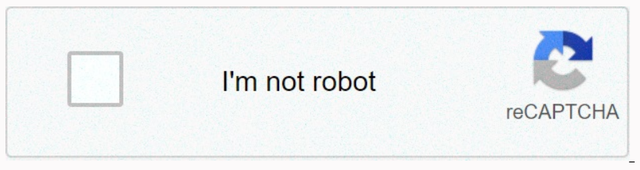

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Inflammatory bowel disease pdf 2018

Inflammatory bowel disease (IBD) affects patients during their peak reproductive years. This raises important questions, both in patients and healthcare providers, about conception, pregnancy, and breastfeeding. Lack of information and insufficient communication among healthcare professionals can leave patients with limited information and even conflicting advice. Given that pregnant and/or nursing IBD patients are excluded from clinical trials, the evidence for many issues relating to pregnancy and postpartum period is limited. However, there is increasing data from case series and cohort studies that allow clinical guidance to be provided. The overall concept is that optimising maternal health is essential to optimise the health of the unborn child and the benefit of continued medical treatment in IBD during pregnancy outweighs possible risks in most cases. This document provides an updated systematic review of the literature on IBD during pregnancy and suggests guidance for issues that healthcare professionals often encounter. © 2020 S. Karger AG, Basel IntroductionInflammatory Bowel Disease (IBD) is represented by Crohn's disease (CD) and ulcerative colitis (UC). The highest age onset of these diseases coincides with childbearing years and approximately 25% of patients will have their first child after being diagnosed with IBD [1]. These diseases can therefore have an impact on fertility, pregnancy, and breastfeeding. Managing IBD during pregnancy can be a challenge for healthcare professionals, as the health of both the mother and the fetus must be considered to make the optimal therapeutic decision. Combating disease activity is essential, especially at conception time, as uncontrolled disease is associated with a higher risk of negative pregnancy outcomes for both the mother [2,3] and the fetus [4-8]. There are many concerns among IBD patients regarding the impact of the disease during pregnancy and the consequences for the child. One report suggested that 50% of women with IBD were concerned about infertility, a quarter thought it was more important to tolerate symptoms than to expose the fetus to their treatment, a third believed that any medication given to IBD would be dangerous for their child, and three quarters were concerned about transmitting the disease to their offspring [9-11]. These concerns may explain why some women stop treatment before conception or during pregnancy and lactation, despite the increasing evidence from recent studies confirming the benefit of continued medical treatment in IBD during pregnancy [12-19]. Counseling patients during this emotional and important period of their lives is important. Management should be multidisciplinary, including gastroenterologist and IBD nurse, obstetrician, primary care provider, pediatrician and if necessary surgeon. Communication between these practitioners is essential to avoid ambivalent or even contradictory advice, an additional source of anxiety for patients as well as potentially suboptimal compliance. In 2015, the European Crohn's and Colitis Organisation published the second consensus on reproduction and pregnancy in IBD, which mainly includes data published until 2013 [20]. Important concepts have recently emerged in the context of case control and large cohort studies. This article aims to incorporate up-to-date evidence regarding the management of IBD before conception, during pregnancy, and postpartum period. The effect of IBD on fertility patients with IBD has fewer children compared to the general population, which can be partly explained by some patients' choice not to have children. Voluntary infertility is reported in 17% of women with IBD compared to 6% of women in the general population [21]. This choice is largely due to fears that are often unwarranted [22], which reinforces the importance of precise advice in this population to help them make their decision. A systematic review of 11 studies found no increased rate of infertility issues in women and men with IBD in remission and without a history of surgery [23]. However, the effectiveness of IBD activity and certain treatments is important for both men and women in terms of fertility and pregnancy outcomes. WomenMedical therapy for IBD, including all biological treatments, steroids, thiopurins, methotrexate, and mesalamine, does not reduce fertility [24-27]. However, women with active IBD may have reduced fertility [28-30] related to dyspareunia in patients with severe perianal or pelvic disease, fallopian tube occlusion secondary to pelvic herds and ovariedy function related to chronic disease or nutritional deficiencies [11]. Suggests that patients who have undergone proctocolectomy with ileal-bag anal anastomosis (IPAA), proctectoma, and permanent stoma have an increased risk of infertility. The decrease in fertility is mainly due to inflammation and scarring of the fallopian tubes [31-33]. Choosing a laparoscopic technique in relation to laparotomy probably reduces infertility risk, and there is therefore no need to avoid important surgery because a patient wants to be pregnant [34, 35]. Inability to conceive for 6 months should lead to referral to infertility evaluation, especially if there is a history of open pelvic surgery [36]. IBD women who have undergone IPAA have a success rate for in vitro fertilization comparable to women without IBD or with IBD, but without surgery [37]. MenLess is known about the effect of disease activity and IBD specific medications on men's fertility and pregnancy outcome. A large internet-based voluntary cohort of IBD patients suggested that it is also important to ensure optimal disease control in male patients trying to have children [38]. Men reported difficulties in conceiving more often when they had active or recently active disease. This association is explained by several factors such as decrease in desire for sexual activity activity anxiety and depression, inflammatory effects and/or side effects of medications on sperm characteristics. Several medicines can interfere with motility or sperm quality. Sulfasalazine causes dose-related decreases in both sperm quality and motility that are reversible. It should therefore be replaced by other 5-ASA formulations in men wishing to reproduce [39]. Corticosteroids can cause a reversible decrease in sperm quality and concentration, but this observation does not appear to affect fertility in men [25,40]. Methotrexate (MTX) is contraindicated due to its teratoogenicity and risk of oligospermia, which is reversible 4-5 months after stopping the drug [41, 42]. No evidence of efficacy on fertility outcomes has been described for either thiopurin or antitumornecosis factor (TNF) used by the father at concept time, although it has not been thoroughly studied [43-46]. Male patients suffering from UC who undergo IPAA may experience erectile dysfunction and retrograde ejaculation, also having surgery performed at specialized center with laparoscopic approach help lower the risk [47, 48]. The effect of pregnancy on during IBDRisk of relapse during pregnancy in IBD women with stable disease is approximately 30%, which is similar to non-pregnant patients [7, 49,50]. Conversely, two thirds of patients with active disease at conception will have persistent active disease during pregnancy [2.51]. Pregnancy also appears to lower the risk of long-term disease relapse [52,53]. The effect of IBD on pregnancy, fetal and neonatal outcomesData on the incidence of fetal abnormalities is contradictory, but reported risks are low [10, 51,54]. Current evidence suggests that most of the time women who have quiescent disease before pregnancy have pregnancy outcomes similar to women without IBD. A 2-fold risk of low gestational weight has been reported compared to non-IBD patients in cohort studies [55]. Active disease is associated with higher numbers of negative outcomes such as fetal loss and stillbirth, premature birth, low birth weight, small for gestational age, thromboembobolic events, caesarean section, increased neonatal intensive care uptake, and low APGAR score [56, 57]. Side effects also result in the degree of activity and its timing during pregnancy. It is difficult to determine whether disease activity itself or other confounding factors such as discontinuation of treatments affect the increased risks. As such, it is recommended to control the disease before conception and to keep the mother in remission and well nourished during pregnancy. Monitoring disease activity during pregnancyThe diagnosis of active disease in pregnant IBD patients can be difficult as biological parameters such as C-reactive protein (CRP), hemoglobin concentration, erythrocyte sedimentation rate and serum albumin are affected by pregnancy [51]. In order to make appropriate decisions and achieve and maintain remission, it is important to monitor patients closely in Period. Endoscopy Recent data suggest that endoscopy is relatively safe during pregnancy. It is contraindicated only in obstetric complications such as placenta abruption, ruptured membranes, or eclampsia. If endoscopy is necessary, the indication should be strong and the procedure performed by experienced endoscopiers to reduce the time of the procedure. Where possible, the procedure should be postponed after the first trimester due to organogenesis. Pregnant women should be placed in the left lateral position or left pelvic tilt to avoid aorta and vena cava compression. A used flexible sigmoidoscopy can be done in any trimester of pregnancy. Colonoscopy should be done with obstetric anesthesia monitoring. Benzodiazepines should be avoided, but propofol is considered safe during pregnancy, also it should preferably not be administered in the first trimester due to insufficient data. Fetal heart rhythm should be detected before and after endoscopy and obstetric support should always be available. Imaging The safest methods of imaging during pregnancy remain ultrasound and magnetic resonance imaging. However, the display of abdominal content with ultrasound can be limited, especially in advanced gestation. When ultrasound results are inconclusive or for more complex cases magnetic resonance imaging without contrast can be suggested. In the absence of safety data, gadolinium is contraindicated during pregnancy. Abdominal X-ray and computed tomography should be avoided as far as possible due to concerns about side effects of foetal irradiation. Biomarkers for IBD Activity during pregnancy and therapeutic drug MonitoringCRP and faecal calprotectine (FC) are useful noninvasive markers used in IBD patients with relatively good correlation with disease activity. Also, their accuracy and correlation with activity during pregnancy has not been well established [58-61], increasing amount of evidence suggests that FC may serve a reliable biomarker in all gestational periods and is less likely to be prone to changes like CRP. A prospective assessment of 30 pregnant women taking thiopurines showed that thiopurinmetabolism for the mother changed during pregnancy, as the concentration of 6-thioguanin decreased and the concentration of 6-methylkethylecaptopurine increased as pregnancy progressed [62]. No antichemical toxicities in the mother were due to this shift, and thiopurin metabolism returned to baseline after birth. There are few data on serum levels in the mother during pregnancy. A small sample size study conducted by Seow et al. [63] showed that infliximab levels (IFX) increased during pregnancy, while adalimumab levels (ADA) remained stable. A recent prospective single-center cohort study suggested that ADA may continue longer during pregnancy because transportation over the placenta is lower than for IFX [64]. Interestingly, recent work in 12 patients at IFX and 4 patients on ADA with at least 2 levels remain stable in patients at stable dosing of IFX or ADA in remission during pregnancy [65]. Additional data is needed to determine if and how pregnancy affects pharmacokinetics of biological treatments. Experts recommend in clinical practice to check the level of maternal troughs in the second trimester and adjust the dosage correctly in the third trimester to provide the maximum range possible before delivery [27]. Drug safety in pregnancyHuman women with IBD will stop their medication before or during pregnancy due to their concerns about drug safety, which may lead to increased risk of relapse and unwanted pregnancy outcome [66,67]. Pregnant and nursing women are typically excluded from clinical trials, and randomized controlled trials on medication safety data are lacking. However, with multiple registry, cohort, and database sources, the safety of IBD medications (other than methotrexate) has been supported in recent literature for conception, pregnancy, and breastfeeding, although the overall evidence is still poor and the potency for most of the recommendations remains weak. Recently, the US Food and Drug Administration has abandoned the product letter categories (A, B, C, D and X) and replaced them with detailed subsections (humans, animals and pharmacologically) describing available information on potential risks and benefits for the mother, fetus and breast-fed children [27] (Table 1). Treatment with IBD during pregnancy (adapted from [27] and [114]) Antibiotic Metridazole and ciprofloxacin are commonly prescribed in IBD patients. A meta-analysis of the first trimester quinnolon exposure did not demonstrate any particular increased risk [68]. Conversely, the use of metronidazole is controversial in pregnancy because the 1 case-control study suggested a possible increased risk of oral clefts when used in the first trimester. However, 2 meta-analyses and 1 systematic review showed no increased risk of congenital anomalies [69]. Amoxicillin-clavulanic acid is considered safe during pregnancy [70]. Rifaximine should be avoided during pregnancy in humans as no safety data have been published in human pregnancy and animal studies revealed signs of teratogenicity. Several large trials are underway regarding the use of probiotics in pregnancies, and preliminary results reported improvement in certain outcomes, including premature birth, allergies, and infections in children [71]. AminosalicylatesAminosalicylates are commonly used to treat flares of mild to moderate UC and for maintenance of remission. Amino salicylates, including sulfa salinazine, are considered safe during pregnancy up to 3 g/day and should be continued in patients in whom remission has been achieved before conception [72,73]. Sulfasalazine interferes with folate synthesis by inhibiting dihydropholate reductase and pregnant women taking sulfasalazine should receive high-dose folic acid supplementation (2 mg/day) to prevent [74]. Mesalamin Mesalamin may be continued during pregnancy with the exception of Asacol containing dibutyphthalate, which in its coating contains dibutyphthalate, which has been associated with congenital anomalies in animals at doses >190 times the therapeutic human dose [75]. Mesalamine enemas and suppositories can be continued without risk. CorticosteroidsCorticosteroids may be needed during pregnancy to treat disease outbreaks. Older studies suggest that exposure to steroids during the first trimester may be associated with an increased risk of lip palsy and palate development [76]. This observation was not reported in a large Danish patient cohort exposed to any type of corticosteroids in the first trimester (OR 1.05; 95% CI 0.80-1.38) [77]. In pregnancy in IBD and neonatal results (PIANO) registry, the use of steroids was associated with an increased risk of certain maternal adverse reactions, premature birth (OR 1.8; 95% CI 1.0-3.1), low birth weight (OR 2.8; 95% CI 1.3-6.1) and gestational diabetes (OR 2.8; 95% CI 1.3-6.0) [78]. Therefore, patients on corticosteroids during pregnancy should receive blood pressure monitoring, glucose tolerance tests and serial growth scans in the third trimester. Literature on the safety of using budesonide during pregnancy is more limited, but this drug seems to be a safe option for the treatment of CD [79]. So farnowing there is no data available on the use of budesonide MMX or beclomethason diproprionate during pregnancy. In conclusion, the use of steroids is possible during pregnancy, and the benefit of disease control outweighs the risk of exposure. It is difficult to separate the effect of disease activity from a side effect of the drug as corticosteroid use reflects that the disease is not in remission. Prolonged exposure should be avoided and this drug should not be considered as a maintenance treatment strategy. Methylprednisolone and hydrocortisone should be the molecules of choice, as their increased placentametabolism reduces the risk of fetal exposure compared to dexamethasone or betamethasone. ImmunomodulatorsMTX is an antimetabolite that blocks the synthesis of thymidin. Exposure to MTX during organogenesis can lead to multiple malformations, mainly of limbs and the skull known as methotrexate embryopathy. This substance is therefore contraindicated during conception and pregnancy. A woman of childbearing age at MTX should have safe contraception. If accidentally conceived, therapeutic abortion should be discussed but not necessarily performed [20]. In addition, after discontinuation of treatment, women should wait 3-6 months before trying to conceive due to the long half-life of terminal elimination of the drug [80,81]. Thiopurines (azathioprine and 6-mercaptopurine) interfere with the synthesis of nucleic acid causing chromosome damage. These medicines are reported to be teratogenic in animal studies at doses similar to those used in humans, but intraperitoneal or parenteral, significantly increasing the bioavailability of the medicinal product [82-86]. However, recent studies agreed on the safety of thiopurins on both the congenital malformation risk and foetal complications [87]. The strongest data supporting safety come from a multicenter retrospective study comparing disease activity and pregnancy outcomes for 187 patients treated with thiopurins, 66 patients treated with anti-TNF agents and 318 unexposed IBD patients. In this study, no difference was found in pregnancy complications among the groups and multivariate analysis reported favorable global pregnancy outcomes, defined as a decreased rate of miscarriage and lack of obstetric complications, associated with thiopurines intake [86]. No increased risk of congenital anomalies or pregnancy complications was observed among >335 thiopurin-exposed pregnancies [88]. Literature conflicts with the risk of infection in children aged 9-12 months exposed to thiopurin plus anti-TNF combination therapy. Some authors reported an increased risk of infection (relative risk 1.50; 95% CI 1.08-2.09) [88], while others did not [89]. In conclusion, it is reasonable to continue thiopurine monotherapy during pregnancy to maintain remission, as the risk of active disease probably outweighs the risks associated with thiopurin use. Starting these treatments during pregnancy should be avoided due to the long delay of action and the unpredictable risk of developing medullary suppression or pancreatitis. Calcineurin inhibitors act by suppressing the production of interleukins 2 and 3, inhibiting chemotaxis of neutrophils and inducing apoptosis in T cells. Data on calcineurin inhibitors during pregnancy are mainly extrapolated from the transplant material. A systematic review in IBD reported a possible link between their use and the incidence of materno-fetal complications such as hypertension, preeclampsia, gestational diabetes, preterm birth, low birth weight, and small-for-gestational-age newborns [51]. European Crohn's and Colitis Organization guidelines discuss the use of cyclosporine as salvage therapy to avoid colectomy in pregnant patients with steroid-refractory fulminant UC flare [90], also this extraordinary strategy should be reserved for expert centers. Compared to cyclosporine, tacrolimus has less risk of maternal hypertension but higher risk of neonatal hyperglycemia. Small MoleculeTofacitinib is an oral, small molecule Janus kinase inhibitor used to treat rheumatoid arthritis, psoriatic arthritis, and UC. As a small molecule, tofacitinib is prone to cross the placenta barrier and animal studies showed teratogenicity. There are no controlled clinical studies designed to determine the effects of tofacitinib in pregnant women and prospectively collected remains limited. Out of 1,157 patients who participated in UC interventionstudies, 301 were women of childbearing age. 11 cases of exposure and 14 cases of paternal exposure to tofacitinib (doses of 5 or 10 mg twice daily) were identified. The results included 15 healthy newborns without fetal deaths, neonatal deaths, and congenital malformations reported. Two miscarriages and 2 medical terminations were described. The results across other tofacitinib studies and postmarketing cases were consistent, with a healthy newborn being the most common outcome and no fetal deaths [91]. However, given relatively few cases of pregnancy reported on this drug, conclusions cannot be drawn and further studies are needed. Biological substancesBiological agents are IgG or fragments that are to varying degrees actively transported over the placenta by the neonatal F.D. receptor, which becomes functional at week 13 of gestation [92]. 80 transfer rates occur in the third trimester and fetal IgG concentrations increase logarithmic from gestational week 20 to delivery [93-95]. As a result of this active transport over the placenta, concentrations of cord blood biological agents may exceed maternal levels by up to 4 times at birth and can be detected in children up to 12 months [66], raising concerns about possible adverse effects on the development of the infant's immune system [96]. Organogenosis occurs before transplacental anti-TNF drug transfer, and to date no link between congenital malformations and biological agents was observed. Anti-TNF agentsThe 4 anti-TNFs approved in IBD are IFX, ADA, certolizumab pegol (CZP) and golimumab. CZP differs from the others in that it is a pegylated Fab fragment anti-TNF agent. This results in clinically negligible levels of medicine in infants. Series of >100 IBD patients exposed during pregnancy to IFX [97], ADA [98] and CZP [99] found no negative impact on pregnancy outcomes. Golimumab is believed to have a similar safety profile. To date, no evidence was found of a link between treatment with TNF α inhibitors for IBD during pregnancy and the risk of congenital anomalies compared to disease-matched pregnancies. More than 500 women in the ongoing PIANO registry have been exposed to the above anti-TNF medications during pregnancy, and no increased risk with negative pregnancy outcomes was observed [88]. A systematic review of Nielsen et al. [94] was consistent with these findings without miscarriages, premature deliveries, stillbirth, low birth weight, congenital malformations and/or infections that were noted even when administered in the third trimester. A recent meta-analysis of 5 studies involving 1,216 IBD patients did not find an increase in adverse reactions in women receiving anti-TNF treatment compared to unexposed controls (OR 1.00; 95% CI

0.72-1.41), including premium delivery (OR 1.00; 95% CI 0.62-1.62), low birth weight (OR 1.05; 95% 0.62-1.78) and congenital anomalies (OR 1.10; 95% CI 0.58-2.09) [100]. However, women who received an anti-TNF in combination with thiopurin had a higher risk of (OR 2.4; 95% CI 1.3-4.3) and pregnancy complication (OR 1.7; 95% CI 1.0-2.2) compared to unexposed women [100]. These observations probably also reflect the fact that these patients had a more active disease. In addition, a risk of delayed infections was reported in infants. Anti-integrin agentsVedolizumab (VDZ) is a gut-selectively humanized IgG-1 monoclonal antibody to α4β7 integrin approved for both CD and UC. A reproduction study of VDZ in pregnant primates showed no signs of adverse effects from the development after intravenous administration of VDZ at doses similar to those recommended for humans [101]. To date, we have limited data available on human pregnancy safety. A recent case series described the development of 24 VDZ treated pregnancies. No new safety problems for pregnancy outcomes were observed in women directly or indirectly exposed to VDZ [102]. An international retrospective study reported pregnancy and neonatal complication in 24 women treated with VDZ with 12 live births, 4 miscarriages and 5 elective abortions [103]. Recently, the same group conducted a retrospective European study in which gastroenterologists were asked to report all VDZ-exposed pregnancies as well as neonatal results via an electronic case report form. There was no difference in abortion rates between the VDZ-exposed group and a control group of patients exposed to anti-TNF (16 vs. 13%, p = 0.71) or a control group of patients exposed neither to immunosuppressors nor biology (16 vs. 10%, s = 0.236). After the exclusion of patients with active disease, the number of abortions was the same between the VDZ group and patients in other groups [104]. Therefore, active disease in pregnancy rather than drug effect seems to have been the driver of this negative pregnancy result. Experts suggest using VDZ for women of childbearing age, if indicated. Still, if the childbearing age of the woman is bionative, most data are available with anti-TNF agents, and therefore perhaps anti-TNF, and especially CZP is most appropriate as the first-line treatment option. Anti-Interleukin IL-12-23Ustekinumab is an IgG1 monoclonal anti-interleukin 12-23 antibody approved for psoriasis, psoriatic arthritis, and recently for CD. A number of 26 exposed pregnancies reported 5 miscarriages (19%), a rate similar to the general population [105]. A cohort of 226 women treated with Ustekinumab for psoriasis or CD will be presented this year and no specific signal is yet reported compared to the general population [106]. Stopping or failing to stop treatment during pregnancy: Is the debate over? The strategy of discontinuation of anti-TNF therapy early in pregnancy poses several problems. Stopping treatment is associated with a higher risk of an outbreak during and during the postpartum period and increased risk of developing antibodies due to lower trough levels, possibly leading to loss of response to the drug after resumption of anti-TNF α during pregnancy may be considered in certain circumstances in patients at very low risk of relapse with an objective persistent endoscopic remission since <6 months before conception, no prior loss of response to anti-TNFs or need for dose optimisation, appropriate therapeutic levels before conception, no-hospitalization in the last 3 years and no prior reinfeiation [107]. As mentioned earlier, there is no evidence that continued anti-TNF treatment during pregnancy has a negative impact on pregnancy or children's outcomes [108, 109]. In patients with active disease in the second trimester, the benefit of continued anti-TNF treatment in the third trimester outweighs the potential risk [26, 88, 89]. To minimize transplacental transmission near the time of delivery, biological dosage can be adjusted to achieve trough or lowest serum matter concentrations on the estimated date. While this strategy is probably certain, we do not have solid data to confirm it, which is why most experts agree to stop biological treatments around week 20 in patients in remission (Table 1) [26]. Delivery ModeWomen with IBD has twice as many cesarean deliveries as women in the general population [31]. Most of the time, a caesarean section is suggested or requested due to unwarranted fear from patients or practitioners. There is also no contraindication for vaginal delivery in most cases [110], a healthy IBD patient should be able to have successful vaginal delivery. Episiotomy should be avoided whenever possible as it can trigger perianal disease. However, women with active perianal or rectal disease involvement and open rectovaginal fistula at the time of birth should have scheduled caesarean sections [111]. In this population caesarean section delivery should be performed by a senior obstetrician to reduce the risk of intraoperative organ damage. IPAA is a relative contraindication for vaginal delivery. Postpartum Period and Breastfeeding PostpartumThe risk of disease fallout is higher in postpartum period. This risk is mainly a consequence of discontinuation of IBD treatments during pregnancy for a longer period of time before treatment is resumed during the postpartum period [112]. In the pregnant IBD population of the French GETAID cohort, 14% of women ceased anti-TNF treatment before week 30 of gestation while in remission experienced a relapse in the last trimester of pregnancy with a complex course of disease in 75 % of cases (8 cases of premitis and 1 case of colectomy for severe acute colitis), and a third of them had an outbreak in the early post-delum period before week 3. The relapse rate was 26% in the early postpartum period among women who continued anti-TNF treatment during pregnancy due to active disease [113]. In the absence of infectious complications, biological treatment could be resumed 24 hours after vaginal birth and 48 h after caesarean section [27]. For For dosing treatments, it is usually recommended to consider the mother's weight before pregnancy. The dose will then be adjusted according to several factors, including disease activity, possible sustained weight gain postpartum and serum concentrations. Other IBD treatments can be continued during the postpartum period. MTX can be restarted postpartum if the mother is not nursing [114]. After a caesarean delivery, patients are at higher risk of developing an ileus, especially patients with IPAA, where the bag was manipulated during childbirth. Supportive measures and early feeding may reduce this risk [115]. Patients with a stoma are more at risk of stoma complications during pregnancy and after birth. It is recommended to avoid excessive weight gain during pregnancy and seek advice for colorectal surgeon and a specialist nurse [114]. In the case of caesarean sections, it is sufficient to cover the stoma with gauze only to protect the operational field [116]. BreastfeedingA significant number of women with IBD do not breastfeed their children, despite the fact that the benefits of breastfeeding have been shown to be significant for both mother and child [117]. The relationship between breastfeeding and disease activity usually reflects the consequence of IBD treatments discontinuation, since 60% of women discontinued their medication during the postpartum period for fear of medication transmission in breast milk [66, 111]. In the PIANO register, the lactation rate was significantly lower in women on immunomodulators and biological treatments [118]. Although the literature is sparse in this area and long-term safety data are lacking, the vast majority of medicines prescribed for IBD are either measurable in breast milk or present in concentrations that are not expected to harm the nursing infant (Table 2) [114]. Clinicians can rely on LactMed, which is a free online database sponsored by the U.S. National Library of Medicine that provides reliable information about drugs and breastfeeding. Treatments derived from mesalamine are generally found in milk, but are well tolerated. Only isolated cases of diarrhoea were reported in at-risk children. 5-ASA agents (mesalamine, balsalazine and olsalazine) can therefore be continued during lactation. These formulations are preferred to sulfasalazine because of the unknown side effects of medicinal metabolite, which are excreted in milk in concentrations higher than in the mother and known for hemolytic and antimicrobial properties. Corticosteroids low dose and thiopurosis are detected in small amounts in milk [119]. Some data suggest that higher levels of prednisone (>20 mg/day) may result in higher levels in the breastfed infant and cause temporary loss of milk supply. Thiopurins are not detected in breast milk 4 hours from dosing. Although it is not absolutely necessary, some experts recommend avoiding breastfeeding 3-4 hours after taking these medications to limit the amount of drug transferred Child. In most studies, concentrations of biological agents found in milk are minimal (<1 % of serum concentration) as the medicinal product breaks down in the child's stomach and no harm from breastfeeding has been described on biological treatments [120]. Data for anti-interleukin 12-23 and anti-integrin are very limited, but due to limited transmission detectable and their monoclonal antibody molecular structures, it is assumed that they are compatible with breastfeeding [121, 122]. Women on tofacitinib are advised not to breastfeed due to a lack of data on this molecule during the lactation period. The recommended duration of breastfeeding is the same as for women without IBD. Exclusive breastfeeding for 6 months, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant recommended for all mothers of the American Academy of Pediatrics. IBD treatment and lactation (adapted from [27] and [114]) Approach to the pregnant woman with IBDIt is now well established that prejudice counseling related to a multidisciplinary approach involving all providers, leading to better outcomes and less anxiety among IBD patients. When different health care professionals and/or family give conflicting advice, patients are most likely to experience anxiety. Preconception counseling has been associated with increased adherence to medication, disease control, and improved outcomes [29]. Preconception CounselingIBD patients of childbearing age should always be asked if they have a pregnancy plan in the near future. In this way, the gastroenterologist will be able to take the time to reassure the patient about the safety of most treatments used during pregnancy and lactation. He will also have the opportunity to reassess disease activity and achieve remission before attempting conception. Laboratory analysis, dosing of FC, and endoscopy before conception, if endoscopic remission has not been assessed before, should be part of the workup. This is also a good time to ensure that basic care has been provided such as screening for anemia and vitamin deficiency, vaccinations update, supplementation for folic acid, and smoking cessation. At this point, Asacol should be replaced by another Mesalamine formulation (Fig. 1). Algorithm of care during the prejudice period (adapted from [114]). CRP, C-reactive protein; FC, fecal calprotectine; MTX, methotrexate; 5-ASA, 5-amino-salaclic acid; DPB, dibutylphthalate; IBD, inflammatory bowel disease. Treatment during pregnancy The risk of adverse reactions increases in women with IBD during pregnancy, even if their disease is in endoscopic remission [123]. Therefore, close monitoring during pregnancy is recommended in this high-risk population. In each trimester, FC and serum inflammatory markers, as well as gestational weight gain, should be monitored for signs of disease activity and poor nutrition. If possible, a low-point level of biological ant can be controlled in the late to determine the timing and dose of biological means in the third trimester. In the third trimester as well as in postpartum, pediatricians should be informed that live vaccines are contraindicated in infants exposed to biological treatments. The handling of flares would be similar to that of the non-pregnant patient, with the exception that traditional serum markers of disease activity, such as sedimentation rate, hemoglobin and albumin, are abnormal during pregnancy (Fig. 2). Algorithm of care during pregnancy (adapted from [114]). IBD, inflammatory bowel disease; CRP, C-reactive protein; GI, gastroenterologist; CBC, complete blood count; TDM, therapeutic monitoring of medicinal products; GA, gestational age; VTE, venous thromboembolism; 5-ASA, 5-amino-salacyclic acid. The effectiveness of IBD for Baby IBD and HeredityGenetic risk for CD is higher than for UC in European cohort studies. Having multiple family members with IBD increases the risk of children with IBD. In monozygotic twins studies, 20-56% of CD and 6-19% of UC had concordance [124]. With maternal CD, the incidence rate for CD is 6.3 in offspring, and the absolute risk of a offspring developing CD is 2.7%. With maternal UC, this incidence rate is 3.7 for UC in an offspring, and the absolute risk of an offspring developing UC is 1.6% [125]. When both parents have the disease, the risk of developing IBD increases to 30% [114]. Currently, there is no genetic test available to predict whether the child will develop IBD. Infection and VaccinationParents and pediatricians should be wary of infections, especially if the child was exposed to a combination of thiopurins and biology. A systematic review of anti-TNF use during IBD pregnancies found no increased risk of infections in the first year of infant life [94]. However, individual cases of serious infection have been reported [47]. In the PIANO registry, there are 1 case of vertical histoplasmosis transfer involving a mother taking IFX 10 mg/kg every 6 weeks that had supratherapeutic IFX levels at birth. It is recommended to minimize unnecessary antibiotic exposure as it may increase the risk of developing CD later in childhood. Clinically significant levels can be found in newborn infants for up to 6 months after birth. Avoidance of live vaccines in infants exposed to biological treatment in the third trimester of pregnancy is recommended until at least after 6 months because significant levels can be found in infants up to 6 months after birth and may lead to clinically relevant neonatal immunosuppression. The rotavirus vaccine compliance is the only live vaccine administered before 6 months in certain countries as in the United States. The first dose should be administered before 15 weeks of age to be more effective. Mental DevelopmentA suggests that babies born to mothers with IBD regardless of medication exposure have no developmental delays. Data on development milestones from the PIANO registry supports the lack of negative IBD treatments on development. In addition, infants with higher anti-TNF drug levels at birth had statistically superior achievement of developmental milestones compared to infants with lower birth drug levels. The hypothesis of the effects of inflammation in the uterus on the developing brain has been reported and pro-inflammatory mediators negatively influence both hippocampal neurogenesis and neuronal cytoarkitture during brain development. The importance of good inflammatory control during pregnancy should therefore be stressed when advising women with IBD [126]. Conclusions OF IBD affecting patients during their peak reproductive years raise important questions, in both patients and healthcare providers, about conception, pregnancy, and breastfeeding. Lack of information and poor communication among healthcare professionals can leave patients with limited information and conflicting advice. Although there are clear limitations to the evidence base in this area, the Expert Group has nevertheless provided clear guidance on how best to answer these questions. Gastroenterologists are an important resource for providing reassurance and guidance during this important period of patients' lives, and they should work with other healthcare providers. The overall concept is that optimizing the mother's health is essential to optimize the child's health and the benefit of continued medical treatment in IBD during pregnancy outweighs possible risks in most cases. RecognitionIne. The Information Statement S.R., L.B., P.H., C.M., and A.M. have no conflicts of interest to declare. M.F.: research grants: Janssen, Pfizer, Takeda. Advice: Abbvie, Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, Takeda, MSD, Pfizer. Speaker's fee: Abbvie, Boehringer-Ingelheim, Chiesi, Ferring, Janssen, Lamepro, Mitsubishi Tanabe, MSD, Pfizer, Takeda, Tramedico, Tillotts, Zeria. A.M: consultancy for Abbvie, Janssen, MSD, Takeda, Pfizer. Speaker fees: Abbvie, MSD, Takeda, MSD. Funding SourcesThere is no funding to declare. Author ContributeSS.R. and A.M.S.: conception and design. S.R. and A.M.S.: drafting of the article. S.R., L.B., P.H., C.M., A.M., M.F., and A.M.S.: critical revision of the article for important intellectual content. S.R., L.B., P.H., C.M., A.M., M.F., and A.M.S.: final approval of the article. References Ng SC, Shi HY, Hamidi Nielsen, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century Lancet. Dec 2018(390)10114):2769-78. Abhyankar A, Ham M, Moss AC. Meta-analysis: the effect of disease activity in conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Sep;38(5):460-6. Pedersen Nielsen, Bortoli A, Duricova D, D Inca Rasmussen, Panelli MR, Gisbert JP, et al.; European Crohn-Colitis Organisation-ECCO Study Group for Epidemiology Committee-EpiCom. 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Sophie Restellini, MDDivision of Gastroenterology and HepatologyUniversity Hospital in Geneva, 4 rue Gabrielle-Perret-GentilCH-1211 Geneva 14 (Switzerland)sophie.restellini@hcuge.ch and sophie.restellini-kherad@mail.mcgill.ca First-Page Preview Received: 11. 2019Ubsublished online: 08 January 2020 Release date: September 2020 Number of printed pages: 16 Number of numbers: 2 Number of tables: 2 ISSN: 0012-2823 (Print) eISSN: 1421-9867 (Online) For more information: