ORIGINAL INVESTIGATIONS

Use of inhibitors of tumor necrosis factor α in women with ankylosing spondylitis during pregnancy

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Objective: *to present our own experience of tumor necrosis factor α (TNFα) inhibitors (iTNFα) usage during pregnancy in women with ankylosing spondylitis (AS), to assess AS activity and outcomes of gestation.*
Patients and methods. *A prospective observation of 55 pregnant women with AS who met the modified New York criteria of 1984. Fifty-six pregnancies were followed. The average age of the patients was 31.7±4.7 years, the duration of the disease was 132.2±85.4 months. The median BASDAI for pregnancy trimesters was 2.4 [1.2; 4.4], 2.7 [1.4; 4.2] and 2.2 [1.5; 4.0], respectively. 14 women received iTNFα 3 months before pregnancy.*
Results and discussion. *In the first trimester, TNFα was used in 9 (16.1%) patients, in the second – in 9 (16.1%) and in the third – in 5 (9.3%); the median BASDAI for trimesters was 2.3 [1.0; 3.7], 3.4 [1.2; 3.5], 3.0 [0.8; 3.4], respectively. All patients who discontinued iTNFα just before or in early pregnancy had indications for resuming therapy in the second half of gestation. Cancellation of iTNFα at the end of the second trimester was not a risk factor for high activity in the third trimester. There was 1 adverse pregnancy outcome. In other cases, childbirth occurred at 38.9±1.4 weeks, newborns' body weight was 3273.1±435.6 g.*
Conclusion. *Women with AS who plan a pregnancy should be prescribed drugs with the maximum allowed duration of use during gestation. Cancellation of iTNFα before and in early pregnancy is a risk factor for high AS activity, while renewal of iTNFα therapy during pregnancy is not always effective.*

Key words: *ankylosing spondylitis; tumor necrosis factor α inhibitors; pregnancy.*
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At the beginning of the 21st century a new therapy strategy «Treat to target» and a widespread introduction of innovative Biologic Disease-Modifying Antirheumatic Drug (bDMARD) into clinical practice allowed to achieve significant progress in the treatment of spondyloarthritis (SpA). Improving the quality of life of these patients, maintaining their functional status and social activity changed the attitude of rheumatologists and patients to pregnancy and, as a result, led to an increase in the number of births in women with SpA [1]. Despite a rapid growth of the number of bDMARDs registered for SpA treatment, data on their safety during pregnancy and its planning significantly lag behind. In the consensus document on the use of anti-rheumatic drugs during gestation, developed by 29 experts from different countries of Western Europe and published in 2006, [2], there were indications only for two TNFα inhibitors (iTNFα): due to the lack of data, etanercept (ETC) and infliximab (INF) were not recommended for use during pregnancy (level of evidence – IV), despite the absence of embryotoxicity and teratogenicity in animal studies, as well as no increase in the risk of congenital anomalies in children whose mothers received these drugs for Crohn's disease or rheumatoid arthritis (RA) during gestation. Updated data on the safety of bDMARDs during pregnancy was published in 2008 [3] as the number of patients of reproductive age who used iTNFα was increasing, but experts had different opinions about the possibility of using such therapy during gestation.

Definitely, analysis of the effect of medicines on the course of pregnancy and its outcome, as well as determining their embryotoxicity and delayed effect on the child's health is a very difficult task. For ethical reasons, pregnant women are not included in pre-registration studies, and in rare cases, if pregnancy occurs, the drug is immediately discontinued, so the information about its embryofetotoxicity and teratogenic effects is limited to the data from preclinical studies on animals, that can only be used to predict possible risks in humans. In addition, the pharmacokinetics of a drug may be affected by physiological changes associated with pregnancy (fluctuations in the level of steroid hormones, activity of liver enzymes, etc.), the appearance of an additional fetoplacental circulation and the placenta itself [4].

Nevertheless, a sufficient number of women received iTNFα during gestation in real clinical practice, notwithstanding the lack of safety data of bDMARDs: since no more than 50% of pregnancies are planned, patients continued therapy without knowing that they were expecting a child [5]. With accumulating evidence on the use of various medicines, including bDMARDs, during gestation, the creation of registers of pregnant women and the increasing need to determine the possibility of using new drugs in pregnant women, the US Food and Drug Administration (FDA), taking into account the limited informativeness of traditional categories of drug safety (A, B, C, D, X), has introduced new requirements for medical drug use instructions, obliging manufacturers to provide generalized information about post-marketing studies, risk/benefit assessment and data from pregnancy registers in 2014. According to the recommendations of the ACR (American College of Rheumatology) summit on the reproductive health of women with autoimmune and systemic inflammatory diseases published in 2015, iTNFα were considered as drugs with a relatively low risk of developing malformations in the fetus, indicating probable compatibility of iTNFα with pregnancy [5].

Most iTNFα were recommended to be canceled at 30–32 weeks of pregnancy to prevent their penetration through the placenta and potential immunosuppression of newborns; the need to delay the use of live vaccines for 5 months in infants exposed to intrauterine iTNFα was also noted. Though the authors emphasized the safety of certolizumab pegol (CZP) due to its minimal transfer through the placental barrier and the absence of an increase in infections during the first year of life in infants whose mothers continued therapy with the drug in the third trimester of pregnancy, there were no clear instructions on the possibility of using this drug during the entire gestation.

2016 was a significant year for rheumatologists in Europe, including Russia, as in that year the EULAR (European Alliance of Associations for Rheumatology) recommendations on the use of anti-rheumatic drugs during planning pregnancy and pregnancy itself, as well as during lactation were published [6]. According to these recommendations, a number of iTNFα: INF, adalimumab (ADA), ETC, CZP were allowed to be used during these periods of women's life (recommendation level – B); moreover, INF and ADA – only in the first half of gestation (up to the 20th week), and ETC and CZP due to the low level of their passage through the placental barrier – even in the second half of pregnancy (up to 30–32 weeks and throughout gestation, respectively). Due to a small number of studies, golimumab (GLM) was not recommended for use during pregnancy or its planning, despite the available data on the absence of an increased level of congenital malformations.

In the Russian clinical guidelines of 2017 [7], among the bDMARDS used for ankylosing spondylitis (AS), iTNFα are considered as low-risk drugs in pregnant women, and four of them are allowed for use during gestation: INF – up to the 16th week, ETC and ADA – until the end of the second trimester, CZP – throughout pregnancy (the level of evidence is B for all the recommendations given). If mother's treatment with ADA and ETC was continued in the third trimester due to the activity of the disease, then the vaccination of the child with live vaccines should be postponed until the age of 7 months (level of evidence – C). Given the low level of evidence of the safety of GLM (in the first trimester of pregnancy the level of evidence is D, in the second half – there is no data), it is not prescribed during gestation.

In accordance with the ACR 2020 recommendations for the management of patients of reproductive age with rheumatic and musculoskeletal diseases [8], iTNFα are also considered compatible with pregnancy: INF, ETC, ADA and GLM are conditionally recommended until the end of the second trimester, CZP – throughout gestation («strongly recommended»).

The frequency of iTNFα use during pregnancy in women with spondyloarthritis (SpA) varies enormously in different studies. Thus, according to the Norwegian National Register [9], in which 177 pregnancies were monitored in 166 women with SpA from 2006 to 2016, 6%, 4%, and 1% of patients received iTNFα in the first, second and third trimester of pregnancy, respectively, while 44% of patients received it before pregnancy. In the study of C.J. F. Smith et al. [10], based on the analysis of a prospective cohort of pregnant women with AS (n=129) and psoriatic arthritis (n=117) from the USA and Canada, the frequency of iTNFα intake was 81.4%. In the work of E. Eworuke et al. [11] databases of 16 US insurance companies for the period from 2004 to 2015 were used, containing information about women with various inflammatory diseases, including 2706 patients with AS, whose pregnancies ended with live births. The control group included 2365 women with AS who did not have gestations during the study period. 26%, 11%, and 9% of patients with AS received iTNFα therapy in the first, second and third trimester of pregnancy, respectively, while in the absence of pregnancy, women with AS were treated with iTNFα in 47% of cases. Interestingly, ETC was prescribed to pregnant women more often from 2004 to 2008, the use of INF and ADA during pregnancy increased from 2009 to 2014, and ADA was the most commonly used iTNFα in 2015. It should be pointed out that the study only included information up to 2015, when reliable data about the possibility of using CZP during the entire gestation was insufficient.

According to our own retrospective study based on a survey of women with AS conducted in 2016–2017, at the time of conception, 6.9% received iTNFα (ADA, ETC), only 2.3% of the respondents received it in the first and second trimesters [1]. As for the safety of iTNFα during gestation in women with immunoinflammatory diseases, according to a systematic review of prospective and retrospective studies conducted in 2015 – 2019 [12], the frequency of spontaneous abortions (0.4%–17.4%), premature births (3.2%–11.5%), congenital malformations (1.9%–6.2%) against the background of ADA, ETC, CZP therapy did not differ from their frequency in general population, which confirms the previously obtained information about the safety profile of iTNFα; serious infections were recorded in 0% – 7.9% of infants. In children whose mothers received INF during pregnancy, serious infections occurred on average in 18.2% of cases. At the same time, only one study involving women with inflammatory bowel diseases revealed a high incidence of acute respiratory infections in children of the first year of life: in 37% – with the treatment of INF in the first half of gestation and in 45.6% – in later periods of pregnancy (the differences are insignificant).

We did not find generalized data on the frequency of iTNFα administration to pregnant women with AS in Russia, the activity of the disease during gestation, outcomes and complications of pregnancy against the background of iTNFα therapy.

The aim of the study is to describe our own experience of using iTNFα during pregnancy in women with AS, to assess the activity of the disease and the outcomes of gestation against the background of iTNFα therapy.

Patients and methods. From 2016 to 2021, V. A. Nasonova Research Institute of Rheumatology (V.A. Nasonova Research Institute) conducted a prospective follow-up of 55 pregnant women with AS who met the modified New York criteria of 1984. All patients signed an informed consent to participate in the study. The average age of women was 31.7±4.7 years, the duration of the disease was 132.2 ± 85.4 months.

Fifty-six pregnancies were traced, of which 54 (96.4%) ended with live births, the median delivery period was 39 [38; 40] weeks. The body weight of newborns was on average 3410.8±418.2 g, length – 51.8±2.1 cm. Adverse pregnancy outcomes were registered in 2 (3.8%) cases: non-developing pregnancy at 18 weeks in a woman with moderate AS activity and a burdened obstetric history; and operative delivery at 23 weeks due to the critical condition of the fetus in a patient with high AS activity due to the severity of axial, extra-axial and extra-skeletal manifestations.

Visits to a rheumatologist were carried out at 10–11, 20–21 and 31–32 weeks of pregnancy. BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score calculated by the

Table 1. Use of iTNFα during pregnancy, n

Medicinal product	Trimester		
	I	II	III
ADA	3	3	–
INF	1	–	–
GLM	1	–	–
ETC	1	1	–
CZP	3	5	5
Total	9	9	5

Table 2. AS activity in pregnant women receiving iTNFa, Me [25; 75th percentile]

Parameter	Trimester		
	I (n=9)	II (n=7)	III (n=5)
BASDAI	2.3 [1.0; 3.7]	3.4 [1.2; 3.5]	3.0 [0.8; 3.4]
ASDAS-СРБ	1.8 [1.2; 1.9]	1.8 [1.3; 1.9]	1.6 [0.7; 2.6]
CRP, mg/l	2.7 [1.3; 6.5]	4.0 [0.7; 4.5]	7.3 [2.2; 11.6]

level of CRP) recommended by ASAS (The Assessment of SpondyloArthritis international Society) were used to determine the activity of AS [13]. The BASDAI values increased in the first trimester (2.4 [1.2; 4.4]) compared with the month of conception (1.4 [0.4; 3.0]; $p<0.05$) and did not change in the second and third trimesters: 2.7 [1.4; 4.2] and 2.2 [1.5; 4.0], respectively. In the second trimester of pregnancy, there was a tendency to an increase in the disease activity according to ASDAS-CRP: 1.9 [1.6; 2.7], 2,3 [1.6; 2.8] and 2.1 [1.4; 2.0] in the I, II and III trimesters, respectively, and an increase in the level of CRP (6.7 [2.5; 14.7]) compared with the I trimester (4.3 [2.1; 8.9]; $p<0.05$), the median (Me) value of CRP in the III trimester was 4.7 [2.3; 11.3].

Nonsteroidal anti-inflammatory drugs (NSAIDs) at the time of conception, and in the I, II and III trimesters were taken by 23 (41.1%), 20 (35.7%), 32 (57.1%) and 24 (42.9%) women, respectively. After inclusion in the study, the drug of choice was ibuprofen, which was discontinued in all patients no later than the 32nd week of pregnancy. To determine the total dose of NSAIDs, the index of NSAID intake was calculated [14]. The index of NSAID intake in the first trimester (5.8 [2.9; 11.8]) was lower than 3 months before pregnancy (28.6 [16.7; 50]) and in the second (15.5 [4.7; 32.1]) and the third (24.4 [8.9; 50.0]) trimesters ($p<0.05$).

Sulfasalazine (SASP) was taken during pregnancy by 7 (12.5%) patients at a dose of 1.25 ± 0.25 g/day. Glucocorticoids (GC) in the I, II and III trimesters were received by 4 (7,1%), 8 (14,3%) and 10 (17.9%) women, respectively. The administration of GC for high AS activity due to the severity of axial and non-axial manifestations did not lead to a decrease in the activity of the disease: BASDAI in the II and III trimesters was 5.5 ± 0.6 and 5.8 ± 1.3 ($p>0.05$).

Fourteen women were treated with iTNFα for 3 months before pregnancy, including ADA – 5, GLM – 1, INF – 4, CZP – 3, ETC – 1. None of the patients had high AS activity at 0–3 months before conception, BASDAI was 2.4 [0.8; 3.5]. At the same time, an increased AS activity was noted throughout gestation in patients who stopped taking iTNFα just before pregnancy: the BASDAI index for trimesters of pregnancy was 5.2 [3.1; 6.0]; 5.7 [5.0; 6.1] and 6.7 [5.3; 7.3], respectively ($p<0.05$ compared with the month of conception).

Statistical data processing was performed using «Statistica 12» software (Data Analysis Software System, StatSoft Inc., USA) in Windows environment using generally accepted methods of parametric and nonparametric analysis. The Mann–Whitney U-test was used to compare two independent groups by quantitative characteristics. The differences were considered statistically significant at $p<0.05$. The data is presented in the form of mean (M) and standard deviation, or Me with an interquartile range (Me [25th; 75th percentile]).

Results and discussion. In the first trimester of pregnancy (Table 1), 9 (16.1%) patients received iTNFα, in the II – 9 (16.1%) and in the III – 5 (9.3%). There were 14 women treated with various iTNFα 3 months before conception. Five of them stopped taking the medication on their own initiative or on the recommendation of rheumatologists who observed them before inclusion in the study. One patient stopped the treatment with iTNFα in the early stages of pregnancy on her own. In the first trimester, we canceled GLM, since it is not recommended for use during gestation. In accordance with the national clinical guidelines, the therapy with ADA and ETC was carried out until the end of the second trimester, with CZP – until the end of pregnancy [7].

During gestation, 12 (21.4%) women had indications for initiation or resumption of treatment with iTNFα. In the second trimester, therapy with CZP was started in 2 patients due to relapses of uveitis and an increase in the severity of inflammatory back pain and morning stiffness in one of them. The high activity of AS due to axial and non-axial manifestations in 10 more patients (7 of them – in the second trimester, and 3 of them in the third trimester) provided indication for administration of CZP, but the treatment was not carried out for non-medical reasons (unavailability of the drug); the prescribed GC failed to effectively control the symptoms of the disease. It is worth noting, that 7 out of 12 pregnant women who had indications for iTNFα use, starting from the second trimester, discontinued them just before the conception or in the early stages of gestation.

The activity of AS in pregnant women who received iTNFα is presented in Table 2. Two patients, who initiated CZP therapy at the 16th and 17th weeks of gestation were excluded from the analysis of the disease activity in the second trimester, but their data were included in the analysis of AS activity in the third trimester.

A high activity of AS according to BASDAI (4.4) with a normal level of CRP (4.0 mg/l) and moderate activity according to the ASDAS-CRP index (1.9) in the first trimester was observed in one patient receiving ETC; the revealed ratio remained in the second trimester. It should be noted that a high activity according to BASDAI was determined by the severity of general weakness/fatigue (7 on the numerical rating scale, NRS) associated with a physiological course of pregnancy, which confirms the need to modify the AS activity indices for their use during gestation. Another patient treated with ADA had a high activity according to ASDAS-CRP (2.8) in the first trimester, with a

moderate increase in the level of CRP (8.9 mg/l) and BASDAI (3.8). No negative dynamics of clinical manifestations of AS, of CRP level, BASDAI and ASDAS-CRP values were found in the rest of women who continued the iTNFα therapy initiated before pregnancy until the terms determined by Russian clinical guidelines [7], and who did not have high disease activity at the time of conception.

In patients who discontinued iTNFα at the end of the second trimester the average BASDAI value in the third trimester (3.0 ± 1.3) did not differ from that in the second trimester (3.5 ± 1.4; p>0.05). Thus, the withdrawal of iTNFα in the second trimester was not a risk factor for high AS activity in the third trimester.

There was a low activity of AS in 3 women who received CZP during the entire gestation: BASDAI during trimesters of pregnancy was 1.2 [0.7; 1.2], 1.2 [0; 1.2] and 0.8 [0.8; 0.8], respectively.

In previous studies, we have shown that iTNFα withdrawal before conception or in the first trimester of pregnancy is a predictor of high AS activity, starting from the second trimester [1, 15]. This conclusion is also confirmed in other studies [16, 17]. However, there are very few publications about the effectiveness of initiating therapy or re-prescribing iTNFα during pregnancy. Of interest is the work of Dutch authors [16], who evaluated the effectiveness of resuming iTNFα therapy in women with axial SpA and RA who had canceled drugs of this group at early stages of gestation. It was shown that administration of iTNFα was required in 41.7% of cases with SpA and in 66.6% with RA. Against the background of the resumption of iTNFα therapy, the activity of the disease statistically significantly decreased in patients with RA, which was manifested in a decrease in the average values of the DAS28 index from 4.3 to 2.6 and the concentration of CRP from 26 mg/l to 8 mg/l, whereas there was only an insignificant tendency to a decrease in values of ASDAS-CRP (from 4.0 to 3.7; p>0.05) and the preservation of an elevated level of CRP, despite its decrease compared with the baseline indicator (from 18.5 to 12 mg/l; p < 0.05) in patients with SpA.

In one pregnant woman with AS who had been included in our study, CZP therapy was initiated in the second trimester after the withdrawal of INF at the beginning of gestation. We present this observation.

***Patient V.**, 36 years old, first pregnancy, was admitted to V.A. Nasonova Research Institute at 13–14 weeks of gestation with complaints of pain in the thoracic spine of the inflammatory rhythm, morning stiffness for 1 hour, pain in her right eye, and a «veil» in front of the same eye.*

History: at the age of 16, episodes of pain in the thoracic spine of the inflammatory rhythm, anterior uveitis of the left eye, were observed for the first time by an ophthalmologist. She felt satisfactory until the age of 23, then she began to worry about pain in the lumbosacral spine of the inflammatory rhythm. The diagnosis was not established, so she took NSAIDs on demand. At the age of 28 (2014), arthritis of the temporomandibular joints (TMJ) developed, which was stopped by taking NSAIDs, arthroplasty of the left TMJ was performed. Anterior uveitis involving both eyes occurred at the age of 30. Since that time, pain in the thoracic spine has become persistent, arthritis of small joints of the right foot has been noted; the level of CRP was 9.2 mg/l, ESR was 10 mm/h. Constant NSAIDs intake.

At the age of 31 (February 2015, 15 years after the onset of the disease), the diagnosis of AS was established. In April of the same year, after a salmonella infection, the manifestations of the articular syndrome increased, dactylitis appeared. SASP 2.0 g/day, etoricoxib 90 mg/day were prescribed, but the effect was insufficient.

From October 2015 to December 2017, she received 300 mg of INF according to the standard scheme. AS activity was low, back pain and uveitis did not recur. NSAIDs were taken on demand, SASP was canceled.

In January 2018, due to a planned pregnancy, INF therapy was discontinued. There was pain of the inflammatory rhythm in all parts of the spine, morning stiffness until the afternoon, relapses of uveitis and coxitis since March 2018; the level of CRP was 26 mg/l and ESR was 30 mm/h. Daily intake of NSAIDs did not give any effect; the effect of ADA, 40 mg subcutaneously every 2 weeks, was insufficient. From June to December 2018, relapses of uveitis of both eyes were observed. Resumption of therapy with 300 mg of INF from January 2019 to August 2020 with a positive effect: BASDAI was 2.0, taking NSAIDs on demand. Due to the pregnancy, INF was discontinued at 4–5 weeks of gestation.

On examination: soreness on palpation in the area of the I, VII sternocostal joints on both sides, attachment sites of the Achilles tendon on the right side of the calcaneus; MASES index (Maastricht Ankylosing Spondylitis Enthesitis Score) was 5. There was no peripheral arthritis. Chest excursion was 4 cm, modified Schober test – 3.5 cm, lateral flexion of the spine – 18 cm, the maximum distance between the medial ankles – 90 cm, rotation in the cervical spine – 75°, the distance «back of the head – wall» – 0 cm.

Blood tests: Hb – 122 g/l, WBC – 10,4·10⁹/l, CRP – 7.2 g/l. The biochemical blood test, general urinalysis within the normal range. Plain radiography of the pelvis (2019): bilateral sacroiliitis, stage II. Ophthalmological examination: recurrent anterior uveitis of the right eye, exacerbation; recurrent anterior uveitis of the left eye; local therapy with GC, NSAIDs, mydriatics.

The diagnosis was established: AS (with juvenile onset), HLA-B27-positive, advanced stage, high activity (BASDAI 5.2, ASDAS-CRP 3.4), with non-axial (enthesitis, coxitis, arthritis in the anamnesis) and extra-skeletal (uveitis) manifestations, FC II. Pregnancy – 13–14 weeks.

It was recommended to take ibuprofen 1200 mg per day; against the background of the therapy for 2 weeks, back pain decreased, but pain in the eye, blurred vision and a «veil» in front of the right eye persisted. Since the 16th week of pregnancy, CZP therapy was initiated.

The course of AS during pregnancy is presented in Table 3.

Standard methods for drug effectiveness evaluating such as ASAS20 etc., were not used in this case, in view of the fact that changes associated with pregnancy can affect the dynamics of the parameters included in them.

There was a decrease in morning stiffness up to 20 minutes, a slight decrease in the intensity of general and nocturnal back pain (by 2 and 1 points according to NRS), a decrease in BASDAI values by 40.4% and ASDAS-CRP by 23.5%, while there was an increase in the level of CRP and preservation of uveitis activity after 5 weeks of CZP therapy. In the third trimester a slight decrease in the severity of night pain remained (by 2 points compared with the baseline level), but the dynamics of other clinical and laboratory parameters was not revealed until the end of pregnancy; due to the continued activity of uveitis, 15 subconjunctival injections of GC were performed. At 38 weeks of pregnancy, an emergency caesarean section (CS) was performed due to premature rupture of the fetal membranes. A girl was born (body weight – 3340 g, body length – 53 cm), the period of early neonatal adaptation proceeded without complications.

Table 3. The course of AS in patient B. during pregnancy

Before conception		Duration of pregnancy				
	0–3 months	5–13 weeks	13–14 weeks (1 visit)	16 weeks (2 visit)	20–21 weeks (3 visit)	33–34 weeks (4 visit)
Parameter	INF, *ibuprofen* 400 mg once per week	Did not receive therapy	Time of admission to V. A. Nasonova Research Institute	Induction dose of CZP, then 200 mg every 2 weeks	CZP, *ibuprofen* 400–800 mg	CZP
Back pain on NRS	3	7	7		5	5
Nocturnal pain on NRS	2	6	6		5	4
Morning stiffness, min	10	70	70		20	20
Enthesitis, MASES	–	–	5		2	4
Uveitis	–	–	OD		OD	OD
BASDAI	2.0	5.2	5.2		3.1	3.0
ASDAS-CRP	–	–	3.4		2.6	2.7
CRP, mg/l	–	–	7.2		12.0	11.6
Hb, g/l	–	–	122		105	114

** OD – right eye.*

The above clinical case once again confirms the fallacy of withdrawal of iTNFα which are allowed for use during pregnancy at the early stage of gestation.

Pregnancies in 10 out of 11 patients who received iTNFα during gestation ended in childbirth at 38.9 ± 1.4 weeks, with the average body weight of the newborns 3273.1 ± 435.6 g, length – 52.3±2.1 cm. In one case, an unfavorable pregnancy outcome was recorded: a patient with a burdened obstetric history (multiple unsuccessful IVF attempts), who was receiving therapy with ADA, had a non-developing pregnancy at the 18th week [18].

Among the complications of pregnancies that ended in childbirth there was a threatening early miscarriage in a woman receiving ETC, and one late premature birth at the 36th week of gestation in a patient with an extra-skeletal manifestation of AS (Crohn's disease), who used CZP throughout gestation and did not have high disease activity.

CS was performed in 5 women, including 2 emergency cases. In the first case, there was a patient who canceled ADA on her own at the 4th week of gestation with the persistence of high AS activity throughout pregnancy, with indications for emergency operative delivery at the 39th week, such as a premature rupture of the fetal membranes, weakness of labor and fetal hypoxia. In another case, an emergency CS was performed at the 38th week of pregnancy due to premature rupture of the fetal membranes in patient V. described above, who received CZP.

In 3 newborns, small anomalies of heart development were detected, all mothers in the first trimester of gestation received iTNFα (ETC, ADA, CZP).

Currently, researchers' opinions about maternal and neonatal pregnancy outcomes in AS remain contradictory. Although most authors believe that the frequency of severe pregnancy complications in AS is not higher than in the general population, a number of studies have shown an increased risk of premature birth and low body weight of newborns [18], while there is no relation between iTNFα therapy and an increase in the frequency of premature births, as well as malformations of newborns. Taking into account the small number of our participants, it is not possible to draw unequivocal conclusions about the influence of iTNFα on pregnancy complications and outcomes.

Conclusion. To clarify the effectiveness and safety of iTNFα therapy in pregnant women with AS, it is necessary to conduct multicenter studies. Women who are planning pregnancy should be prescribed drugs with the maximum allowed period of use during gestation. Withdrawal of iTNFα before pregnancy and in its early stages is a risk factor for high AS activity, while resumption of iTNFα therapy during pregnancy is not always effective.

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