REVIEWS

Problems of prescribing nonsteroidal anti-inflammatory drugs for reproductive-aged women with ankylosing spondylitis

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line medications for ankylosing spondylitis (AS); their action is associated with blockade of the enzyme cyclooxygenase 2 and with a mediated decrease in the synthesis of prostaglandins (PGs). However, PGs play an important role in regulating the functions of the female reproductive system. The paper presents an update on the participation of PG in folliculogenesis, ovulation, implantation, and development of the embryo, and labor activity. Based on experimental and clinical findings, the authors discuss whether due to inhibition of the synthesis of PGs, NSAIDs are able to cause ovulation failure, including luteinized unovulated follicle syndrome and spontaneous abortions. Further investigation is justified to determine the most optimal NSAID therapy regimens when planning pregnancy and during gestation in women with AS.

Keywords: *ankylosing spondylitis; nonsteroidal anti-inflammatory drugs; luteinized unovulated follicle syndrome; pregnancy.*
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For reference: *Krichevskaya OA, Dubinina TV, Karateev AE. Problems of prescribing nonsteroidal anti-inflammatory drugs for reproductiveaged women with ankylosing spondylitis. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2020;14(3):132–139.*
DOI: *10.14412/1996-7012-2020-3-132-139*

At the end of 20th – beginning of the 21st century, significant progress was achieved in the diagnosis and treatment of spondyloarthritis (SpA). On the one hand, the developed new SpA concept divided these diseases into two forms, depending on their clinical manifestations: mainly axial and mainly peripheral [1, 2]. Axial SpA was further subdivided into nonradiographic axSpA (NR-axSpA) and ankylosing spondylitis (AS). Identification of NR-axSpA initiated a series of comparative studies that not only proved the similarity of clinical manifestations of NR-axSpA and AS, but also contributed to the removal of axSpA from the category of mainly «male» diseases [3–5]. On the other hand, the scheme of managing patients with AS has been significantly revised; the principles of innovation therapy with genetically engineered biological drugs (GEBDs) have been formulated, and approaches to the prescription of non-steroidal anti-inflammatory drugs (NSAIDs) have been changed. The achievements in rheumatology have become objective prerequisites for the possibility of rational pregnancy planning and its favorable outcomes in patients with AS. However, at present, a number of issues remain unspecified, in particular, the correction of drug therapy at the stage of preparation for gestation.

NSAIDs are an extensive group of drugs that differ in chemical structure but have a common pharmacological mechanism – blockade of the enzyme cyclooxygenase-2 (COX-2) and mediated reduction of prostaglandin synthesis (PG) [6]. Depending on the ability to block various isoforms of cyclooxygenase (COX-1, COX-2), NSAIDs are divided into COX-2 selective (c-NSAIDs, or coxibs) and non-selective (n-NSAIDs); a number of experts distinguish NSAIDs with moderate selectivity for COX-2. COX-1 is a constitutive enzyme located in many tissues (constantly synthesized regardless of the conditions or the presence of a corresponding substrate), it regulates the physiological effects of PGs, including the synthesis of cytoprotective PGs in the gastrointestinal (GI) mucosa, which determines the difference between c-NSAIDs and n-NSAIDs in terms of the degree of their negative effects on the gastrointestinal tract. COX-2 production is inducible and increases with inflammation under the influence of growth factors, proinflammatory cytokines, and bacterial toxins in almost all tissues, which, in turn, leads to the synthesis of proinflammatory PGs [7]. At the same time, COX-2 is constitutive for the brain, the juxtaglomerular apparatus of the kidneys, the female sex glands and is produced there continuously. Despite the fact that the main mechanism of anti-inflammatory action of NSAIDs is due to COX-2 blockade, and COX-1 inhibition is associated with adverse reactions, mainly with NSAID-induced gastro- and enteropathy, it should be noted that both COX isoforms contribute to the formation of autoregulatory and homeostatic prostanoids, and both can contribute to the release of prostanoids during inflammation [8]. Based on the data obtained in mouse models, R. Langenbach et al. [9] concluded that the 75% of PGE2 production is caused by COX-2 and 25% – by COX-1. Blocking of both COX isoforms by NSAIDs leads to a decrease in the synthesis of PGs, including PGF2_ and PGE2 which play an important role in the regulation of the female reproductive system.

The role of NSAIDs in the treatment of AS

J. D. Niringiyumukiza et al. [10] in the literature review concerning the role of PGE2 in ovulation, implantation, and early embryo development in mammals, concluded that it is necessary to limit NSAID therapy in women with reproductive disorders. This review was published in 2018. However, in AS, NSAIDs are the first-line drugs, and long-term use of NSAIDs is preferable to short courses due to the potential ability of these drugs to prevent/inhibit structural changes – ectopic ossification against the background of COX-2 hyperexpression [11, 12]. In several studies at the beginning of the 21st century, it has been shown that continuous use of NSAIDs reduces radiographic progression in the spine in some cases, regardless of the initial disease activity and severity of radiologic changes [13]. Currently, the pathogenesis of syndesmophytes formation is not completely understood, and the effect of PGs on bone metabolism, in particular PGE2 receptor 4 (ER4) encoded by the *PTGER4* gene in the human body is being discussed. Signal transmission via this receptor mediates increased activity of osteoblasts and osteoclasts. Another gene closely related to the severity of radiological changes in the spine in AS is *PTGS1* which encodes COX-1 [14]. In addition, the influence of PGE_2 synthesized by fibroblasts on the production of interleukin (IL) 23 is being examined [15], which is extremely important in AS, whose pathogenesis is associated with the activation of the IL23/IL17 axis. F.M. Milanez et al. didn't reveal any reduction in initially high levels of PGE_2 and IL23 in patients with AS treated with tumor necrosis factor alpha inhibitors in combination with NSAIDs, despite a decrease in clinical and laboratory activity of the disease, which may indicate alternative regulation of PG in the IL23/IL17 axis [15]. It should be noted, that some authors call into question the ability of NSAIDs to inhibit the formation of syndesmophytes only by suppressing the synthesis of PGE2 due to the multifactorial effect of PGs on bone remodeling (PGs under certain conditions participate in stimulating the differentiation of both osteoblasts and osteoclasts and can have an inhibitory effect on differentiated osteoblasts and osteoclasts) [16]. However, currently NSAIDs are considered the main pathogenetic drugs in AS treatment, that can induce and maintain remission of the disease; so the use of basic anti-inflammatory drugs or GEBDs is not a reason for NSAIDs discontinuation. In relation to this information, the question of continuing/discontinuing NSAID therapy at the stage of pregnancy planning and during gestation continues to be extremely relevant.

The principles of prescribing NSAIDs before and during pregnancy were thoroughly described in the previous work [17]. The updated recommendations of EULAR (European League Against Rheumatism) on the use of medicines during pregnancy planning and onset [18] and Russian clinical recommendations [19] indicate that the use of n-NSAIDs is possible during planning and in the first-beginning of 3rd trimester of pregnancy. At the same time, it is emphasized that taking NSAID in the first trimester has to be careful, and they must be canceled no later than 32 weeks of gestation due to the risk of premature closure of the arterial duct, oligohydramnios and impaired kidney function in a newborn. The safest NSAIDs in the first two trimesters of pregnancy are ibuprofen and diclofenac, which are classified by the FDA (Food and Drug Administration of the USA) in these periods as category B (there is no evidence of risk) [20]. Due to the lack of data on the safety of c-NSAIDs, their intake during pregnancy planning and gestation is not allowed, and therefore, the transition to n-NSAIDs is indicated at the stage of pregnancy planning. It is recommended to temporarily discontinue any NSAIDs before conception in women with fertility problems due to the ability of NSAIDs to suppress ovulation, [20, 21] which can certainly lead to increased AS activity even before pregnancy, especially if the preparation for pregnancy takes several months. Thus, modern approaches to the use of NSAIDs in AS, namely their long-term use and minimization of the grounds for their discontinuation, require clarification when planning pregnancy.

The value of prostaglandins in the regulation of female reproductive system functions

PGs participate in the process of ovulation, fertilization, implantation of the ovum, induction of labor, regulation of menstrual bleeding.

1. The participation of PGs in folliculogenesis and ovulation

When ovulation occurs, the basement membrane of the mature follicle breaks and the oocyte comes out of it. The ovulatory peak of luteinizing hormone (LH) induces COX-2 gene expression [22] and leads to a 50–100-fold increase in PG content in preovulatory follicle cells. COX-2 and PGs play an important role in the formation of the intercellular matrix of the cumulus-oocyte complex, the expansion of cumulus cells, the meiotic maturation of the follicle and the rupture of the wall of the mature follicle.

For normal follicle maturation, a close connection is necessary between the oocyte and the surrounding somatic cells: the mural granulosa lining the follicle cavity and the cumulus cells directly surrounding the oocyte [23]. In the process of folliculogenesis, a mature cumulus-oocyte complex is formed under the action of LH, in which cumulus cells are closely connected to the oocyte through special gap junctions that allow for metabolic exchange and transport of signaling molecules, which directly affects the development of the follicle and the nuclear and cytoplasmic maturation of the oocyte. An important process of the final stage of folliculogenesis, necessary for the normal development of the oocyte and ovulation, is the expansion of the cumulus cells, characterized by their growth with the simultaneous loss of close junctions between the cells. In the process of expansion, the cumulus cells produce hyaluronic acid, which contributes to the «swelling» of the cumulus-oocyte complex. Several genes are involved in the expansion of the cumulus cells, including the gene for hyaluronan synthetase 2 *(HAS2)* and amphiregulin *(AREG)*, whose expression in the cumulus cells correlates with the degree of expansion, oocyte quality indicators, and embryo development [24]. In recent studies, PGE2 has been shown to enhance the expression of *HAS2* and *AREG* in the granulosa and cumulus cells, stimulating expansion [10]. In addition, PGE2 interacts with signaling intracellular cascades, such as MAPK types 1 and 3 (mitogen-activated protein kinase cascades) and cAMP (cyclic adenosine monophosphate), taking part in the regulation of meiotic maturation of the oocyte [10, 22]. Some researchers note the contribution of PGs to the induction of expression and increased activity of ADAMTS-1 metalloproteinase and other proteases, which is one of the

main factors of follicular wall degradation [10]. PGs also contribute to the development of inflammatory response in the follicle wall and stimulate smooth muscle activity, facilitating the exit of the oocyte. In a series of experimental studies on mouse models with mutations in the COX-2 gene and a deficiency of the PG_2 ER2 surface receptor, it was demonstrated that disturbance of the ovulation process is caused by both a defect in the expansion of the cumulus-oocyte complex and a failure of the follicular wall rupture [10, 22, 25].

2. Transport of the oocyte and influence on the mechanisms of fertilization

After ovulation, the cumulus cells continue to be associated with the oocyte, contributing to the capture of the cumulus-oocyte complex by the epithelial cells of the fallopian tube infundibulum and its further progress through the tube into the uterus [23]. Cumulus cells secrete chemokine receptors and chemokines CCL7, CCL2 and CCL9, which increase the viscosity of the intercellular matrix of the cumulus-oocyte complex, thus providing mechanical protection of the oocyte, but this is one of the factors that prevent the passage of spermatozoa and complicate fertilization. PGE_2 by activating the cAMP cascade inhibits the secretion of CCL7 and CCL2 and thereby reduces the viscosity of the intercellular matrix of the cumulus-oocyte complex, which facilitates the penetration of spermatozoa [10]. The ability of PGE2 to protect spermatozoa from neutrophil phagocytic activity in the fallopian tubes by participating in the inhibition of formation of neutrophil extracellular traps is also described [10]. PGs affect the contractile activity of the fallopian tubes: they cause a contraction of the isthmical part of the tubes in the follicular phase. PGs also cause relaxation of the isthmical part, increased peristalsis of the ampulla that promotes penetration of the ovum into the uterus in the luteal phase [26]. By the time of ovulation, the content of $PGF_{2\alpha}$ in the follicles increases rapidly, which plays an important role in strengthening the contractile function of the fallopian tubes, and its deficiency is regarded as one of the possible factors of ectopic pregnancy.

3. Participation of PGs in the implantation and early development of the embryo

When the ovum enters the uterine cavity, PGs continue to participate in the transport of the ovum, affecting the myometrium: on the way from the tube angles towards the bottom of the uterus, the stimulating effect is replaced by an inhibitory one and, thus, contributes to the nidation of the blastocyst [26]. Gradual increase in the content of PGE_2 in embryos was shown at the stages from the two-cell embryo to the blastocyst. PGE_2 contributes to the «hatching» of blastocysts from the zona pellucida (the initial stage of implantation); the ability of PGs to accelerate the proliferation of trophoblasts and influence their invasion by stimulating the production of chemokines in the endometrium is also discussed [10]. PGE_2 supports luteinization, protecting the corpus luteum from regression by participating in the expression of LH receptors in the corpus luteum, leading to an increase in the synthesis of progesterone, which stimulates endometrial growth. In addition, it increases blood circulation in the uterus and ovaries by increasing the activity of adenylate cyclase and the synthesis of nitric oxide which is a vasodilator [10]. 17-β estradiol produced by the embryo leads to an increase in the secretion of PGE2 and a decrease in the production of $PGF_{2\alpha}$, which prevents regression of the corpus luteum at the early stages of pregnancy. If the oocyte doesn't get fertilized, then the concentration of PGF2_ increases in the cells of the main cover of the corpus luteum, which together with endothelin 1 causes spasm of the vessels of the corpus luteum, leading to luteolysis (along with inhibition of LH secretion). The importance of COX-2 and PG for successful embryo implantation has been confirmed in a number of experimental studies: COX-2 deficiency led to impaired fertilization and implantation, while the introduction of exogenous PGE_2 neutralized these effects [27, 28]. In the work of F. Vilella et al. [29], it was shown that during the «implantation window» the concentration of $PGF_{2\alpha}$ and PGE_2 in the endometrial fluid increases both in the natural menstrual cycle and in the cycles with controlled ovarian stimulation. There was an increased level of PG in endometrial fluid samples obtained from women with successfully implanted transferred embryos. The authors suggested that the concentration of PG 24 hours before the planned embryo transplant may serve as a marker of successful implantation, but this conclusion requires further clarification. Currently, a low level of PG is considered one of the possible reasons for systematic failure of embryo implantation in the framework of assisted reproductive technology programs [27].

4. The Role of PG during pregnancy and childbirth

PG plays an important role in the pathogenesis of preeclampsia. Insufficient production of prostacyclin, PGE, and hyperproduction of PGF and thromboxane lead to generalized vascular spasm in combination with hypercoagulation, increased overall peripheral vascular resistance, decreased cardiac output, decreased blood flow and glomerular filtration of the kidneys, and impaired microcirculation in the placenta [30].

One of the main «reproductive» functions of PG is the preparation of the cervix for childbirth and participation in labor. PGE2 synthesized in the cervix reduces the amount of cervical collagen and causes its destabilization by activating proteolytic enzymes, has a relaxing effect on smooth muscles, which leads to softening and expansion of the cervix. PGF2_ is synthesized in the decidual membrane and myometrium, increases the sensitivity of the myometrium to oxytocin and is the main modulator of labor activity.

5. Regulation of menstrual bleeding

The intensity of menstrual bleeding is determined both by the structure of the endometrium at the time of its rejection, and by the contractility of the myometrium, arterioles, and platelet aggregation, which is closely related to the degree of $PGF_{2\alpha}$ synthesis [26].

PG is involved in the pathogenesis of menstrual disorders. Increased production of $PGF_{2\alpha}$ and PGE_2 is one of the main factors in the development of primary dysmenorrhea. Thus, PGs are critically important for neurohumoral regulation of the female reproductive system, and PG deficiency or imbalance can lead to reduction of fertility and reproductive losses.

Effect of NSAIDs on ovulation

In numerous experimental studies conducted since the 1970s and continuing at the present time using modern

approaches, it has been shown that NSAIDs can inhibit ovulation in various mammalian species [31]. One of the most widely used drugs in the earlier studies was indomethacin, later – c-NSAIDs. However, nowadays, the mechanisms underlying the suppression of ovulation by NSAIDs remain unclear. Most researchers agree that the effect of NSAIDs is associated with an impediment to rupture of the follicle wall by inhibiting the activity of a number of proteolytic enzymes, which is the cause of the development of luteinized unruptured follicle (LUF) syndrome in both experimental animals and women [31]. Along with this, a number of authors believe that the effect of NSAIDs is not due to blocking the rupture of the follicle in a prepared area (stigma), but due to the induction of an abnormal rupture of the follicular wall as a result of an imbalance of proteolytic homeostasis. It has been shown that against the background of indomethacin administration, follicle rupture occurs randomly at any place, which seems to explain the normal ovulation of 30% of oocytes even under the influence of high doses of indomethacin (LUF develops in 35% of cases, 35% of oocytes enter the ovarian interstitium through a gap on the basolateral sides of the follicle wall) [32]. Currently, the possibility of NSAIDs to block ovulation by disrupting processes in the cumulus-oocyte complex, including cumulus expansion, is also being discussed [32]. In addition, research of COX-independent pathway for the anti-ovulatory effect of NSAIDs continues. In clinical practice, LUF syndrome with NSAIDs intake was described in the mid-1980s. [33]. A number of studies conducted later [34], using ultrasound imaging of ovulation and determining the level of hormones, showed that both c-NSAIDs and n-NSAIDs cause 50–100% of cases of LUF or delayed follicle rupture after the ovulatory peak of LH; however, the hormonal status of women was not disturbed, except for a decrease in progesterone levels in one third of the participants in one of the studies. It should be noted that all studies were conducted with a small number (13–20) of healthy volunteers.

One of the first studies concerning the development of LUF in women with rheumatic diseases (RDs) was performed by M. Akil et al. [35]. The authors described 3 cases (2 women – with AS, one – with rheumatoid arthritis [RA]) of reversible infertility against the background of long-term administration of indomethacin at a daily dose of 150 mg in one case, and diclofenac at a daily dose of 100–200 mg in the other two cases. After excluding other causes of infertility, NSAIDs were withdrawn, and all patients became pregnant during the first menstrual cycle.

Interesting data were obtained by M. C. Micu et al. [34] when studying the effect of NSAIDs of different classes and half-lives on ovulation: etoricoxib 90 mg/day, diclofenac 150 mg/day, ibuprofen 1600 mg/day, ketoprofen 200 mg/day, celecoxib 200 mg/day and nimesulide 200 mg / day. The first group included 14 patients (10 patients with RA, and 4 with AS) who took NSAIDs continuously from the 1st day of the menstrual cycle until the beginning of the third day after the ovulatory peak of LH. A total of 59 menstrual cycles were analyzed. The second group consisted of 29 women without RD who received NSAIDs from day 1 to day 8 of the menstrual cycle due to non-inflammatory back pain. The control group included 449 women who did not have RD and did not take NSAIDs, but were observed for secondary infertility. All those included in the study had at least one previous pregnancy. Intravaginal ultrasound imaging was used to control ovulation. It is noteworthy that the size of the dominant follicle and the duration of the menstrual cycle did not differ in all examined groups. The frequency of LUF syndrome in the first group was 36.5%, that was significantly higher than in the third group (3.4%) and did not differ significantly from the frequency of LUF in the second group (24.1%), regardless of the intake of a particular NSAID. In women with AS, LUF was observed in 5 (23.8%) of the 21 cycles followed. LUF syndrome occurred more often when taking etoricoxib, while no cases of LUF were recorded when ibuprofen, ketoprofen, celecoxib and nimesulide were used. The results obtained by M. C. Micu et al., differed from an earlier study in which LUF syndrome occurred in 60% of cases when using ibuprofen at a dose of 2400 mg per day, which the authors explained as dose-dependent inhibition of follicle rupture. The relationship between the dose of NSAIDs and impaired reproductive function was also demonstrated in the study of meloxicam [36]: ovulation disorders occurred in 50% of cases when taking the drug at a dose of 15 mg per day and in 91% – when taking 30 mg per day. Based on the results of their research, M. C. Micu et al. also concluded that NSAIDs increase the risk of developing LUF to a greater extent in patients with low RD activity; however, in our opinion, considering small number of the group, such conclusion is premature. Continuing to study the role of meloxicam in ovulation disorders, C. Jesam et al. [37] conducted a study to determine the possibility of using this drug as a non-hormonal contraceptive. However, it has been shown that while taking meloxicam at a dose of 30 mg per day from 5 to 22 days of the menstrual cycle, 20% of oocytes continue to ovulate normally.

In 2014, the results of the work of B. Q. Sherif et al. [38], who studied the effect of NSAIDs on ovulation in women with back pain who visited a rheumatological clinic (unfortunately, the diagnosis of patients was not specified in the article), were published. Sixteen of them received diclofenac 100 mg per day, 12 – naproxen 1000 mg, 11 – etoricoxib 90 mg from the 10th to the 20th day of the menstrual cycle. The control group included 10 healthy women who did not take NSAIDs. Diclofenac had the strongest negative effect on ovulation compared with other drugs. In the group of patients receiving diclofenac, normal ovulation occurred only in 6.3% of cases, LUF syndrome developed in 75% of women, while with naproxen it developed in 25% and 33.3%, and with etoricoxib – in 27.3% and 18.2% of cases, respectively. The increase in progesterone levels on the 20th day of the menstrual cycle in women who took NSAIDs was less pronounced than in the control group. In addition, the authors described in 1/3 of patients functional cysts at the site of the anovulated follicle, which were not detected in the next cycle after discontinuation of NSAID therapy.

Brazilian researchers [39] evaluated the incidence of LUF syndrome during NSAID therapy in patients with juvenile idiopathic arthritis (JIA). LUF syndrome was observed in 25% of cases and only in patients (n=8) who were prescribed naproxen 1000 mg per day in addition to the main therapy. In the healthy controls (n=11) and patients with JIA who did not receive NSAIDs (n=15), LUF syndrome was not detected. All participants in the study were comparable in age, hormonal status, and ovarian reserve, and the patients with JIA were comparable in the duration of the disease.

Thus, the presented papers demonstrated the ability of NSAIDs to influence ovulation, including ovulation in patients with AS. However, most studies contain a small number of observations, and the data on the occurrence and type of ovulation disorders while taking specific medications differ significantly. In addition, nowadays the frequency of LUF syndrome when prescribing NSAIDs «on demand» in the preovulatory phase of the menstrual cycle has not been established, exact doses causing the «anti-ovulatory» effect of widely used drugs are unknown, and the relationship between the development of LUF syndrome and the activity of AS has not been clarified.

Effect of NSAIDs on an embryo implantation and development

Taking into account the role of PG in blastocyst implantation and decidualization of endometrial stromal cells supporting the embryo trophism from the moment of implantation to the appearance of the first foci of utero-placental blood circulation, the ability of NSAIDs to affect negatively on implantation and early development of the embryo is being discussed. A number of experimental studies [40] have shown that the administration of NSAIDs prevents the implantation in mammals. Data on the effect of PG synthesis inhibition on the implantation success in women have also been obtained.

A study conducted in the United States [41], based on a survey of 1055 women, found that taking NSAIDs in the periods preceding or close to the conception increases the risk of miscarriage in early pregnancy (hazard ratio [HR] – 1.8), and the frequency of adverse outcomes increases when using NSAIDs during conception (HR – 5.6) or taking them for 7 or more days (HR – 8.1). However, it should be noted that there were only 53 (5%) women who had a miscarriage in this group of respondents, so the obtained results must be confirmed.

The data from a Danish population study [42], based on the analysis of the birth register of one of the regions of Denmark from 1991 to 1998, according to the authors, confirm the association between the use of NSAIDs (at a dose equivalent to 400–600 mg of ibuprofen) 30 days before conception and during pregnancy and spontaneous abortions. The risk of miscarriage increased within a week after taking NSAIDs (HR – 6.99), but persisted even after 7–9 weeks after the end of the therapy (HR – 2.69). This study has a number of limitations, since the timing of pregnancy losses, indications for NSAIDs and duration of their use were not specified, and other possible causes of adverse pregnancy outcomes were not analyzed. However, the dose-independent effect of NSAIDs taken during pregnancy on the frequency of spontaneous abortions was also shown in a later study of a Canadian cohort of women (n=4705) [43]: the risk of miscarriages before the 20th week of gestation increased when taking various NSAIDs, in particular, HR with diclofenac therapy was – 3.1, ibuprofen – 2.2, celecoxib – 2.2, and with combination therapy with several drugs – 2.6.

On the other hand, studies on assisted reproductive technologies [40] have shown that a single analgesic injection of 100 mg of diclofenac after oocyte collection does not affect embryo implantation and pregnancy development.

Thus, the safety of prescribing NSAIDs in the month of conception and at the early stages of pregnancy remains not fully understood. This problem is most relevant for women with AS, because unreasonably early withdrawal of NSAIDs can lead to increased activity of the disease in the first weeks of gestation. New knowledge about the relationship between NSAIDs and spontaneous abortions is necessary for successful pregnancy planning in patients with AS.

Effect of NSAIDs on neonatal outcomes

The effect of NSAIDs on the risk of congenital abnormalities was described in detail earlier [17, 44]. Here we just point out that questions about the increased risk of small heart abnormalities and gastroschisis when taking ibuprofen in the first trimester of pregnancy should be discussed. After the 20th week of gestation, all NSAIDs can cause narrowing of the arterial duct and impair fetal kidney function. The link between the use of ibuprofen and diclofenac in the second and third trimesters of gestation and an increased risk of bleeding in childbirth, as well as the development of asthma in children under 18 months of age, remains controversial.

In conclusion, we note that the problem of prescribing selective and non-selective COX-2 inhibitors to women of reproductive age with AS, taking into account potential impact of this group of drugs on ovulation, embryo implantation and fetal development, continues to be extremely relevant. Further research is needed to determine the most optimal treatment regimens for NSAIDs in preparation for pregnancy and during gestation with due regard to the effectiveness of treatment and the preservation of women's reproductive health.

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Received/Reviewed/Accepted
5.07.2020/22.08.2020/30.08.2020

Conflict of Interest Statement
The investigation has been conducted within the framework of scientific topic э 398 ББPathogenetic features and personalized therapy of ankylosing spondylitis and psoriatic arthritisБв approved by the Academic Council of the V.A. Nasonova Research Institute of Rheumatology.

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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