear of adverse effects caused by the IBD medication or its metabolites excreted into the breast milk. While most of the drugs used in the therapy of IBD can be detected in breast milk, standard medications are safe for the use during breastfeeding.[154] Nevertheless, it is important to notice that there are no data available regarding the safety of medications during breastfeeding in case of preterm birth or other conditions impairing the metabolism of the infant. Generally, the health status of the nursing infant should be attended carefully even if the maternal medication was considered to be safe.

Mesalazine and sulfasalazine

The concentrations of mesalazine and sulfasalazine in breast milk of patients receiving therapeutic doses of this medication are low and the use is generally considered safe during breastfeeding,[155–159] although anecdotal reports described bloody diarrhoea in infants induced by mesalazine via breast milk.[156, 160, 161] Breastfeeding should be stopped immediately in case of bloody diarrhoea of the infant during maternal mesalazine therapy.

Corticosteroids

Prednisolone and prednisone levels in breast milk depend directly from the serum concentrations. A study in six women with a daily dose of prednisolone up to 80 mg reported only low milk concentrations.[162] A study examining the prednisolone levels in breast milk in asthma patients receiving parenteral doses of 50 mg prednisolone found also only very low amounts of the medication and concluded that there is no significant risk to the nursing infant.[163]

Budesonide

Data on budesonide in breastfeeding women only exist for inhaled budesonide in asthmatic mothers,[164] negligible systemic exposure to budesonide was reported for breastfed children. Studies dealing with orally taken budesonide in breastfeeding are missing. However, about 90% of oral budesonide is hepatically transformed to metabolites with very low activity (about 1%) compared to budesonide. Thus, systemic plasma levels in mothers as well as systemic exposure to breastfed infants are assumed very low. Decision on using oral budesonide during nursing should be made case-by-case.

Thiopurines

Since the concentration of thiopurines and their metabolites are very low in human breast milk and in the serum of breastfed infants, the use of these medications in standard doses is not contraindicated during breastfeeding. While most studies could not find any detrimental effect of the maternal use of thiopurines during breastfeeding, genetical changes impairing the metabolism of thiopurines (e.g. TPMT genotypes) may pose a potential risk for adverse effects. Recent cohort studies could not find an increased risk of infections or other complications, but only included small numbers of patients/infants.[165–169]

Methotrexate

Methotrexate is a folate antagonist, has teratogenic effects, and is excreted into human breast milk.[170] Its use is contraindicated in male and female patients wishing to conceive, during pregnancy and breastfeeding.[171] A systematic review on the safety of MTX in the context of pregnancy and breastfeeding in rheumatoid arthritis could not find articles, fulfilling acceptable quality criteria.[14]

Biologicals

In contrast to earlier studies,[172] recent analyses could detect infliximab in the human breast milk in very low concentrations.[173, 174] Like the other anti-TNF-antibodies ADA could be detected in human breast milk in low concentrations as well. One case report could not find ADA in the serum of the infant while the mother received scheduled therapy. None of the infants in the available studies exhibited signs of adverse reactions to the maternal medication.[110, 175, 176] Similar findings were made when examining serum and breast milk levels in patients treated with CZP and their neonates.[177] Small amounts of Infliximab, ADA and CZP as well as golimumab might be transferred to the infant via breast milk. Although no adverse effects have been observed in small case series, the biological effects of these agents in the neonate remain unclear.

Calcineurine inhibitors

Ciclosporin and tacrolimus can be detected in breast milk of nursing mothers receiving standard doses of this

medication. Ciclosporin levels are varying considerably. Case reports from renal and liver transplantation programs indicate that the medication levels in the breast milk and the absorption by the neonate are very low. The authors concluded that both medications could be compatible with breastfeeding.[178–185] A follow-up study could not find adverse effects after maternal tacrolimus exposure.[186]

Antibiotics

Ciprofloxacin and metronidazole are not generally incompatible with breastfeeding.[187, 188] Both antibiotics are excreted into breast milk in relevant amounts and potentially cause diarrhoea in the infants. The development of a pseudomembranous colitis after maternal ciprofloxacin use has been described.[189] The long-term effects of a ciprofloxacin or metronidazole exposure on breastfed infants have not been studied sufficiently. The indication for a systemic therapy with both agents has to be critically evaluated. Long-term treatment should be avoided generally.

Probiotics

Probiotics (e.g. *E. coli* Nissle, VSL#3) are natural components of intestinal flora and are expected to be safe in breastfeeding. Furthermore, specific probiotics have been shown to be effective in reducing the risk of eczema in breastfed children.[190]

Metoclopramide, simethicone, loperamide

Metoclopramide has been used as galactogogue, because it increases maternal prolactin levels.[191] Although it is secreted into breast milk, no relevant side effects in the breastfed neonates have been observed in studies.[192, 193] The use of metoclopramide during lactation over a short period of time is safe.

The bioavailability after oral ingestion of loperamide is very low but in can be detected in breast milk in low concentration.[194] The effects of these very small amounts on the infant have not been studied systematically. Nevertheless, the use of loperamide over a short period of time during lactation seems to be safe.

Simethicone is not absorbable and often used in neonates to treat abdominal discomfort. The use of simethicone during breastfeeding is safe.

Bile acid sequestrants

All bile acid sequestrants (cholestyramine, colestipol, colesevelam) may impair the absorption of medications and vitamins. As they are generally not absorbed from the gastrointestinal tract, the use during lactation appears safe under medical observation. Safety data from controlled studies are missing.

Proton pump inhibitors

Data on the use of PPI during breastfeeding are only published for omeprazole and pantoprazole.

A case report of a single mother using omeprazole (20 mg/day) while breastfeeding,[195] reported peak omeprazole concentrations in breast milk of less than 7% of peak serum concentrations. In a nursing mother taking pantoprazole (40 mg/day), exposure to the breastfed infant was about 7.3 μg (0.14% of weight-normalised dose).[196]

If PPI are indicated omeprazole and pantoprazole should be preferred.

KEY POINTS IN MANAGEMENT OF IBD IN PREGNANCY AND BREASTFEEDING

Women and men diagnosed with CD or UC without signs of active disease, disease specific medication and without a medical history of surgical interventions are generally as fertile as the general population. In contrast to UC, active CD is reported to have a negative influence on fertility rates. The standard medication including mesalazine, sulfasalazine and corticosteroids do not have any known negative influence on fertility in female CD and UC patients.

Pregnancies in IBD will develop normally in about 80% of patients (see Table 1). Female IBD patients wishing to become pregnant should be advised to plan pregnancy in a phase of stable remission, if possible.

The ultrasound examination of the abdomen is the diagnostic method of choice in pregnant women. Gastroscopy, sigmoidoscopy and colonoscopy with propofol sedation are assumed safe, especially in the second trimester. Safety of diagnostic approaches in pregnancy is summarised in Table 3.

The basic principles of the medical IBD therapy before and during pregnancy are: (i) An acute flare has to be treated prompt and effectively. (ii) An effective therapy should not be discontinued if not contraindicated. (iii) The individual course of disease and the medical history have to be considered when planning medical therapy. (iv) A medical therapy for maintenance of remission has to be discussed with the patient regarding all risks and benefits. (v) If possible, the medication with the minimal risk for mother and child should be chosen. (vi) The optimal time point of conception is in stable remission.

The use of possible IBD medications during pregnancy is summarised in Table 5.

The mode of delivery should generally be chosen according to obstetric recommendations. In case of active perianal or rectal disease Caesarean section is recommended. After IPAA Caesarean section is advised.

Breastfeeding is not associated with a worsening of the course of disease or the development of acute flares in IBD. The use of possible IBD medications during breastfeeding is summarised in Table 5.

AUTHORSHIP

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