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Review Article

Female reproductive health and inflammatory bowel disease: A practice-based review

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ABSTRACT

Inflammatory bowel diseases, namely ulcerative colitis and Crohn's disease, occur worldwide and affect people of all ages, with a high impact on their quality of life. Sex differences in incidence and prevalence have been reported, and there are also gender-specific issues that physicians should recognize. For women, there are multiple, important concerns regarding issues of body image and sexuality, menstruation, contraception, fertility, pregnancy, breastfeeding and menopause. This practice-based review focuses on the main themes that run through the life of women with inflammatory bowel diseases from puberty to menopause. Gastroenterologists who specialize in inflammatory bowel diseases and other physicians who see female patients with inflammatory bowel diseases should provide support for these problems and offer adequate therapy to ensure that their patients achieve the same overall well-being and health as do women without inflammatory bowel diseases.

1. Introduction

Inflammatory bowel disease (IBD), namely ulcerative colitis and Crohn's disease, is a pair of chronic, benign diseases of increasing incidence worldwide. Sex differences in incidence and prevalence have been reported in IBD as in other immune-mediated disorders such as rheumatoid arthritis, scleroderma, multiple sclerosis, and systemic lupus erythematosus [1,2]. Gender may influence patients' perception of the disease, their body image, and their clinical symptoms [3].

Currently, the prevalence of IBD in the Western world is almost 0.5% [1,2]. According to population-based studies, there is slight predominance of females among all patients with Crohn's disease (CD) [4]. A few studies found a small male prevalence in ulcerative colitis (UC) [5]. IBD onset, in Western populations, occurs most frequently in the second to fourth decades of life [6], although for UC a second peak in incidence in the 60-79 years age group has been reported [7]. After 25 years of age, women have a 16% to 47% higher risk of CD than men do, according to an age-stratified meta-analysis [4].

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To help gastroenterologists, gynecologists and even neonatologists who see women with IBD, this article reviews the current state of knowledge regarding the management of IBD at different stages of a woman's life, including puberty, pregnancy and menopause.

2. Puberty and menstruation

IBD can affect the onset and progression of puberty. Girls with IBD may have delayed puberty and secondary amenorrhea [8,9]. Delayed puberty may be due to malnutrition and to the negative effects of pro-inflammatory cytokines such as interleukin (IL) 1 and tumor necrosis factor (TNF) α on sex hormone production [8].

IBD symptoms can exacerbate during the menses [10], and this can be a confounding element in discriminating dysmenorrhea from intestinal disease relapse. The exacerbation of symptoms may be due to endometrial prostaglandins, which increase inflammation and intestinal motility [10], or to the presence in the gastrointestinal tract of estrogen receptors that are involved in visceral hypersensitivity and motility [10].

3. Sexuality

According to the World Health Organization, sexual health is the "state of physical, emotional, mental and social well-being in relation to sexuality" [11]. Sexual health can be affected by IBD, especially when the disease is in an active phase [11–13]. In a questionnaire survey [14], 54% of IBD women reported sexual dysfunction; these rates were higher than those reported by healthy controls (28%).

Body image can be negatively influenced by surgical scars, stoma, and weight variation due to excessive steroid use, malabsorption or perianal disease [15,16]. These manifestations can interfere with sexual satisfaction, decrease libido and cause dyspareunia [17]. IBD patients also may have more anxiety and depression than healthy persons, as reported in a Turkish survey [18]. These emotional moods impact on women's sexual well-being and desire [19]. Socioeconomic factors, social status, age, comorbidities and complications of IBD also alter sexual function in both women and men [19]. Therefore, the clinical management of IBD women should include assessment and counseling for psychological status and sexual health, which are important elements of quality of life.

4. Preconception period

According to a multinational survey [20], most female IBD patients feel that issues of family planning and pregnancy are not adequately addressed by their physicians during medical consultations. Indeed, knowledge of family planning and pregnancy issues is poor in nearly one half of women with IBD [21].

Up to 19% of IBD women are voluntarily childless [21]. IBD women with poor knowledge about family planning and pregnancy are more likely to be voluntarily childless than knowledgeable IBD women [21–23].

Preconception counseling, preferably starting at the time of IBD diagnosis, significantly reduces the frequency of voluntary childlessness [22–25], the risk of nonadherence to treatment [26], and the risk of IBD relapses during pregnancy [27]. It's suitable IBD pregnancy clinic that was co-managed by obstetricians and IBD subspecialists [22].

The American Gastroenterological Association's IBD Parenthood Project Working Group recommends that pregnancies be scheduled only after 3-6 months of stable clinical remission, 3 months after withdrawal of a teratogenic drug (e.g. methotrexate), and about 6 months after the last administration of any experimental drug [24]. Oral hormonal contraceptives have an acceptable safety profile in women with IBD [28], but progestogen-only contraceptives are preferred to reduce the risk of venous thromboembolism [29]. However, the effectiveness of oral formulations can be reduced by ileal malabsorption in extensive ileal CD and in those who had multiple abdominal surgeries [30].

Having a sick child is one of the biggest concerns of women with IBD, and therefore this risk requires special attention during preconception counseling. In a Danish national study, 12% of all cases of CD and 9% of all cases of UC had familial inheritance [31]. For the child of a parent with CD, the relative risk of developing IBD was 6- to 7.5-fold higher than that of a child whose parents do not have CD. Similarly, the relative risk that a child develops UC was 4-fold higher when a parent has UC than when both parents are healthy. Having two or more affected first-degree relatives further increased the incidence rate ratio, to 9.77 for CD and 6.63 for UC. Nevertheless, the absolute risk for a child whose siblings have IBD to develop IBD was less than 3% [31]; this is the datum that needs to be extensively discussed with patients.

In a prospective case-control study, women with IBD had similar pregnancy outcomes to women without IBD, in terms of the frequency of abortions, preterm deliveries, cesarean sections, congenital abnormalities and low-birth weight [32]. According to a meta-analysis, women who start pregnancy with active IBD have higher risks of low-birth-weight babies (risk ratio [RR] = 2.0) and small-for-gestational-age babies (RR = 1.3) than women who start pregnancy when in clinical remission [33].

Similarly, the effects of pregnancy on IBD should be discussed. According to a meta-analysis, the risk of relapse or persistent disease activity during pregnancy is higher when conception had occurred during active disease than during remission, with risk ratios of 2.0 for both CD and UC [34] and in multiparous women, a history of disease flares during a prior pregnancy associated with relapse during a subsequent gestation [35]. In a prospective study that compared women who started pregnancy with IBD to non-pregnant IBD [36], pregnant women with UC were at higher risk of relapse during the course of study than non-pregnant UC women, while no difference was observed between the two groups of women with CD. In UC, relapse was mostly recorded in the first and second trimesters and in the postpartum period. Pregnancy may also exert a positive effect on IBD in the long term. Two studies observed a lower rate of relapse in the years following pregnancy than in the period before pregnancy in both UC and CD [37,38].

Misconceptions about drug safety during pregnancy and breastfeeding may influence patient choice and negatively affect the pregnancy or the health of the mother and infant. Up to 40% of women reported not adhering to medical prescriptions prior to or during pregnancy (even for drugs with proven safety profiles), because they considered the substances potentially dangerous for fertility or for the baby [22,26,39,40]. Moreover, according to a study in Australia [41], obstetricians and gynecologists often expressed concerns about starting IBD medications around conception and during pregnancy, and did not feel adequately trained about the safety of IBD medications. IBD-expert gastroenterologists should discuss pregnancy and breastfeeding issues with patients when starting or changing medications, and they should support obstetricians and gynecologists in the management of pregnant women with IBD.

5. Fertility

Fertility can be an important issue for IBD women, even though studies indicate that, in the inactive phase of disease, fertility is normal and infertility rates are low.

Despite normal fertility in quiescent IBD, other studies have documented an increase in voluntary childlessness. A questionnaire study of mostly white, IBD women from Illinois, United States, found that respondents had fewer children than the general population [42]. The Scottish survey found that 36% of CD women were voluntarily childless compared with 7% of women in the general population [43]. These findings were confirmed in a systematic review of eleven studies that found a 17-44% reduction in fertility in CD compared with controls, mostly due to voluntary choice [44]. The reasons for voluntary childlessness are thought to be: fears of disease transmission and of the possible impact of pregnancy on the disease course, concerns about drug safety, and consequences of pain and other symptoms on sexual activity [45,46].

Another indicator of fertility is the time to pregnancy. In a Danish population study [47], women with CD were 1.54 times more likely to self-report a time to pregnancy of >12 months than were women without IBD. Women who had had CD surgery were 2.54 times more likely to report a prolonged time to pregnancy.

5.1. Drugs and fertility

There are no reported effects of IBD medications on the fertility of IBD women. Mesalazine, corticosteroids, thiopurines, and anti-TNFα agents have not been shown to negatively impact female fertility [48]. Methotrexate, a second-line immunosuppressive treatment for IBD, does not appear to cause infertility in women, but because it has teratogenic effects, its use is contraindicated during both pregnancy and the preconception period [49].

Some IBD patients are treated with the therapeutic antibodies vedolizumab (anti-alpha4beta7 integrin) and ustekinumab (anti-IL-12 and anti-IL-23) or with the janus kinase inhibitor tofacitinib, but data on the effects of these drugs on female fertility are lacking. So far, there is only one case report of a woman with CD who became pregnant while taking ustekinumab [50]. According to the American Gastroenterological Association's IBD Parenthood Project Working Group, tofacitinib should not be used as a first-line treatment for IBD women who are planning to conceive due to the limited safety data in humans and the increase of fetal malformations in animal studies [24].

5.2. Surgery and fertility

Active IBD may diminish fertility secondarily through surgery [51]. According to the Scottish questionnaire study [38], women with CD who had IBD surgery were more likely to have infertility than those treated with medical therapy (12% vs. 5%, respectively). One study found that ileal pouch–anal anastomosis (IPAA), which is the surgical intervention of choice for UC, severely decreased fertility in UC women [52]. A systematic review found that the infertility rate in 945 UC women was 12% before surgery but 26% after IPAA [53]. A meta-analysis revealed a three-fold greater infertility rate in women who had restorative proctocolectomy with IPAA than patients who only had received medical treatment only (48% vs. 15%) [54]. Another meta-analysis of women with UC or familial adenomatous polyposis (FAP), found that the infertility rate one year after IPAA was 63% and that the relative risk of infertility 12 months after IPAA was 3.91 [55].

The main causes of reduced fertility after IPAA are postoperative adhesions and fallopian tube scarring due to deep pelvic dissection [55,56]. Considering the negative impact of IPAA on fertility, the laparoscopic surgical approach is recommended by the European Crohn's and Colitis Organisation (ECCO) [57]. Compared to open surgery, laparoscopy was found to be less detrimental to fertility in a single-center study of 63 women with UC or FAP [58]. This finding was contradicted by another study of 519 women with IBD or FAP who had laparoscopic or open IPAA in which high rates of infertility after surgery (61% vs. 65%) were found [59]. However, in this study, the median time to conception was shorter for patients who had laparoscopic surgery (3.5 vs. 9 months). A surgical option to preserve fertility is the two-stage intervention with preliminary total colectomy and temporary ileostomy followed, after childbearing age, by IPAA as the second stage [55].

5.3. In vitro *fertilization*

In vitro fertilization (IVF) is frequently used to treat infertility. Several factors can impact the outcome of IVF, including poor embryo quality (e.g. advanced maternal age, diminished ovarian reserve), poor endometrial receptivity, or suboptimal embryo transfer [60,61].

Numerous studies have examined the success of IVF in IBD patients. Another retrospective study found that the rates of live births after six IVF cycles were similar between UC women who had IPAA and those who did not (64% and 71%) [62]. Afterward, the same research team identified younger age, shorter duration of disease, and clinical remission status or mild disease activity as independent predictors of successful IVF for UC patients; they also identified younger age, lower body mass index (BMI), and lower cycle day 3 follicle-stimulating hormone levels as independent predictors of successful IVF in CD patients [63]. Previous exposure to biological therapies was associated with a lack of IVF success (no live birth) in UC patients only, but this finding must be cautiously interpreted given that only 3 UC patients used biological therapies. Among other factors studied, such as parity, causes of infertility, surgery and medications, none was found to affect the IVF success rate [63].

The largest cohort study reported so far was based on Danish nationwide registries, containing data on 432 UC, 182 CD and 52,489 non-IBD women who had assisted reproductive technology (ART) treatment over a 20-year period [64]. UC patients had a lower chance of live birth for each embryo transferred than non-IBD women (crude odds ratio [OR] = 0.79), and this reduced success remained after adjusting for comorbidities (using the Charlson index [65]), women's and partners' ages, calendar year of treatment, type of ART used, infertility diagnosis, BMI, and tobacco or alcohol use (adjusted OR = 0.73). The impact of IBD activity was not included in the analysis, since, in Denmark, only patients with quiescent disease can access ART treatment. In the same study, children of women with UC were at increased risk of preterm birth (OR = 5.29). For women with CD, surgery before ART reduced the probability of a live birth for each embryo transferred compared to non-IBD patients (adjusted OR = 0.51). In a follow-up study, the same research team reported that the risk of unsuccessful ART within 18 months of the first cycle was higher for CD with a history of abdominal surgery (for a live birth, OR = 0.29), especially when the procedure had been performed less than 2 years before [66]. An increased risk of ART unsuccess was not observed for women with UC, irrespective of the type of surgery [64–66].

A recent study, also from Denmark, found that in a cohort of 13,560 UC women the use of ART treatments was three-fold higher among those who had IPAA than those who did not [67]. However, the chances of success were comparable between the two groups of women and, in this paper, the authors concluded that an IBD diagnosis does not complicate the success of IVF.

6. Pregnancy

6.1. Nutritional status and gestational weight gain

A woman's nutritional requirements increase during pregnancy [68], and a mother's diet can influence fetal development, pregnancy outcome and life course of her offspring [69,70]. There are

no specific nutritional recommendations for pregnant women with IBD [57]. Preconception care, including attention to maternal nutritional status, can positively influence birth outcomes by protecting against preterm delivery (before 37 weeks of gestation), low birth weight (<2500 g), and small for gestational age (SGA) [27,71].

Patients with IBD are prone to malnutrition and diarrhea [72,73]. Furthermore, they often restrict food intake, especially of dairy products and fiber-containing products, to avoid abdominal pain [72,74]. Active IBD impairs nutrient absorption and leads to nutrient loss [73]. The most common deficiencies reported are iron, folic acid, calcium, vitamins, protein, fat and zinc, which all require supplementation [75–77]. In a Finnish retrospective study, IBD women were three times more likely to have anemia during the third trimester than non-IBD controls [78].

Serum iron and folate levels should be monitored regularly and in case of deficiency should be supplemented and checked at each visit [77,79]. The World Health Organization advises once daily iron administration until three months after delivery or abortion, and twice daily in cases of anemia, which occurs in approximately in 25% of IBD patients and has been linked to adverse pregnancy outcomes [79]. Iron administration may worsen constipation, which often accompanies normal pregnancies, and may exacerbate abdominal pain [24].

Folic acid supplementation should be encouraged, especially in CD patients on low-residue diets and those on medications such as sulfasalazine, which interferes with folic acid metabolism [24,80]. Calcium and vitamin D supplementation should be administered primarily to patients who have required steroid courses in the past and those who are currently taking steroids [80]. Inadequacy of trace minerals (e.g. selenium, copper, chromium) is rare in IBD patients except in those requiring parenteral nutrition [81].

Another issue for fetal development and growth is an adequate gestational weight gain (GWG, i.e. the difference between pre-pregnancy weight and weight at birth) [82]. Inadequate GWG is a strong independent predictor of adverse pregnancy outcomes in IBD [71]. Several studies have shown associations between inadequate GWG and the birth of both preterm and SGA babies [83–85]. In a retrospective Canadian study, low GWG was more common in women with CD than in healthy controls [86]. CD mothers delivered babies with significantly lower birth weight than did control mothers, and 24.6% of the babies born to CD mothers were classified as SGA [86].

The majority of IBD mothers with inadequate GWG have normal pre-pregnancy BMI. Inadequate GWG was slightly more frequent among UC than CD mothers in two cohort studies [71,82]. CD and UC mothers with inadequate GWG had a 2.5-fold increased risk of preterm birth [71]. Moreover, disease activity is associated with inadequate GWG among IBD mothers. In one cohort study, approximately 30% experienced flares during pregnancy [71]. Flares happen in UC mothers more frequently than in CD mothers [71,82]. Nevertheless, inadequate GWG similarly increased the risk of preterm birth for CD and UC mothers, independent of disease activity, suggesting that factors other than disease activity contribute to inadequate GWG in IBD [71].

In a Norwegian cohort study, disease activity was not associated with inadequate GWG, and flares were similarly distributed among mothers with adequate and inadequate GWG [82].

Although the causes of inadequate GWG remain unclear, these findings may be explained by the fact that IBD patients are prone to malnutrition before conceiving and even more so during the early period of pregnancy when there is rapid placental development. Nutritional intervention is required in cases of inadequate weight gain. For severely malnourished pregnant women, total parenteral nutrition can be lifesaving [87]. Therefore, physicians treating pregnant IBD women should aim to maintain proper maternal nutritional status and disease quiescence.

6.2. Medical therapy

Most medications used in IBD, including conventional therapy and the first generation of biological therapies, are safe in pregnancy and their use reduces the risk of active disease [40]. Moreover, as new drugs with different mechanisms of action have been approved, more safety data must be obtained before these new drugs are used. This section summarizes current recommendations and risks of IBD medical therapy during pregnancy (Table 1).

6.2.1. Aminosalicylates

Formulations of 5-aminosalicylic acid (5-ASA) are one of the most prescribed therapies for IBD. Their safe use in pregnancy has been reported in case series and population-based cohorts. According to a meta-analysis of seven studies, there was no increased risk of congenital abnormalities, stillbirths, spontaneous abortions, or preterm deliveries among the 642 women who used 5-ASA compared to the 1158 women who did not [88].

There are different formulations of 5-ASA, with or without a dibutylphthalate coating, although the teratogenic effect of dibutylphthalate was not confirmed in humans. When sulfasalazine treatment is chosen, folate supplementation (folic acid >2 mg/day) is recommended [57].

6.2.2. Corticosteroids

Systemic, low-bioavailability steroids are commonly used to induce remission during IBD flares. All corticosteroids can cross the placental barrier, but their rapid conversion into less active metabolites results in low fetal blood concentrations [89]. Budesonide, due to its low bioavailability, is considered to be safe during pregnancy but data are scarce.

There have been concerns that corticosteroids have teratogenic effects, including orofacial malformations (cleft lip/palate). However, in a large population-based study including 51,973 pregnancies exposed to corticosteroids during the first trimester, no association with orofacial malformations was found [90].

6.2.3. Metronidazole and ciprofloxacin

The antibiotics metronidazole and ciprofloxacin are used to treat perianal CD [91] and pouchitis, sometimes as combination therapy [92]. These medications do not increase the risk of spontaneous miscarriage or congenital anomalies [93,94]. However, infants of women exposed to metronidazole in the second to third months of pregnancy had higher rates of cleft lip with or without cleft palate [95]. For these reasons, metronidazole and ciprofloxacin should be avoided in the first trimester, in accordance with ECCO guidelines [57].

6.2.4. Immunomodulators

Thiopurines, including azathioprine and 6-mercaptopurine, are used as maintenance therapy in IBD. Thiopurines cross the placenta, but their discontinuation in women with well-controlled disease is not recommended. According to the Toronto Consensus Statements, thiopurines “should be continued throughout pregnancy” [96]. In a meta-analysis considering 3045 IBD pregnant women, the use of thiopurines was associated with preterm births (OR = 1.67), but not with congenital abnormalities or low birth weight [96]. A large Swedish registry study found an increased risk of preterm birth due to thiopurine use in IBD women with stable disease (OR = 2.41) and active disease (OR = 4.90) [97].

Methotrexate has strong teratogenic and abortive effects, and thus must be discontinued prior to conception. Women who plan to conceive should discontinue methotrexate and use contraception for at least 3 months before conception [96,98].

Cyclosporine is a calcineurin and cytochrome P450 inhibitor. It demonstrated short-term efficacy and safety in the treatment of

Table 1
Use of IBD drugs during fertility and pregnancy.

Medicine group	Drugs	Recommendation	Risk
Aminosalicylates	Mesalazine Sulfasalazine Balsalazide Olsalazide	Maintain pre-pregnancy doses. With sulfasalazine, supplement folate (>2 mg/day)	Low
Corticosteroids	All	Reserve for active flares	Low
Antibiotics	Metronidazole	Avoid in the first trimester	Low
	Ciprofloxacin	Avoid in the first trimester	Low
Immunomodulators	Azathioprine	Continue as monotherapy	Low
	6-Mercaptopurine	Continue as monotherapy	Low
	Methotrexate	Stop >3 months before conception	High
	Cyclosporine	Use only as rescue therapy	Unclear
Anti-TNFα	Infliximab	Discontinue during 2^{nd}-3^{rd} trimesters	Low
	Adalimumab	Discontinue during 2^{nd}-3^{rd} trimesters	Low
	Golimumab	Discontinue during 2^{nd}-3^{rd} trimesters	Low
	Certolizumab	Continue use	Low
Anti-$\alpha4\beta7$ integrin	Vedolizumab	Personalized decision	Unclear
Anti-IL-12 and anti-IL-23	Ustekinumab	Personalized decision	Unclear
Janus kinase inhibitors	Tofacitinib	Contraindicated	High
	Filgotinib	Contraindicated	High
	Upadacitinib	Contraindicated	High
Sphingosine-1-phosphate receptor modulator	Ozanimod	Contraindicated	High

steroid-refractory acute UC, and can be used as rescue therapy for acute severe UC [99–103]. No data on pregnant IBD women treated with cyclosporine are available. A meta-analysis of studies of pregnant transplant recipients did not find an increased rate of congenital malformations, but did find an increased risk of prematurity (OR = 1.52) [104].

6.2.5. Anti-TNFα agents

The anti-TNFα agents infliximab, adalimumab and golimumab are commonly used in IBD. Certolizumab pegol, an anti-TNF agent not approved in Europe for IBD, is often used in CD patients with rheumatologic co-morbidity. These agents are IgG1 monoclonal antibodies. Infliximab, adalimumab and golimumab cross the placenta, starting from the second trimester, in a progressive way due to a specific FcRn receptor-mediated mechanism [105]. Infliximab and adalimumab levels can be higher in infant and cord blood than in maternal peripheral blood [105]. Certolizumab pegol, which is an Fab fragment of IgG1, does not cross the placenta.

A meta-analysis of five cohort studies did not find any significant difference in unfavorable pregnancy outcomes between IBD pregnant women on and without anti-TNF therapy, suggesting that these therapies are safe [106]. However, ECCO guidelines suggest stopping anti-TNF therapy around gestational week 24 to minimize transplacental transfer [57]. In some cases, early discontinuation may lead to disease relapse with consequences on management of the pregnancy. Therefore, the decision about stopping therapy should be based on both disease activity and the patient's risk profile [57].

Data from the Crohn's Therapy Resource Evaluation and Assessment Tool (TREAT) registry [107] and the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry [108] show no increased risk of congenital abnormalities, neonatal complications or preterm delivery and infections. The European retrospective multicenter TEDDY study [109] evaluated 841 children of IBD mothers, including 388 children exposed to anti-TNFs in utero and 453 children not exposed. The study found similar rates of severe infection among the two groups (2.8% vs. 1.6% per person-year, respectively; hazard ratio, 1.2). Only pre-term delivery was significantly associated with a higher risk of severe infection. No differences in the frequencies of premature rupture of membranes, placenta previa, chorioamnionitis, eclampsia, or fetal growth were observed between the groups.

Another study focused on the long-term outcomes of infants, comparing IBD mothers exposed to anti-TNFs with healthy non-IBD mothers [110]. No differences in congenital abnormalities, perinatal complications or percentages of infants with low birth weight were found. Furthermore, the two groups of children had similar rates of infection and allergy, and similar growth and psychomotor development at a median follow-up of 36 months [110].

6.2.6. Vedolizumab

Vedolizumab is a humanized, monoclonal IgG1 antibody against $\alpha4\beta7$ integrin.

Vedolizumab is transferred across the placenta to the fetal circulation like other IgG antibodies [111]. The safety of vedolizumab during pregnancy was assessed using data from six clinical trials (81 pregnancies) [112]. The analysis did not find any adverse effect of the drug on pregnancy outcomes.

A multicenter, retrospective study of 24 pregnancies exposed to vedolizumab identified complications (premature rupture of membranes, pre-eclampsia, miscarriage and stillbirth) in six pregnancies [111]. Among the 23 live births, complications (prematurity, intrauterine growth retardation, congenital malformations and SGA) were seen in eight infants. Recently, a multicenter case-control study (CONCEIVE) compared pregnancy outcomes between vedolizumab-exposed women, anti-TNF-exposed women, and control women who had received neither drug [113]. Among the three groups, no significant differences in the rates of live births and of miscarriage were observed. Moreover, the groups had comparable neonatal outcomes regarding median gestational age, birth weight, median Apgar score, and incidences of congenital anomalies, infections and malignancies after 1 year.

At present, due to the lack of data from prospective, controlled trials, an individualized decision should be made as to whether the benefits of vedolizumab to the mother outweigh the risks. Strict monitoring of any pregnant patient receiving vedolizumab has been recommended [114].

6.2.7. Ustekinumab

Ustekinumab is a human IgG1 antibody that inhibits the p40 subunit of IL-12 and IL-23. Research in pregnant cynomolgus macaques found low levels of active transplacental transport until the end of the second quarter of pregnancy [115].

Ustekinumab has been shown to be effective in the management of CD [116]. Data regarding the use of ustekinumab in IBD women during pregnancy are limited to a conference presentation [117] and a case report [118]. So far, no safety signals with neonatal outcomes have been reported. For three pregnant women treated

with ustekinumab for psoriasis, gestation was uneventful and the pregnancies were completed without complications [119]. The limited data available suggest that ustekinumab is unlikely to negatively impact on pregnancy outcomes. For the moment, personalized decision for the IBD population can be made; further data are required.

6.2.8. Tofacitinib

Tofacitinib is an oral inhibitor of janus kinases 1 and 3 that has recently been approved for the treatment of UC.

Tofacitinib is a small molecule taken orally, so it is reasonable to assume that it can cross the placenta. According to the manufacturer, Pfizer, tofacitinib is teratogenic in animals, and causes malformations such as anasarca, membranous ventricular septal defects, and skeletal abnormalities [120]. The manufacturer recommends that women being treated with tofacitinib also take contraception.

At the moment, data regarding its effects on human pregnancy are limited. Among 47 women who became pregnant while taking tofacitinib for rheumatoid arthritis or psoriasis, the rates of healthy newborns, fetal deaths and malformations were similar to those for the general population [121]. The safety for UC during pregnancy was assessed from data reported in five clinical trials, allowing the identification of 11 cases of maternal exposure and 14 cases of paternal exposure to the drug [122]. No fetal deaths or congenital malformations had been reported.

6.2.9. Small molecules in pipeline

In the next few years many new small molecules will be used in the treatment of IBD. Other janus kinases inhibitors as Filgotinib and Upadacitinib, boths janus kinase 1 inhibitors, will shortly be used in CD and UC treatment respectively [123,124]. Sphingosine-1-phosphate receptor modulator as Ozanimod has been completed phase II studies in UC and CD [125,126].Their lack of immunogenicity, the low half-life and the oral administration make the small molecules very attractive for patients and physicians. Actually, there are no data in pregnancy and they are contraindicated [127].

6.3. Probiotics

There are no literature data that support the use of probiotics during the gestation of patients with IBD both as a protection of the disease activity and as a prevention of the onset of the same in the unborn child.

However, data from the recent study by Torres et al. suggests that, in the future, the study of the microbiota composition and its modulation during pregnancy in women with IBD could be a possible weapon to predict and prevent the development of the disease in the unborn child [128].

6.4. Impact of delivery mode on IBD outcome

A few studies have analyzed the impact of delivery mode on the long-term outcomes of IBD. Two retrospective studies reported no significant differences in the rates of symptomatic flares after cesarean or vaginal delivery [129,130]. Another study (161 cesarean, 199 vaginal delivery) found no association between the mode of delivery and IBD natural history over 4 years, considering the need for IBD-related hospitalization or surgery and the initiation of immunosuppressants or anti-TNFα therapy [131].

According to a systematic review [132], the mode of delivery was not associated with differences in the rate of new or relapsed perianal CD. However, two-thirds of women with active perianal disease experienced a worsening of symptoms after vaginal delivery. In patients with IPAA uncomplicated vaginal delivery moderately influenced pouch function, without a significant difference in terms of stool frequency or incontinence. However complicated vaginal delivery negatively impacted on pouch function.

6.5. Choice of delivery mode

No guidelines exist regarding the choice of delivery mode, standard vaginal delivery is commonly recommended by gastroenterologists in cases of quiescent or mild disease.

Data on clinical outcomes following cesarean or vaginal delivery in women with IPAA are conflicting. On one hand, some cohort studies found no increased rates of adverse pregnancy outcome and no change in pouch function after vaginal delivery [133–135], including the rate of incontinence [136]. On the other hand, one study found that sphincter integrity and physiology and manometric pressures were more frequently altered by vaginal delivery in patients with IPAA than by cesarean section [137]. As a consequence, cesarean delivery should be considered an option in patients with IPAA, in order to minimize the risk of anal sphincter injury.

There are also conflicting data on the impact of delivery mode on perianal disease. Some retrospective studies raised concerns that vaginal delivery may trigger or worsen perianal disease [138,139]. Active perianal disease has been associated with a high risk of fourth-degree laceration during delivery [140,141]. Conversely, other studies reported that vaginal delivery did not exacerbate the disease in cases of inactive perianal disease, and that cesarean delivery did not reduce the risk of flares in women with previous perianal disease [129,130]. Finally, a retrospective cohort study [142] found no difference in the incidence of cesarean delivery between women with and without CD, but a higher incidence of cesarean delivery was observed among women with perianal disease. Given these considerations, cesarean delivery is commonly recommended by gastroenterologists for patients with active perianal disease, while for other situations the decision should be made on a case by case basis, taking into account the past severity of the perianal disease and the previous surgery of the perianal area.

Regarding ileostomy or colostomy, data are extremely limited. CD outcomes after deliveries have been reported in four women with ileostomy and one with sigmoidostomy: in all but one pregnancy, the delivery occurred by cesarean, and no stoma complication was observed [143]. Of note, ileostomy obstruction can occur in pregnancy, and small bowel obstruction is associated with maternal and fetal morbidity and mortality [144]. Ileostomy obstruction may be caused by post-surgical adhesions or by the enlarging gravid uterus. In this latter case, it can be treated conservatively according to a case report [145]. The mode of delivery for women with ileostomy or colostomy should be discussed on a case by case basis in consultation with the gynecologist and gastroenterologist.

In conclusion, decision-making about the mode of delivery for women with IBD is influenced by many factors. In specific situations such as IPAA and perianal disease, the mode of delivery should be decided after a multidisciplinary discussion between gynecologists, gastroenterologists, and colorectal surgeons. In the absence of IPAA or perianal disease, the decision between vaginal and cesarean delivery should be based on obstetric indications and patient preference, as for women without IBD.

7. Breastfeeding

IBD may flare during the postpartum period for various reasons: hormonal changes, the resumption of smoking or the discontinuation of therapies [146]. Fear of possible adverse effects on the newborn is the main reason why mothers discontinue therapy during breastfeeding or prefer bottle feeding over breastfeed-

Table 2
Use of IBD drugs during breastfeeding.

Medicine group	Drugs	Recommendation	Risk
Aminosalicylates	Mesalazine Sulfasalazine Balsalazide Olsalazide	Discontinue in cases of infant diarrhea	Low
Corticosteroids	All	Breastfeed 4 h after taking	Low
Antibiotics	Metronidazole	Breastfeed 12-24 h after taking	Low
	Ciprofloxacin	Breastfeed 48 h after taking	Low
Immunomodulators	Azathioprine	Continue use	Low
	6-Mercaptopurine	Continue use	Low
	Methotrexate	Contraindicated	High
	Cyclosporine	Contraindicated	High
Anti-TNFα	Infliximab	Continue use	Low
	Adalimumab	Continue use	Low
	Golimumab	Not recommended	Unclear
	Certolizumab	Continue use	Low
Anti-$\alpha4\beta7$ integrin	Vedolizumab	Not recommended	Unclear
Anti-IL-12 and anti-IL-23	Ustekinumab	Not recommended	Unclear
Janus kinase inhibitor	Tofacitinib	Not recommended	Unclear
	Filgotinib	Not recommended	Unclear
	Upadacitinib	Not recommended	Unclear
Sphingosine-1-phosphate receptor modulator	Ozanimod	Not recommended	Unclear

ing [147]. Physician recommendations and personal preferences are other reasons why women favor bottle feeding [148].

Physicians should educate patients to avoid drug safety misconceptions, and should emphasize the delicate balance between disease control and potential toxicity for the newborn.

Whenever possible, breastfeeding should be encouraged in all women due to its benefits to both the mother and infant [149–151]. Two systematic reviews found that children who breastfeed have lower risks of developing early-onset IBD [152,153].

Despite the fears of women, many drugs can be safely taken during breastfeeding (Table 2). Mesalazine, sulfasalazine and thiopurines can be detected in breast milk, but in relatively small amounts [57]. For example, in a study of eight women, the level of sulfasalazine in milk was about half that in maternal serum (milk/serum ratio, 0.48) [154]. Bloody, watery diarrhea has been reported in two infants of UC mothers using 5-ASA [155,156]. In such cases, the treatment should be stopped. A case–control study that investigated 30 babies, half of whose mothers had taken azathioprine in pregnancy and during lactation, found that the exposed babies had normal physical and mental development without a greater risk of infection [157].

Regarding corticosteroids, one study of six lactating women found low concentrations of prednisolone in breast milk, and concluded that breastfeeding can be safe if mothers wait for 4 hours after a dose [158].

The antibiotics metronidazole and ciprofloxacin are excreted into breast milk [159,160]. Their long-term use should be avoided, while short-term use is possible with some precautions. The American Academy of Pediatrics recommends interrupting breastfeeding for 12–24 hours after a single 2 g oral dose of metronidazole, and for 48 hours after the last dose of ciprofloxacin, to allow their clearance [160,161].

Methotrexate and cyclosporine are contraindicated during breastfeeding. Methotrexate is excreted into breast milk [162] and can accumulate in neonatal tissues with possible adverse effects including immune suppression, neutropenia and a potential link with carcinogenesis [162]. As regards cyclosporine, current recommendations by the American Pediatric Association are to avoid breastfeeding due to potential alterations in cellular metabolism of newborns [162].

Infliximab, adalimumab and certolizumab are safe. These drugs have high molecular weights, so they likely transfer into breast milk in only small amounts. One study of three women found low amounts in breast milk [163]. In addition, when one of these three drugs is ingested by a breastfeeding baby, it should be inactivated by digestive enzymes in the gastrointestinal tract and therefore not absorbed [164,165]. For golimumab, vedolizumab, ustekinumab and tofacitinib, safety data are lacking. Therefore, breastfeeding by women taking these drugs is not recommended.

It is mandatory that physicians inform mothers about the risks of treatment during breastfeeding. Mothers must make their decisions consciously considering that, for many drugs, the benefits of breastfeeding outweigh the risks to the infant.

8. Newborn vaccinations

There are no specific recommendations for vaccinations of children born to IBD mothers taking conventional therapy. All vaccines should be administered according to each country's vaccination schedule.

Intrauterine exposure to anti-TNFs, vedolizumab or ustekinumab does not affect antibody responses to inactivated vaccines (e.g. vaccines for diphtheria-tetanus-pertussis, poliomyelitis, *Haemophilus influenzae* type b, hepatitis B, and pneumococcal infection). Therefore, the British Society of Gastroenterology recommends that newborns complete their vaccination schedule [166]. Indeed, a study of 179 women found no significant differences in the rates of serological responses to *Haemophilus influenzae* type b and tetanus vaccines in infants of IBD women who were exposed or not to biologics during pregnancy [167].

European vaccine schedules recommended waiting until an infant is 6 months of age before giving a live vaccine (e.g. vaccines for measles-mumps-rubella, varicella) [168]. This recommendation holds true even for infants exposed to biologic therapy during the third trimester of gestation (i.e. after 27 weeks). This is because detectable drug levels can be found in infants up to 6 months after birth, and may lead to clinically relevant neonatal immunosuppression [169,170]. For this reason, the oral administration of live rotavirus vaccine (not mandatory in most countries), scheduled for the first 6 months of age, should not be given to newborns exposed in utero to biological drugs [171].

9. Menopause

The last period of a woman's life, in terms of hormonal activity, is menopause. There are conflicting data on whether the age of onset of menopause differs between IBD and non-IBD women, but a recent study found no difference [172]. Menopausal symptoms such as vulvovaginal discomfort (mainly vaginal dryness and dyspareunia) can worsen intestinal manifestations. These complaints

could worsen sexual health and alter the quality of life of women with IBD [173].

Hormone replacement therapy (HRT) may protect against disease activity and may provide relief from menopausal symptoms [174,175]. According to a Cochrane review, HRT "may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with uterus)" [176]. Therefore, HRT is only suitable for short-term use in low-risk women [177].

10. Conclusions

Women with IBD are particularly affected by issues involving puberty, sexuality, conception, pregnancy, breastfeeding up to menopause. Disease control is undoubtedly the key to ensuring women with IBD have a positive view of sexuality, body image and general well-being. To ensure that women with IBD can live their lives like healthy women, unaffected by intestinal disease, a multidisciplinary approach involving gastroenterologists, gynecologists and neonatologists is required. Studies on the safety of using the newest drugs during pregnancy and lactation are needed. The overall goal is to help IBD women achieve disease remission in the shortest time, so they can run through life safely.

Declaration of Competing Interest

None.

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