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Conservative treatment of inflammatory bowel diseases during pregnancy. Review of current safety and efficacy data

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ABSTRACT *The incidence of ulcerative colitis (UC) and Crohn's disease (CD) worldwide falls on the childbearing age. High activity of inflammatory bowel diseases (IBD) during pregnancy is a risk factor for the development of obstetric complications, and therefore it is necessary to control the course of diseases. Due to the lack of safety information, drug therapy is often unreasonably canceled during pregnancy. The publication provides up-to-date on the safety of basic and targeted therapy of UC and CD in pregnant.*

KEYWORDS: *ulcerative colitis, Crohn's disease, inflammatory bowel diseases, pregnancy.*

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LIST OF ABBREVIATIONS

IBD — inflammatory bowel diseases
5-ASA — 5-aminosalicylic acid

GEBT — genetically engineered biological therapy

In the XXI century, the prevalence of IBD is becoming global, affecting ethnic groups and regions that were previously not susceptible to these diseases. The prevalence of UC and CD is highest in industrially developed and developing countries [1]. According to experts, the peak prevalence of IBD has not yet been reached. The most vulnerable to IBD is the age group of 20–39 years, i.e. persons of childbearing, socially active age. Approximately half of them are women. Modern IBD therapy has significantly expanded the possibilities of the disease control and, in many cases, allows patients to achieve reliable remission and to lead a normal socially active life, one of the components of which is childbirth. In this regard, reproductive health issues in patients with IBD are becoming increasingly relevant. The prevalence of IBD in Western countries is 0.5% [2]. In the USA, IBD affects about 800,000 women [3]. In Russia, data on the prevalence of IBD are scattered and limited to only some individual regions.

Pregnancy in women with IBD, as in many chronic immuno-inflammatory diseases, is associated with an increased risk of obstetric complications [4–7]. These complications include spontaneous miscarriage, premature birth and low weight of the fetus relative to the gestational age. However, it should be noted that the risk of these complications is directly related to the activity of inflammation in the intestine. The outcomes of pregnancies occurring against the background of persistent remission of UC and CD, in general, do not differ from a healthy population [8].The UC and CD during pregnancy is largely determined by the inflammatory status of diseases at the time of conception. Thus, the activity of the inflammatory process in the intestine at conception in two-thirds of cases is a predictor of the persistence of inflammation or its intensification [9–11]. Prolonged persistent remission at the onset of pregnancy correlates with its preservation in 80% of cases throughout the

gestation period. Factors that additionally contribute to the recurrence of IBD during pregnancy include the cancel of supportive drug therapy, exacerbation of the disease in previous pregnancy, the presence of UC, prolonged or complicated CD, requiring the immunosuppressive therapy [3,12]. These data became the basis for guidelines on optimal pregnancy planning for the period of reliable controlled remission of UC and CD [9,10].

Conservative treatment of IBD during pregnancy is aimed not only at controlling the activity of inflammation in the bowel, but also indirectly plays an essential role in maintaining the normal pregnancy and preventing perinatal complications.

It is known from practice that only half of women previously committed to drug treatment continue therapy during pregnancy [13]. The explanation for this may be a lack of awareness about the safety of IBD conservative treatment during pregnancy. Published in 2021 by a group of German researchers, the results of a survey of 533 women with IBD confirmed the insufficient level of knowledge among women with UC and CD about pregnancy planning with their disease. Of the total number of survey participants, 36% of women expressed concern about the possible adverse effects of taking medications for the fetus, among which the most often were the fear of congenital malformations, miscarriage, as well as the possibility of offspring inheriting the mother's disease [14].

In recent years, the data on the safety of IBD drug therapy in pregnant women has been continuously updated. The present paper discusses modern pharmacotherapy of UC and BC during pregnancy and breastfeeding.

5-ASA and Sulfasalazine Drugs

Mesalazines or 5-aminosalicylic acid agents (5-ASA) overcome the placental barrier and are detected in the fetal bloodstream in minimal amounts due to their rapid metabolism and renal clearance. According to meta-analysis data, the use of this group of agents is not associated with an increase in the risks of fetal abnormalities, miscarriage and premature birth [15]. Oral drugs containing dibutylphthalate in the shell have a restriction for use. In the experiment, cases of impaired development of the genitourinary system and skeleton were demonstrated in animals, as well as in humans — disorders of thyroid function and the formation of the reproductive system [16–18].

Sulfasalazine, in addition to the mesalazine molecule, contains sulfapyridine, which penetrates the placenta and is found in umbilical cord blood. An undesirable property of sulfasalazine in pregnant women is its ability to disrupt folic acid metabolism, and although no cases of teratogenic and embryotoxic effects have been reported, it should be used in combination with folic acid at a dose of 2 mg/24-hr, or be replaced with mesalazinedrugs [9,19].

Steroids

Systemic steroids are used to induce remission of moderate and severe IBD. The drug penetrates the placental barrier, but, due to the rapid conversion of placental enzymes into less active metabolites, it appears in umbilical cord blood in low concentrations [20]. In early studies, concerns were expressed about the relationship of the use of steroids in the first trimester of pregnancy with the risk of facial malformations, namely cleft palate. In a later large population study [21], which included 51,973 pregnancies in women who received steroids in the first trimester, these data were not confirmed.

At the same time, in a number of studies, steroids in high doses over long courses was associated with an increased risk of gestational diabetes mellitus, premature birth, low body weight and adrenal suppression in a newborn [22–24]. Taking into account that steroids are prescribed with high activity of diseases, in most cases it is difficult to differentiate the true cause of complications.

Budesonide is a topical steroid, significantly, up to 80–90% metabolized during the first passage through the liver. In recommended doses (3–9 mg per 24 hours), the drug has significantly fewer systemic side effects characteristic of systemic steroids. It can be assumed that due to these metabolic features, budesonide penetrates less into the fetal blood in comparison with systemic steroids [25]. Published data on the budesonide during pregnancy in patients with IBD are limited to a small case series. Thus, in one of the published studies [26] with cohort of 6 patients with CD who took budesonide during pregnancy, there was no increase in the risk of gestational diabetes

mellitus, congenital malformations of the fetus, hypertonia or adrenal suppression. Also, according to a recently published study [27], taking budesonide during pregnancy in 5 patients with autoimmune hepatitis was not associated with the adverse side effects from the fetus and pregnancy outcomes.

Despite the fact that limited data indicate possible undesirable effects of steroids during pregnancy, it should be taken into account that the high activity of inflammation in the intestine itself represents a more significant risk of complications. In this regard, if indicated, steroids may be prescribed with caution regarding the development of gestational diabetes mellitus, preeclampsia in the mother and adrenal insufficiency in the newborn [9,28,29].

Thiopurines

Thiopurines have a low risk of adverse effects on pregnancy and fetus [30,31]. Azathioprine and its metabolites are able to be transported through the placenta into the fetal blood, while the concentrations of these substances in umbilical cord blood are significantly less than in maternal [32]. In addition, it has been shown that the activity of some enzymes involved in drug metabolism, including azathioprine, increases significantly during pregnancy. As a result, the balance of thiopurine metabolites shifts from the 6-thioguanine nucleotide towards the less toxic and pharmacologically inactive 6-methylmercaptopurine [33]. The enzyme inosinate phosphorylase, which converts azathioprine into its active metabolites, is not expressed in the neonatal liver, which can be regarded as another factor of fetal protection from the clinical effects of the drug [34].

The effect of azathioprine on anemia/cytopenia in newborns demonstrated in early studies has not been confirmed in later studies [33]. Two meta-analyses in 2013 demonstrated minimal risk of taking azathioprine during pregnancy. In the first of them, there were no differences in the incidence of congenital malformations of the fetus, the small weight of the newborn (< 2,500 gr) in comparison with pregnant women with thiopurines intake[31]. Significant differences were noted in the rate of congenital malformations in comparison with the general population, which were not significant when compared with patients with IBD. In the second meta-analysis, these risks for the fetus were not confirmed [35]. At the same time, both meta-analyses revealed an increase in the rate of premature birth (earlier than 37 weeks of pregnancy), which was associated with high activity of IBD during pregnancy.

In a prospective cohort study involving 309 pregnant patients with IBD, 35% of whom got thiopurines, there was no increase in miscarriage, adverse pregnancy outcomes and morbidity in children in the first year of life [36]. These data are confirmed in the meta-analysis published in 2021 [37]. The authors analyzed pregnancy outcomes in 1,201 patients with IBD who received thiopurines during gestation compared with 4,189 women who received other therapy for UC and CD. The rate of congenital malformations in the fetus, low birth weight and low body weight for gestational age were comparable in the two groups.

The American Gastroenterological Association, the Toronto Consensus on the Management of Pregnancy in Women with IBD and the European Organization for the Study of UC and CD (ECCO) recommend the continuation of taking thiopurines during pregnancy [29,30,38]. A similar opinion is shared by the European Anti-Rheumatic League (EULAR), which does not note sufficient basis for stopping thiopurines during pregnancy, and recommends continuing their intake at a dose not exceeding 2 mg/kg of body weight [39]. The Russian clinical guidelines of the Association of Rheumatologists also classify thiopurines as safe drugs during pregnancy [40, 41]. However, thiopurines are not recommended for the first time during pregnancy due to the risks of pancreatitis, leukopenia and delayed response to therapy [9]. Also, due to the increased risk of infections in a child in the first year of life, as shown in some studies [30, 42], combination therapy with tumor necrosis factor inhibitors α and thiopurines is not recommended. Nevertheless, the decision to cancel thiopurines should be made individually, taking into account the indications for combination therapy and the severity of the course of the disease [9].

Methotrexate and cyclosporine are not recommended during pregnancy due to the high risk of teratogenicity. Patients with IBD who are taking methotrexate and planning pregnancy are advised

to stop taking it at least 3 months before trying to get pregnant in order to minimize the risk of teratogenicity [29,38].

Rifaximin

The drug is used in the treatment of IBD, including the treatment of chronic pouchitis [43]. According to the manufacturer's instructions, in an experiment, the administration of rifaximin to animals during pregnancy at doses many times higher than therapeutic ones led to the development of teratogenic effects [44]. Rifaximin is a broad-spectrum antibiotic with a low ability to intestinal absorption, and presumably does not reach clinically significant concentrations in maternal blood or breast milk [45,46]. Due to the fact that the number of publications on the use of rifaximin in humans during pregnancy is extremely small, the issue of its administration should be decided individually with discussion by a multidisciplinary medical team.

Genetic Engineering Biological Therapy

Drugs of genetically engineered biological therapy (GEBD) are monoclonal IgG antibodies that are able to overcome the placenta, starting from the middle of the second trimester. Active transport of GEBD is carried out using a neonatal Fc-receptor located in the placenta. In the first trimester of pregnancy, the Fc-receptor is not expressed by syncytiotrophoblast cells, and from the middle of the second trimester of pregnancy, its expression increases linearly [47]. From this moment, during pregnancy and until the moment of delivery, the transplacental transport and the concentration of GEBD in the fetal blood increases in parallel. The IgG structure has infliximab, adalimumab, golimumab, vedolizumab and ustekinumab. Certolizumab pegol does not have in its molecule the Fc-fragment necessary for active transfer through the placenta, and overcomes it in minimal quantities due to passive transport [48].

Inhibitors of Tumor Necrosis Factor α

The levels of tumor necrosis factor α (anti-TNF) inhibitors in umbilical cord blood correlate with the duration of pregnancy and exceed the maternal serum concentration at the time of birth [48, 49]. Clearance of anti-TNF in children in the first months of life is slower than in adults, which is associated with immaturity of the reticulo-endothelial system. Monoclonal antibody molecules are in the bloodstream of a child up to six months old. Some cases are described when infliximab was determined in a child up to one year old [48,49].

Certolizumab pegol, due to its reduced antibody structure, practically does not overcome the placenta, and its ratio in the blood of a newborn to the maternal concentration is 0.0009. These minimal clinically insignificant concentrations are an argument in favor for pregnant women to continue taking certolizumab pegol until delivery [50].

To date, significant data have been accumulated on the safety of taking anti-TNF drugs by pregnant women. Thus, in a meta-analysis and systematic review [51] with an analysis of more than 1,500 pregnancies against the background of anti-TNF, the risks associated with pregnancy complications, miscarriages, premature birth, congenital malformations and intrauterine fetal growth retardation were not confirmed.

In the prospective American PIANO-register (Pregnancy and Neonatal Outcomes in Women with IBD) [52], which includes data on the course of pregnancy in more than 1,000 patients with IBD followed by four-year follow-up of the health of children who received intrauterine anti-TNF, there was no increase in the frequency of infections and developmental delay. In a large multicenter prospective observational study by Mahadevan U. et al., the outcomes of 1,490 pregnancies in patients with IBD were evaluated by five parameters (congenital malformations, spontaneous miscarriages, premature birth, low fetal body weight and the incidence of infections in the child) when the mother used thiopurines, biological drugs or a combination thereof during pregnancy [53]. In the same study, the health status, including the frequency of infections and psychomotor development, was monitored in 1,010 children throughout the year.

In general, in terms of the fetal malformations rate, spontaneous miscarriages, low fetal weight, infections in the first year of the child's life and premature birth, the group did not differ from the general population. At the same time, the activity of the disease in the mother directly correlated with the rate of spontaneous miscarriages, premature births and infections in the first year of the child's life. When analyzing IBD during pregnancy, it was found that patients with UC had an increase

in disease activity more often than women with CD. At the same time, the probability of an exacerbation during pregnancy was higher in patients who did not receive immunosuppressive therapy with thiopurines or anti-TNF.

There was also no relationship between the incidence of pregnancy complications and the class of GEBD.

Similarly, there was no correlation between congenital malformations and medications taken or the nosological type of the disease (UC or CD). These results indicate both the role of controlling the activity of the disease during pregnancy and the safety of the use of biological therapy and thiopurines during this period [53]. The European retrospective multicenter study TEDDY [54] compared pregnancy outcomes and health status in 388 children whose mothers received anti-TNF therapy during pregnancy with 453 children whose mothers did not receive this therapy. The incidence of infections in the two groups of children did not differ during 4 years of follow-up. At the same time, premature birth was associated with severe infections (1.6% vs. 2.8%, HR = 1.2 [95% CI 0.8–1.8]). In the comparison groups, there were no differences in the incidence of obstetric complications, including premature discharge of amniotic fluid, placenta previa, chorioamnionitis, eclampsia and intrauterine fetal growth retardation.

It is worth noting that previously there was a strong belief about the need to stop the use of anti-TNF therapy in the II-III trimester due to the fear of potential risks of neonatal immunosuppression and the impact on the subsequent formation of the fetal immune system as the transport of drugs through the placenta increases in the second half of pregnancy.

This is reflected in the consensus of the British Society of Rheumatology (BSR), ECCO, EULAR, the American College of Rheumatology and Russian clinical guidelines for the treatment of ankylosing spondylitis and rheumatoid arthritis, published in 2018 and 2020, respectively [28,39,40,41,55]. At the same time, studies of the last few years have questioned the validity of the fear of the risks of a prolonged biological therapy during pregnancy.

The results of a long-term 5-year follow-up of the health status of 1,000 children from mothers with IBD, 20% of whom received anti-TNF during pregnancy, demonstrated associations of the use of GEBD by the mother with an increase in the risk of infectious diseases, adverse reactions to vaccination, developmental delays, autoimmune and oncological diseases in children [56]. Similar data were obtained in another retrospective study [53] involving 869 women with IBD, in which the risks to the fetus and pregnancy complications were not confirmed with the continuation of anti-TNF monotherapy or in combination with thiopurines in the second and third trimesters of pregnancy. In a retrospective analysis of the National Database of the French Healthcare System, the use of anti-TNF during pregnancy in 1,457 patients did not correlate with an increase in perinatal risks and infectious morbidity in the first year of a child's life [57]. Another argument in favor of the expediency of continuing biological therapy during pregnancy turned out to be data on an increase in the incidence of exacerbations in late pregnancy after its cancellation [57]. These data are confirmed in two recently published studies by Truta B. et al., which evaluated pregnancy outcomes in patients with IBD with "early" (more than 90 days) and "late" (less than 90 days before the expected date of delivery) withdrawal of infliximab or adalimumab [58,59].

With the "early" discontinuation of anti-TNF, there was an increase in the incidence of IBD reactivation in late pregnancy or an increase in the activity of inflammation in the initial absence of remission, requiring steroids. Reactivation of the disease in the group of patients with early suspension of drug intake significantly correlated with an increase in the incidence of premature birth. It is important to note that in the group of patients with late withdrawal of GEBD, the rate of pregnancy complications, miscarriage, intrauterine fetal growth retardation, congenital malformations of the fetus did not differ from the general population. The data obtained in the studies, according to the authors, indicate the absence of positive effects on the fetus with early withdrawal of infliximab and adalimumab. In contrast, the continuation of therapy in the third trimester of pregnancy contributes to maintaining remission of IBD and minimizes the risk of their exacerbations [58].

The given data on the safety of anti-TNF were the basis for the guidelines of the American

Gastroenterological Association on the continuation of therapy with GEBD throughout pregnancy with their last administration before childbirth at a time equal to the interval of planned administration of the drug [9]. The British Society of Gastroenterologists and ECCO advise discussing with pregnant women the possible risks and benefits of continuing anti-TNF therapy, but at the same time recommend continuing this therapy throughout pregnancy to patients with active IBD or having a high risk of exacerbation of the disease [28,43].

As for **golimumab**, there are significantly fewer publications on the use during pregnancy in the available literature in comparison with studies of other anti-TNF, but they indicate a low risk of adverse outcomes for pregnancy and fetus [60, 61].

Biosimilars

Biosimilars, due to their affordability, are increasingly entering clinical practice. The first reports of pregnancy observations in women who received anti-TNF biosimilars during this period appear in the literature. In the first published retrospective study, the course of pregnancy was evaluated in 18 patients receiving biosimilars of infliximab, adalimumab and etanercept for various indications [55]. The study included 9 women suffering from rheumatological diseases (ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis), 6 with IBD and 2 patients with combined forms of autoimmune inflammatory diseases. The use of biosimilars was not associated with an increase in cases of congenital malformations of the fetus, premature birth and other perinatal complications. Anti-TNF cancel during pregnancy directly correlated with childbirth in the earlier stages of pregnancy, as well as the exacerbation of maternal diseases during pregnancy or in the postpartum period.

Another study published in abstract form [62] presents data on the use of infliximab biosimilar (CT-P13) in 20 pregnant patients with IBD. In 19 cases, pregnancy ended with the birth of full-term live, healthy children, in 1 case — premature birth with a live fetus, and in one case a spontaneous miscarriage was recorded. There were no cases of perinatal complications and severe fetal malformations in the studied group, with the exception of 1 case of cleft palate. These results correspond to the available data on the safety of the original anti-TNF and the absence of risks of congenital malformations, perinatal and obstetric complications [10,63,64]. The results obtained, despite the limited number of cases, demonstrate the first convincing evidence of the safety and necessity of the use of biosimilars by pregnant women, comparable to those shown for the original anti-TNF drugs [55,62]. Without a doubt, a continuation of the evidence base is required to finally confirm the initial optimistic data on the safety of biosimilars during pregnancy.

Vedolizumab

Vedolizumab is a humanized monoclonal antibody that specifically binds to $\alpha 4\beta 7$-integrin located on lymphocytes. The recent data obtained on the safety of vedolizumab is significantly less than is available for anti-TNF, and they are mainly limited to small cohorts.

Like other GEBD with the IgG1 structure, vedolizumab overcomes the placental barrier, but is found in umbilical cord blood concentrations lower than maternal [65,66]. In the study by Mitrova K. et al., the ratio of umbilical cord and maternal concentrations of vedolizumab at the time of delivery was 0.59 [67].

In animals, the administration of the drug in supraphysiological doses was not associated with disorders of pre- and postnatal development [68].

In 2019, the results of a retrospective case-control multicenter international study on the safety of the use of vedolizumab in pregnant CONCEIVE were published [69]. In this study [69], there was no evidence of adverse effects of vedolizumab in relation to the course and outcomes of pregnancy and the health of the child in the first year of life. The incidence of spontaneous miscarriages, premature birth, congenital malformations of the fetus, fetal weight at birth and assessment on the Apgar scale, as well as the health indicators of children in the first year of life, the incidence of oncological and infectious diseases did not significantly differ from those of women with IBD who received anti-TNF or basic IBD therapy.

Another study [70] analyzed the course and outcomes of pregnancy in 24 pregnant women taking vedolizumab, compared with 82 women treated with anti-TNF and 224 pregnant patients on basic IBD therapy. Basically, the vedolizumab group

consisted of patients who suffered from CD and had a more severe, refractory course of the disease and had a history of inefficiency of one or more biological agents. In this group, the rate of exacerbations of IBD at the time of conception was higher than in other observation groups — 30% of cases. Spontaneous miscarriages (20.8%) and premature birth (20%) were significantly more common in patients receiving vedolizumab. Such a high rate of miscarriage, according to the authors, could be associated with the initially high activity of diseases in a larger number of patients in this group, which has been proven to be interrelated with pregnancy complications in patients with IBD. In this group of patients, there were other independent risk factors for miscarriage: older age and the use of assisted reproductive technologies.

According to the authors, the use of vedolizumab in this study was not associated with an increased risk of adverse pregnancy outcomes.

In another prospective study [67] involving 39 patients, the use of vedolizumab during pregnancy was not associated with an increased risk of miscarriage, intrauterine fetal growth retardation, congenital malformations of the fetus, as well as disorders of psychomotor development, infectious, allergic diseases in a child during the first year of life.

In a systematic review and meta-analysis in 2020, an increase in the rate of premature birth and spontaneous miscarriages associated with taking vedolizumab compared with taking anti-TNF was shown [71]. According to the researchers, this may be due to a smaller number of cases of pregnancies against the background of vedolizumab, a more severe phenotype of diseases and an older age of patients.

Ustekinumab

Ustekinumab is a fully human monoclonal antibody of the IgG1 class, the target of which is the p40 subunit common to the IL-12 and IL-23 receptors.

Like other genetically engineered drugs, ustekinumab overcomes the placental barrier starting from the second half of pregnancy. At the time of delivery, its level is maximal and the ratio of fetal and maternal levels of ustekinumab in the blood is 1.67 [67]. In animals, ustekinumab did not increase the risks of fetal malformations and disorders of neonatal development in offspring [72]. Data from observational studies are few and do not demonstrate an increase in the number of cases of undesirable effects during pregnancy and an increase in infectious complications in children whose mothers took ustekinumab during pregnancy [43,53,61,73,74]. The use of the drug in the second and third trimesters of pregnancy in a number of studies also did not increase the rate of adverse pregnancy outcomes [75,76].

In 2022, the materials of the ustekinumab global safety database on all cases of use of the drug during pregnancy registered in the world were published [77]. In total, the outcomes of 420 pregnancies did not differ from the general population. There was no increase in the frequency of spontaneous miscarriages, congenital malformations of the fetus, premature birth and stillbirth. Pregnancy outcomes were also similar, regardless of the indications for the administration of ustekinumab, the duration of its use during pregnancy and the prescribed dose (45 mg and 90 mg). There is no consensus in the international recommendations regarding the possibility of continuing taking vedolizumab and ustekinumab. There is no information about ustekinumab and vedolizumab during pregnancy in the ECCO consensus of 2015. By the time of publication in 2016 of the North American Consensus in Toronto, cases of pregnancy against the background of the use of the drug were sporadic. At that time, it was proposed to suspend the administration of vedolizumab and ustekinumab with the onset of pregnancy. The guidelines of the American Gastroenterological Association were published 5 years later, in 2019, when information about the safety of these drugs during pregnancy was significantly updated [9]. This became the basis for recommendations on the safety of continuing therapy with vedolizumab and ustekinumab during gestation [9]. The Italian group of experts on the study of IBD in a review released in 2022 suggests discussing the possibility of using vedolizumab and ustekinumab during pregnancy in individual cases, if there are indications [78]. Despite the positive data available at the time of publication on the safety of vedolizumab and ustekinumab, further studies are required to finally understand their impact on

pregnancy outcomes and routine guidelines for use.

Tofacitinib

Due to its small size, Tofacitinib is able to diffuse freely through the placenta and penetrate into the fetal bloodstream. In animals in supratherapeutic doses during pregnancy, tofacitinib increased the risk of malformations in offspring [79]. The first few data from clinical and post-marketing studies did not demonstrate an increase in perinatal and maternal risks in comparison with the general population [52,80]. Nevertheless, currently, the use of tofacitinib during pregnancy, until sufficient data on its safety is obtained, is contraindicated [34]. According to the manufacturer's instructions, after taking the last dose of the drug, women of childbearing age should use reliable contraception for 4–6 weeks.

Breastfeeding

Conservative treatment in the postpartum period and during breastfeeding does not lose its significance due to the high probability of reactivation of the inflammatory process in the intestine, especially in patients with UC [81]. The causes of exacerbations of IBD after childbirth or an increase in the activity of inflammation may be hormonal influences, discontinuation of drug therapy, psychoemotional factors [82]. Women with IBD are more likely than in the general population to refuse breastfeeding due to fear of adverse effects on the child of drugs secreted into breast milk [83]. About 56% of women with IBD consider medications for the treatment of their disease contraindicated during breastfeeding [84]. At the same time, breastfeeding has undeniable benefits for both mother and child. According to systematic reviews, breastfeeding can partially offset the risk of early IBD in children from parents with IBD by up to 30% [85]. The probability of developing undesirable effects of drug therapy taken by the mother in a breastfed child is determined by the toxicity and ability of the drugs to be secreted into breast milk, reaching clinically significant levels.

Most drugs used in the treatment of IBD are detected in breast milk in concentrations that are safe for the child.

Mesalazine is minimally excreted into breast milk, reaching less than 0.1% of the maternal plasma concentration, which has no clinical significance [86]. At the same time, the levels of sulfapyridine in breast milk when the mother takes sulfasalazine are significantly higher than mesalazines [87]. Cases of fever, bloody diarrhea and vomiting in children when taking sulfasalazine by the mother are described [88]. In this regard, it is considered safer to replace sulfasalazine for nursing mothers with mesalazinedrugs. International recommendations define mesalazines as compatible and safe drugs during breastfeeding [28].

Azathioprine is found in breast milk in trace amounts of less than 10% of the maternal serum level [89]. The peak concentration of azathioprine in breast milk is reached 4 hours after taking the drug. In an observational case-control study in 15 children whose mothers took azathioprine while breastfeeding, there were no abnormalities in physical and mental development, as well as an increase in the risk of infections [90].

Methotrexate and cyclosporine are contraindicated during breastfeeding. Methotrexate is secreted into breast milk and can accumulate in the tissues of a child with the risk of immunosuppression, neutropenia and has the potential for the development of oncological processes [7]. Breastfeeding while taking cyclosporine according to the latest recommendations of the American Pediatric Association is contraindicated [7].

Steroids are detected in breast milk in low concentrations, which are maximal in the first 4 hours after their oral taking. In this regard, it is recommended to observe a 4-hour interval between taking corticosteroids and breastfeeding [91]. With intravenous prednisolone, its concentration in breast milk is only 0.025% of maternal and is not regarded as clinically significant for a child [92].

Antibacterial drugs (metronidazole and ciprofloxacin) are capable of excretion into breast milk, and therefore their use is not recommended [13,92].

Short courses of admission with the precautionary measures are considered acceptable. According to the guidelines of the American Academy of Pediatricians, breastfeeding is recognized as safe 12–24 hours after a single dose of metronidazole at a dose of 2 g and 48 hours after taking the last dose of ciprofloxacin [13,93].

Genetically engineered biological drugs are large molecules with a high molecular weight that do not penetrate well into breast milk. In studies that evaluated the content of anti-TNF in breast milk, the level of drugs was about 1% of the maternal serum concentration [94–96]. In the study by Matro R. et al., the rate of infections in the first year of life and deviations in psychomotor development in children from mothers with IBD who received and did not receive GEBD (infliximab, adalimumab, golimumab or ustekinumab) did not significantly differ [97]. Once in the gastrointestinal tract of a child, GEBD are proteolized by digestive enzymes, and only a small part of them is absorbed and then enters the systemic circulation. Theoretically, these trace concentrations do not carry clinically significant risks for the child [9].

As in the case of transplacental transfer, the absence of the Fc-fragment in the structure of the certolizumab molecule determines its lower secretion into breast milk in comparison with the other anti-TNF. In the CRADLE study, certolizumab pegol was detected in breast milk of women suffering from CD, rheumatoid arthritis, axial spondyloarthritis or psoriatic arthritis, in 0.15% of its serum concentration [98].

International European and American recommendations of recent years define the use of anti-TNF as safe and compatible with breastfeeding [9,79,99].

Domestic clinical recommendations of the Association of Rheumatologists of Russia also classify anti-TNF as safe during lactation [40,41]. The exception is golimumab due to the small number of publications about its use during breastfeeding.

Data on the safety of golimumab, vedolizumab and ustekinumab during breastfeeding are still limited.

In the work by Sun, W. et al. the average level of vedolizumab in breast milk in 11 lactating women with IBD was 0.4–2.2% of the maternal serum concentration [100]. In two other small studies, the maximum concentrations of vedolizumab in breast milk were also low and amounted to 1% or less of the serum content [101,102].

European experts in the published guidelines (joint consensus of the Austrian Society of Gastroenterologists, Hepatologists, Rheumatologists and Rehabilitologists, 2019; review of the Italian IBD study group 2021) take a more cautious position regarding the safety of vedolizumab and ustekinumab and do not recommend breastfeeding while taking them [78,99]. However, in the guidelines of the American Gastroenterological Association, the use of all GEBD is classified as compatible with breastfeeding [9].

Vaccination — Transfer

Anti-TNF drugs, vedolizumab and ustekinumab circulate for a long time in the child's body and can potentially have an immunosuppressive effect on the production of antibodies in response to vaccines.

This is directly related to the ability of the child's immune system to form an adequate post-vaccination response, as well as possible vulnerability to the introduction of live vaccines. In studies, the level of antibodies in response to inactivated vaccines and toxoids (for example, tetanus) in children whose mothers received GEBD during pregnancy did not differ from the control group [103].

The data from the register of the Dutch National Vaccination Program indicate that there are no differences in the effectiveness and safety of vaccination against viral hepatitis B in children who received intrauterine anti-TNF from the mother, compared with the control group [104]. These data substantiate the possibility of immunizing the cohort of children under discussion with inactivated vaccines according to the national standard vaccination schedule [103]. A multicenter study involving 28 gastroenterological clinics in France evaluated the response to live vaccines (Bacillus Calmette-Guérin — BCG, rotavirus, MMR-measles, mumps, rubella vaccine) in children from 143 mothers who received anti-TNF during pregnancy. The aim of the study was to evaluate the incidence of vaccinations with live vaccines of children before and after 6 months of life, against the background of breastfeeding by a mother taking GEBD, and to identify the rate of undesirable effects [105]. Half of the women in the group breastfed their children without developing any complications during vaccination. Before

the recommended period of administration, earlier than 6 months, BCG was administered in 19 (16%) cases, rotavirus vaccine — in 5 cases and MMR — in 6 cases. There was 1 post–vaccination reaction to BCG in the form of an abscess at the injection site and in 1 case, an increase in temperature was noted. Recommendations on the need to adjust the vaccination schedule came mainly from gastroenterologists (in 86% of cases) and much less often from obstetricians and pediatricians (23% and 12% of cases, respectively). This underlines the need to better inform obstetricians and pediatricians about the features of vaccination of children who were prenatally influenced by the GEBD received by the mother [105]. Thus, vaccination with live vaccines is recommended to be carried out no earlier than the first half of the life of a child born to mothers treated with GEBD, and the introduction of rotavirus vaccine should be abandoned due to the lack of clinically significant benefit after 6 months of life [43].

CONCLUSION

Drug therapy of UC and CD during pregnancy provides not only control over the activity of diseases, but also indirectly contributes to the prevention of complications of pregnancy and the antenatal period.

Most of the drugs for the treatment of IBD are compatible with pregnancy and breastfeeding.

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