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Review Article

New drugs for the treatment of IBD during conception, pregnancy, and lactation

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ABSTRACT

The management of inflammatory bowel disease requires continuous medical therapy to achieve and maintain disease control. Thus, women can be exposed to different drugs during conception, pregnancy, and lactation with potentially harmful effects on the mother, foetus, or nursing infant. Conventional drugs and anti-tumour necrosis factor (TNF)-α are considered safe and can be maintained throughout all these phases. Emergent, although limited, data support safety of vedolizumab and ustekinumab, with pregnancy, as well as maternal and neonatal outcomes comparable to women unexposed or treated with anti TNF-α drugs. Placental pharmacokinetics differ between these two biologics, with an inverse infant-to-maternal ratio for vedolizumab, whereas ustekinumab shows a similar profile to anti TNF-α drugs. The clearance of vedolizumab in exposed offspring seems to be faster than anti TNF-α, estimated around 15 and 19 weeks of age, respectively. Currently, the decision to interrupt or maintain these treatments is up to physicians' judgement on a case-by-case basis. In animal studies, Janus kinase (JAK) inhibitors and ozanimod have shown embryotoxicity and teratogenicity. Moreover, tofacitinib and filgotinib seemingly affect female fertility. This review summarizes all existing data on the effects of administration of non-anti-TNF-α biologic agents and small molecules, during conception, pregnancy, and lactation.

1. Introduction

Inflammatory bowel diseases (IBD) are long-life systemic conditions, of unknown aetiology, characterized by alternating periods of relapse and remission, with a peak of incidence in the reproductive ages (20–40 years old) [1,2]. Accordingly, most women suffering from IBD are on chronic medical therapy for disease control when they become pregnant. Drug safety during pregnancy and lactation is categorised by the Food and Drug Administration, according to the presence/absence of appropriately controlled human and/or animal studies demonstrating their risk/benefit profile [3]. Drugs administered to a pregnant woman have different potentials to harm based on the gestational age: (1) fertilization/implantation (conception to 17 days), when there is an increased risk of pregnancy failure; (2) organogenesis (18–55 days), associated to a potential risk of malformations or spontaneous abortion; (3) second and third trimesters, when functional abnormalities can occur.

In regard to IBD drugs, consistent data show the low risk of most of the conventional therapies (but methotrexate, which is contraindicated) when given throughout the pregnancy and during lactation [4]. When administered during pregnancy, anti tumour necrosis factor (TNF)-α antibodies can cross the placenta and reach the foetus [5]. However, there is convincing evidence supporting the safety of anti TNF-α drugs throughout the whole pregnancy and even during lactation, as they do not correlate with increased risks of pregnancy adverse outcomes nor infections during the babies' first year of life [6–9]. Accordingly, current guidelines recommend continuation of anti TNF-α throughout pregnancy for both women with active disease and those in remission [10]. Of note, in infants, complete drug clearance may require up to 12 months: therefore, it is recommended to defer live vaccines after this timing [11]. Few data have been reported so far on non-TNF-α biologic agents and small molecules: therefore, the decision to interrupt or maintain these treatments is up to physicians' judgement on a case-by-case basis. The purpose of this review is to give an overview of all existing data on the effects of administration of non-anti-TNF-α biologic agents and small molecules, during conception, pregnancy, and lactation.

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Table 1
Safety of non-anti-TNF biologics and small molecules for inflammatory bowel disease treatment on fertility, pregnancy and lactation.

	Fertility	Pregnancy	Lactation
Vedolizumab	No deleterious effect	No deleterious effect in animals Limited data in humans but it seems of low risk	Limited data in humans but it seems of low risk
Ustekinumab	No deleterious effect	No deleterious effect in animals Limited data in humans but it seems of low risk	Limited data in humans but it seems of low risk
Tofacitinib	No deleterious effect	Teratogenic in animals at dose several fold higher the dose in humans Few data in humans Not recommended in pregnancy	Not recommended
Upadacitinib	No deleterious effect	Teratogenic in animals at dose several fold higher the dose in humans Few data in humans No recommended in pregnancy	Not recommended
Filgotinib	No deleterious effect	Teratogenic in animals at dose several fold higher the dose in humans No data in humans Not recommended in pregnancy	Not recommended
Ozanimod	No deleterious effect	Teratogenic in animals at dose several fold higher the dose in humans Few data in humans Not recommended in pregnancy	Not recommended

2. Methods

We conducted a comprehensive electronic search on Medline electronic database through January 2023 with no language restrictions using the following search terms: ((“IBD”) OR (“Crohn’s Disease (CD)”) OR (“Ulcerative Colitis (UC)”)) AND ((“pregnancy”) OR (“Lactation/Breastfeeding”)). To extrapolate information about other indications, we specifically also searched for ((“Janus Kinase (JAK) inhibitors”) OR (“Ustekinumab”) OR (“Anti Interleukin (IL)-23″) OR (“Sphingosine 1-phosphate (S1P) receptor (S1PR) modulator”) OR (“Vedolizumab”)) AND ((“pregnancy”) OR (“Lactation/Breastfeeding”)). In addition, conference abstracts (European Crohn’s and Colitis Organization, Digestive Disease Week and United European Gastroenterology Week annual meetings) from 2014 to 2022, as well as references of review articles on this topic were manually searched for additional studies. Only drugs approved for IBD were considered. Two independent reviewers (DP and MC) independently evaluated the title and abstract of studies identified in the primary search and then the full text of selected articles. The main results are summarized in Table 1.

3. Results

3.1. Fertility

Because of the mechanisms of action of drugs, some of them might have potential impact on female and male fertility. On one hand, a drug could have a systemic effect on the hypothalamic-pituitary-gonadal axis. This could lead to sexual dysfunction (low libido, erectile dysfunction, or ejaculatory dysfunction), ovulation disorders, or impaired spermatogenesis. Regarding male fertility, they may also have a deleterious effect during spermatogenesis through a direct cytotoxic or inheritable effect on the sperm cells if the drug can cross the blood-testis hedge, which protects these cells during spermatogenesis. Further, transmission of drugs in the exclaim can affect the sperm cells or have a teratogenic effect on the foetus.

3.1.1. Vedolizumab

Vedolizumab is a monoclonal humanized immunoglobulin G_1 (IgG_1) directed against the $\alpha4\beta7$ integrin, blocking its interaction with the mucosal addressing cell adhesion molecule-1 (MAdCAM-1) and selectively modulating lymphocyte homing into the gut mucosa. It has been approved for the treatment of UC and CD, and, more recently, of chronic pouchitis as well [12]. Of note, MAdCAM-1 is also expressed on the placental surface [13], but the exact role of this binding in the placenta development still needs to be clarified. Recently, pathologic features were observed, on histology examinations, in the placenta of two vedolizumab-treated patients, and *in vitro* experiments with primary cytotrophoblast cultures revealed that anti-integrin therapy might negatively affect the invasion and adhesion capabilities of the cytotrophoblast [14].

Animal research on pregnant rabbits, treated with a single intravenous infusion at a dosage up to 100 mg/kg on gestation day 7, showed no significant impact on fertility nor damage to the foetus, compared to untreated controls [15]. An analogous safety profile was shown in Cynomolgus monkeys, administered with doses up to 100 mg/kg of vedolizumab every 2 weeks from gestational day 20 to 132. Moreover, no vedolizumab-related effects on offspring development, weight gain and grip strength were recorded [15].

Later, data of incident pregnancies in humans, occurred during the GEMINI program, showed a good safety profile, with no additional warnings [16]. Out of 24 pregnancies in women exposed to vedolizumab, 11 living births, 5 elective terminations, 4 spontaneous abortions and 4 undocumented outcomes were reported. A congenital agenesis of the *corpus callosum* was recorded in a healthy volunteer exposed to a single dose of vedolizumab 79 days before the estimated conception, but a definite relationship with the drug exposure cannot be ascertained. Recently, 3 cases of agenesis of the *corpus callosum* were identified in the post-marketing, pharmacovigilance EudraVigilance databases among foetuses exposed to vedolizumab (versus none among those exposed to other biologics); of note, 2 of them were associated with other neurological conditions. Hence, a genetic aetiology might be responsible for at least 2 of these cases, but a causative association with vedolizumab cannot be ruled out [17]. With regard to 19 pregnancies occurred in female partners of men exposed to vedolizumab, 11 live births, 3 elective terminations, 3 unknown outcomes and 2 spontaneous abortions were reported [16].

3.1.2. Ustekinumab

Ustekinumab, a monoclonal antibody against the p40 subunit common to interleukin (IL)-12 and IL-23, has been shown to be effective in the treatment of CD and UC and is increasingly used [18–21]. Animal studies on anti-IL12/23 agents in Cynomolgus monkeys did not show any effect on female and male fertility [22]. In the recently published study by Meserve and colleagues, pregnancies from 114 cases of paternal exposure toto ustekinumab did not have an increased risk for congenital anomalies, preterm birth, or low birth weight (LBW) [23]. Further data are needed on the effects of ustekinumab on human semen quality, the amount excreted in seminal plasma, and effect on DNA integrity, but outcome studies are encouraging thus far in this patient group. The data regarding female exposure are reassuring, and as a result, ustekinumab

is recommended in the United States for female patients with IBD throughout pregnancy [24]. Updated guidelines from the European Crohn's and Colitis organisation on sexuality, fertility, pregnancy, and lactation do not recommend against the use of ustekinumab in patients planning to have family [10].

3.1.3. JAK-inhibitors

Currently, tofacitinib (a non-selective, pan-JAK inhibitor) [25] and two more selective JAK1 inhibitors (upadacitinib and filgotinib) [26–29] are approved for the treatment of UC; upadacitinib has also been approved for CD. Studies on the effects of JAK inhibitors on human female fertility are not available. In animal models, no effect on fertility was observed for upadacitinib [30]. Conversely, research on rats suggests that tofacitinib and filgotinib might affect female (decrease of pregnancy rates, numbers of corpora lutea and implantation sites) and male fertility, respectively [25,31].

Preliminary data on filgotinib from two open-label, placebo-controlled studies, enrolling 240 male patients with immune-mediated diseases, showed no significant difference in the proportion of patients with a $\geq$ 50% decrease in sperm concentration at week 13 (pooled primary endpoint: 6.7% *vs.* 8.3% for filgotinib and placebo, respectively) and week 26 [32].

3.1.4. Ozanimod

Ozanimod is an oral sphingosine 1-phosphate (S1P) receptor modulator which binds with high affinity to S1P receptor subtypes 1 and 5 [33]. No fertility data are available in humans. In animal studies, ozanimod had no effect on male and female fertility up to approximately 150-fold the systemic exposure to total active substances (combined ozanimod and the metabolites CC112273 and CC1084037) at the maximum human dose of 0.92 mg ozanimod. However, ozanimod has shown embryotoxicity and teratogenicity in animals and, therefore, it is contraindicated during pregnancy and 3 months before conception (see pregnancy section) [33].

3.2. Pregnancy

3.2.1. Vedolizumab

The multicentre, retrospective, case-control CONCEIVE study reported data on 79 pregnancies in 73 women exposed to vedolizumab, compared to 186 pregnancies occurred in 164 women with IBD treated with anti TNF-α and 184 pregnancies in 155 controls with IBD. In the vedolizumab group, 64 live births, including three dizygotic twins, were recorded. No significant differences emerged among groups in terms of miscarriage rates, although women treated with vedolizumab had a more severe disease and a higher rate of steroid exposure at conception. Moreover, median gestational age, birthweight, Apgar score, as well as rates of prematurity and frequency of congenital anomalies of living births were comparable among groups. Of note, 4 patients (5%) started vedolizumab after conception for a disease flare and 23 (38%) maintained vedolizumab throughout the whole pregnancy [34].

Similar findings emerged from a study by The Groupe d' Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID), reporting data on 44 consecutive pregnancies in 41 women treated with vedolizumab for a median time of 10.0 months (IQR: 5.7–19.5) before conception. Most patients (98%) had been previously exposed to anti TNF-α drugs, and 57% of patients were primigravidae. Overall, vedolizumab exposure was limited to 2 months prior to conception in 15 pregnancies (34%), to the first trimester in 16 pregnancies (36%) and prolonged throughout the entire pregnancy in 13 cases (30%). Pregnancy outcomes, as well as maternal and neonatal complications, were similar between women who stopped vedolizumab before conception and those who maintained it during pregnancy [35].

On the other hand, two recent systematic reviews and meta-analyses, despite including few studies (4 each), showed a relative increase in overall pregnancy-related adverse outcomes, early pregnancy losses and preterm births among patients treated with vedolizumab compared to unexposed patients [36] and of early pregnancy losses and preterm births compared to women treated with anti-TNF-α drugs [7].

The pharmacokinetics of vedolizumab during pregnancy seemingly differs from that of anti-TNF-α drugs. Maternal serum trough levels of vedolizumab progressively decrease during pregnancy (median in first, second and third trimester and at delivery of 19.1 μg/ml, 15.1 μg/ml, 9.5 μg/ml and 5.5 μg/ml, respectively) [37] and, at delivery, are significantly higher compared to those found in the umbilical cord [38–40]. Both maternal and cord levels were found to correlate with the gestational week of the last vedolizumab administration [39]. Of note, Flanagan et al. explored the clearance of vedolizumab in 5 offspring and observed it to be faster than anti TNF-α drugs, with undetectable levels at no later than 15 weeks of age [37].

3.2.2. Ustekinumab

Ustekinumab is an IgG1 and therefore crosses the placenta through the FcRn receptor as is the case with anti TNF-α drugs. Information about the safety of ustekinumab during pregnancy is still limited. In this respect, Wills et al. published a retrospective study including 29 pregnancies in women exposed to ustekinumab (during pregnancy and/or two months before conception), which were compared with 44 pregnancies exposed to vedolizumab and 88 pregnancies exposed to anti TNF-α [35]. Eleven patients (38%) had active disease at conception and seven patients (24%) interrupted the treatment within two months before conception. Among 22 patients who received ustekinumab during pregnancy, 13 stopped it during the first trimester and nine continued the drug until delivery. Overall, the 29 pregnancies resulted in 26 (90%) live births, two (7%) spontaneous abortions during the first trimester, and one (3%) elective termination. Mild maternal complications were reported in two patients: one gestational diabetes and one threat of premature labour. No differences in adverse pregnancy, neonatal or maternal outcomes was observed between patients who stopped ustekinumab before conception and those who maintained it during pregnancy. The rate of life births and spontaneous abortions was not different between the ustekinumab and anti TNF-α groups. Authors reported three (12%) foetal complications (intrauterine growth retardation) in 26 live births of women receiving ustekinumab. Five (19%) neonatal complications were reported including two (8%) preterm deliveries, one (4%) LBW and one late premature birth at week 36 with LBW. One child had a cardiac malformation (tetralogy of Fallot) and received surgical correction without further complications. The rate of premature birth, LBW and admission in the intensive care unit was not different between the ustekinumab and anti TNF-α groups [35].

Flanagan et al. published a prospective observational study including women exposed to ustekinumab during pregnancy [41]. The study's aim was to evaluate ustekinumab pharmacokinetics in women with IBD during pregnancy and in the exposed infants. Authors did not find any safety signal, in pregnancy and infant outcomes, including preterm delivery and LBW (results were comparable with the background population). In this study, ustekinumab drug levels appeared stable across the three trimesters, in accordance with previous reports. This study was the first to explore the time to ustekinumab clearance in infants following in-utero exposure. On the other hand, infant ustekinumab levels at birth were higher than maternal levels, consistent with other reports, which reflects the exponential increase in active placental transport of

IgG1 biologics and the delayed foetal clearance due to an immature reticuloendothelial system. In addition, ustekinumab levels at the time of delivery were inversely related to the timing of last maternal antenatal dose. In this cohort, the median time to ustekinumab clearance was relatively rapid (nine weeks), and it correlated negatively with the number of days from final antenatal dose to delivery. The maximum clearance was 19 weeks in a baby exposed to ustekinumab 23 days prior to delivery.

Avni-Biron et al. evaluated the maternal and neonatal outcomes in patients with IBD treated with ustekinumab during pregnancy [42]. A total of 129 patients (27 exposed to ustekinumab, 52 to anti-TNF-α and 50 non-exposed to biologics) were prospectively included. All patients continued ustekinumab after conception and most of them (25 patients) continued ustekinumab throughout the third trimester. Overall, pregnancy, neonatal and newborn outcomes were satisfactory, with no significant differences among patients treated with ustekinumab, anti-TNF-α and non-biologics for maternal complications (11.5%, 23.1% and 8.2%, $p = 0.095$, respectively), preterm-delivery (4.3%, 18.4% and 5.7%, $p = 0.133$), LBW (4.2%, 10.2% and 8.3%, $p = 0.679$) or first year newborn hospitalisation (9.1%, 8.2% and 6.1%, $p = 0.885$). Authors concluded that pregnant patients with IBD treated with ustekinumab had outcomes comparable to those in patients treated with anti-TNF-α or other therapies.

Mahadevan et al. published a study reporting cumulative data on medically confirmed ustekinumab exposed pregnancies from the manufacturer's Global Safety Database (all safety events reported from any data source such as clinical trials, post-marketing studies, and voluntary reports) [43]. Reports could be prospective or retrospective. A total of 681 medically confirmed reports of maternal ustekinumab exposed pregnancies were identified; most of them (92.1%) had been exposed during the first trimester and only 120 (17.5%) of them during the third trimester of gestation. Among exposed pregnancies, there were 214 patients with CD and 16 with UC. Overall, a total of 340 (81%) live births, 51 (12.1%) spontaneous abortions, 25 (6%) elective abortions, three (0.7%) stillbirths and one (0.2%) ongoing pregnancy associated with congenital abnormality (persistent left superior vena cava detected during foetal ultrasound) were reported across all indications. Of the 340 live births, 33 (9.7%) infants were born preterm, and 17 (5%) infants had LBW. Among the 17 infants with LBW, one reported ustekinumab exposure prior to pregnancy, 15 reported exposure at least during the first trimester and one reported exposure in the second and the third trimesters. The overall rates of pregnancy outcomes were consistent across different diseases for which ustekinumab was prescribed. Major congenital abnormalities were reported in five (4.3%) CD patients and in no UC patient. Infants were born preterm in 16 (13.7%) CD patients and in no UC patient. More infants were delivered *via* caesarean section when born to women with CD in comparison to other indications. The rate of spontaneous abortions was 14.1%, and 16.7% for patients with CD and UC, respectively. Elective abortion rates were 6.7% for CD, and 8.3% for UC. Ustekinumab-exposed pregnancy outcomes were similar by underlying disease indication, dose of ustekinumab, or timing and duration of maternal exposure during gestation. With respect to congenital abnormalities, no unexpected trend or pattern in congenital abnormalities was observed with maternal exposure to ustekinumab. There were 133 pregnancies with paternal exposure to ustekinumab across all the indications and there were no safety signals.

Mitrova et al. performed a prospective study in consecutive women with IBD exposed to ustekinumab or vedolizumab two months prior to conception or during pregnancy [39]. A total of 54 pregnancies exposed to ustekinumab and 39 exposed to vedolizumab were included. In addition, data on a control group were retrospectively collected, consisting of consecutive pregnant IBD patients exposed to anti-TNF-α treatments; the control group comprised 90 pregnancies in 81 women with IBD exposed to anti-TNF-α therapy during pregnancy. In the ustekinumab group, 43 (79.9%) resulted in live births, and 11 (20.4%) led to spontaneous abortion. No significant difference in pregnancy outcomes between ustekinumab and the control group was observed. Similarly, there was no negative safety signal in the postneonatal outcome of exposed children regarding growth, psychomotor development, and risk of allergy/atopy or infectious complications. Pharmacokinetic parameters were available in 26 and 23 infant-mother pairs exposed to ustekinumab and vedolizumab, respectively. In all but in 3 cases the levels of ustekinumab in cord blood were higher than in maternal blood at the time of delivery, with a median infant-to-maternal ratio of 1.67. In contrast, except for three cases, vedolizumab cord blood levels were lower than maternal ones, leading to an infant-to-maternal ratio of 0.59. Drugs levels in cord blood positively correlated with gestational age at last administration and maternal levels at birth. A negative correlation with time to delivery was observed. Placental pharmacokinetics differed between the two biologics, with ustekinumab being like anti-TNF, whereas an inverse infant-to-maternal ratio was observed with vedolizumab.

3.2.3. JAK-inhibitors

In vitro and *in vivo* studies excluded mutagenic and genotoxic potentialities for tofacitinib, upadacitinib and filgotinib [25,30,31]. Preclinical studies suggest a potential teratogenic role for tofacitinib; however, the significantly higher doses administered to pregnant rats renders the interpretation of such results unreliable [25]. A teratogenic potential was observed for upadacitinib in both rats (increased musculoskeletal malformations at exposures comparable to those achieved in humans) and rabbits (embryonic lethality, decreased foetal weight and increased cardiovascular malformations at higher exposures compared to those achieved in humans) [30]. As for filgotinib, embryotoxicity and teratogenicity (causing malformations of central nervous, musculoskeletal, respiratory and cardiovascular systems) were demonstrated in rats and rabbits at exposures comparable to the 200 mg daily dosing regimen in humans [31].

The JAK/STAT pathways mediate signal transduction of several immunological signals [44], and a recent study on rats suggests the involvement of the JAK family in regulating the immunological interface between the mother and the foetus within the placenta [45]. However, current evidence is insufficient to formulate any hypothesis as to whether and how the inhibition of JAKs – and, more specifically, which JAK – during the second and third trimesters, might affect pregnancy outcomes.

Data on women exposed to tofacitinib at conception and during pregnancy are scarce. A 2016 study, considering 47 pregnancies occurred during the development programs of tofacitinib in rheumatoid arthritis and psoriasis, reported a frequency of spontaneous abortion of 15% and foetal malformation of 2% [46]. In the phase 3 OCTAVE RCT, 15 pregnancies in mothers exposed to tofacitinib occurred, with 2 (13.3%) spontaneous abortions reported [47]. A 2018 study collected 45 postmarketing cases of tofacitinib exposure (42 of which were of maternal exposure): the incidence of spontaneous abortions and malformations were 10.7% and 3.6%, respectively [48]. Comprehensively, the frequencies reported in these studies are consistent with the background risk of the general population [49]. A 2019 study, including mothers affected by various immune mediated diseases matched to healthy controls, investigated the infective risk in infants after in-utero exposition to non-anti-TNFα and tofacitinib: 1 serious infection in tofacitinib-exposed children was identified [50]. Human data neither on upadacitinib nor on filgotinib are currently available [31].

The 2022 ECCO guidelines on Sexuality, Fertility, Pregnancy, and Lactation contraindicate the use of tofacitinib and filgotinib during pregnancy [10]; similar recommendations can also be made for upadacitinib. Regular use of contraceptives should be encouraged while assuming JAK inhibitors. Of note, given the increased risk of thromboembolic events in patients assuming tofacitinib 10 mg bid who have additional risk factors for venous thromboembolic events, a careful consideration should be reserved to the choice of the female contraceptive method, specifically in regard to combined hormonal contraceptives [25]. When planning a pregnancy, as per manufacturers' indications, tofacitinib and upadacitinib should be suspended at least 4 weeks before conception [25,30], while a 1-week wash-out is recommended for filgotinib [31].

3.2.4. Ozanimod

The receptor affected by this drug (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development. Nonclinical reproductive safety assessments with S1P modulators in rats and rabbits have shown embryo-foetal toxicity, including embryo-foetal deaths and visceral malformations in the absence of maternal toxicity. Based on these data, ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment, and for 3 months after treatment discontinuation [33].

Limited data are available on the outcomes of pregnancies exposed to ozanimod in humans. Dubinsky et al. presented in 2021 at the ECCO congress the results of pregnancies under ozanimod [51]. All pregnancies, including participant and partner pregnancies, in the ozanimod clinical development program with an initial diagnosis prior to a cut-off date of September 30, 2020 were assessed for pregnancy outcomes. A total of 83 pregnancies among 4131 participants were reported in the safety database of participants treated with ozanimod or their partners. All pregnancy exposures occurred during the first trimester. Of the 60 pregnancies in females in ozanimod clinical trials, only nine were reported in patients with UC, and three in patients with CD. Participants discontinued study medication promptly except for those who elected pregnancy termination and did not discontinue study medication. Among all pregnancies in the ozanimod clinical development program, the incidence of spontaneous abortion in clinical trial participants was 15%, and the rate of preterm birth was 10.7%; these figures were similar to that reported in the general population. No teratogenicity was observed. Outcomes in patients with UC (nine patients) included two live births that resulted in two full-term healthy newborns, two ongoing pregnancies, two spontaneous early losses, and three elective terminations. The authors concluded that, while pregnancy should be avoided in patients on and three months after stopping ozanimod, and clinical experience with this drug during pregnancy is limited, it has not been reported any increase of foetal abnormalities or adverse pregnancy outcomes associated with ozanimod exposure in early pregnancy [51].

3.3. Lactation

The overall rate of breastfeeding amongst patients with IBD reported in the PIANO registry was 75%, which is slightly lower than the average rate in the general population [9]. In addition, significantly fewer women taking immunomodulators and biologics breastfed compared to women not taking these medications. The most common reasons for not breastfeeding were concern for the drug transfer to the infant and personal preference. Breastfeeding is recommended for at least 6 months after birth. Breastfeeding should be of low risk in patients under current approved biologic drugs, because IgA is the predominant immunoglobulin found in breast milk, and the biologic agents used to treat IBD are all in IgG subclass [52]. Therefore, secretion and transfer in breast milk should be minimal.

3.3.1. Anti-integrin

In the abovementioned study on cynomolgus monkeys, vedolizumab, administered at the dosage of 100 mg/kg every 2 weeks, was detected at low concentrations in the breast milk from 3 of 11 animals on post-partum day 28 [15]. The first data on humans have been reported on 5 breastfeeding women with IBD, from which serum and breast milk samples were collected before infusion, 30 min later and for the following 14 days. The lowest vedolizumab concentrations (ranging from 0.124 to 0.228 mg/mL) were detected in breast milk samples collected before the infusion and reached the peak of 0.318 mg/mL on days 3 through 7, a concentration estimated to be less than 1% of serum levels. Considering the amount of milk ingested by a baby, the maximum amount of vedolizumab received is estimated to be 0.048 mg/kg per day [53].

Later, Lahat et al. found similar findings on 5 post-partum women on maintenance therapy with vedolizumab, from which serum and breast samples were collected 1 h and the following days after the infusion. The amount of vedolizumab detected in breast milk resulted about 1% of the matching serum sample (maximum concentrations detected of 18 μg/mL and 478 ng/mL) and reached the peak after 3–4 days from infusion, followed by a progressive decline [54]. Finally, more recent data from 11 nursing women showed an average milk concentration of approximately 0.13 µg/mL with a peak up to 0.56 µg/ml after 3–4 days from the infusion and a slight variability depending on the scheduled infusion intervals [55].

3.3.2. Ustekinumab

Studies in macaques have shown that there is about 1/1000 of serum blood concentration of ustekinumab in the breast milk; this concentration is considered too low to result in systemic immunosuppression of the child [52,56]. Matro et al. published results on the concentration of different biologics in breast milk in patients included in the PIANO registry [9]. In a cohort of 824 infants, breastfeeding while receiving biological therapy did not affect the rate of infection or achievement of developmental milestones compared with no breastfeeding. In total, six patients treated with ustekinumab provided breast milk samples. None of them were treated with another immunosuppressive drug. Ustekinumab was detected in four of six (67%) samples, with peak concentrations seen between 12 and 72 h after the injection (range, 0.72 −1.57 μg/mL). All the mothers with detectable concentrations submitted samples out to seven days, and three of those had concentrations detected beyond 48 h. Authors concluded that lactation is compatible with the use of maternal biologic therapy, including ustekinumab, based on minimal transfer rates in breastmilk and no association with infants' infections and achievement of developmental milestones [9]. The concentration of ustekinumab in breastmilk was also analysed by Saito et al., and it was found to be 1/1400 of that in maternal serum, which was similar to that found in a previous study on macaques and other case studies with CD [57].

Finally, Klenske et al. reported for the first time the drug levels in a patient with CD who re-initiated ustekinumab after delivery [58]. The authors found that breast milk levels and serum trough levels collected directly after therapy reinduction were in a similar range. Ustekinumab breast milk levels detected in subsequently

collected samples were markedly lower and decreased in the time interval between applications.

3.3.3. JAK-inhibitors

It is currently unknown whether JAK inhibitors can be found in human milk following the administration to lactating women. Tofactinib has been found in the milk of lactating rats, after a single 10 mg/kg dose, with a concentration that parallels the one found in serum (about 2-fold higher) [25]. Similarly, upadacitinib can be found in milk when administered to lactating rats, with 30-fold higher concentration in milk compared to plasma [30]. Filgotinib was detected in nursing pups following its administration to lactating rats; nevertheless, the exposure in pups was less than 6% compared to maternal levels, so the results of the postnatal development study were considered inconclusive [31].

Being orally administered drugs with gastrointestinal absorption, it is reasonable to assume that babies might be exposed to effective concentrations of JAK inhibitors if breastfed by women who are assuming them – until proven otherwise. Hence, a risk-benefit evaluation should be performed, to decide whether the therapy can be suspended, or lactation should be avoided.

3.3.4. Ozanimod

The effects in the nursing infant are unknown. Animal studies revealed that this drug was detected in the milk of lactating animals at levels higher than those in maternal plasma. There is no information of the excretion of the drug in humans. Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed [33].

4. Discussion

In recent years, new molecules have been approved for the treatment of IBD. It is important to know the influence of these new treatments on fertility, pregnancy and lactation in order to make appropriate decisions for each patient. The most recently approved biologics and those in development are IgG1, like anti-TNF-α. In animal studies, they have not been associated with a risk of teratogenicity or effects on fertility. On the other hand, these drugs cross the placenta from the second trimester of pregnancy onwards, so the foetus is exposed to these drugs when their mothers receive them during pregnancy. The concentration of biologics in cord blood is, with the exception of vedolizumab, higher than in maternal serum. The clearance time of these drugs in the newborn is variable, but in general, the clearance of vedolizumab and ustekinumab is faster than previously described for anti-TNFs. This is important for the administration of live virus vaccines in the first months of life since, in the presence of detectable drug levels, such vaccines should be avoided.

In the case of small molecules, such as JAK inhibitors and ozanimod, which cross the placenta freely, they have been reported to be teratogenic in animals, administered at doses several times higher than therapeutic doses in humans. There are insufficient human data to make recommendations on their use during pregnancy, but at least no pattern of teratogenicity or complications has been observed in these patients.

Finally, biological drugs, being IgG1, are poorly excreted in breast milk, where IgA is the main Ig excreted and, due to degradation in the infant's digestive tract, exposure is unlikely to be of any clinical relevance. Small molecules are excreted in breast milk, so breastfeeding should be contraindicated in mothers on treatment with these drugs.

The increasing incidence of IBD together with the increasing use of these drugs makes it necessary to generate knowledge about their safety. On one hand, publication of the results of pregnancies exposed to these drugs in clinical trials is important. On the other hand, it is crucial to join efforts to communicate the experience with these drugs in clinical practice.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Daniela Pugliese has served as speaker/consultant for Takeda, Pfizer, Janssen, Galapagos, MSD and has participated in advisory boards for Janssen and Pfizer.

Giuseppe Privitera has served as speaker/consultant for Janssen and Alphasigma.

Javier P. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma.

María Chaparro has served as speaker, consultant or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Biogen, Gilead and Lilly.

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