ORIGINAL INVESTIGATIONS

Back pain and functional status in patients with ankylosing spondylitis during pregnancy

Krichevskaya O.A., Gandaloeva Z.M., Demina A.B., Glukhova S.I., Dubinina T.V.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia
34A, Kashirskoe Shosse, Moscow 115522

Inflammatory rhythm back pain and enthesitis are one of the main clinical manifestations of ankylosing spondylitis (AS), which increase in severity during pregnancy. However, addition of back pain and, possibly, enthesis in the second half of gestation, which is associated with normal pregnancy, needs to make a differential diagnosis for clarifying the genesis of pain and choosing the right management tactics, which determines the relevance of this study.

***Objective**: to investigate the course of pain in the back, enthesis, and inguinal region, as well as the functional status in AS patients during pregnancy and to reveal clinical signs that most accurately reflect inflammatory activity during gestation.*

***Patients and methods.** A study included 36 pregnant women with a reliable diagnosis of AS according to the modified New York criteria (1984). Their mean age was 31.6±4.8 years, the mean age at the onset of AS was 21.8±10.9 years; the duration of the disease was 134.9±89.3 months. A control group comprised 30 healthy pregnant women with no history of back pain and arthritis; their mean age was 28.2±4.5 years. The pregnant women of both groups were matched for parity. They made visits at 10–11, 20–21, and 31–32 weeks of pregnancy. Pain intensity was estimated using the numerical pain rating scale (NPRS) and the functional status was assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was used to assess enthesitis.*

***Results and discussion.** During pregnancy, 94% of AS patients had back pain; its intensity by trimesters was 3 [2; 4], 4 [3; 5.5], 3 [2; 7] and was higher than in healthy pregnant women (p<0.0001). In the study group, there was a rise in pain intensity at night with increasing gestational age (n=23–28): 2 [1; 4] in the first trimester; 3 [0; 5] II in the second trimester; 3 [1; 6] in the third trimester (p< when comparing the first, second, and third trimesters) and an increase in the duration of morning stiffness (n=): 10 [5; 20], 15 [10; 55], and 15 [5; 60] min, respectively. Moreover, the number of women who reported improvements after exercise (85–63%) and no improvement at rest (88–56%) declined (p<0.05 when comparing the first, second, and third trimesters).*

In the control group, 1 and 3 patients had morning back stiffness and night pain, respectively. The healthy pregnant women more frequently reported a reduction in back pain after exercise in the third trimester (66.7% of those with pain) than in the first trimester (20% of those with pain) (p<0.05).

By the third trimester, the patients with AS showed a change in the nature of back pain: 43.7% of the patients reported an improvement at rest; 42.4% noted an increase in pain after exercise, while the frequency of elements of mechanical back pain was less than that in the control group (p < 0.05).

The intensity of groin pain (2.4±1.9, 3.3±2.4, and 4.3±3.0 in the first, second, and third trimesters, respectively) did not differ in AS patients with and without coxitis or pelvic enthesitis. The frequency of enthesitis and MASES scores in the study group were higher than in the control group (p<0.05), the MASES scores increased with gestational age, amounting to 0 [0; 1] in the first trimester and 2 [0; 3] in the third trimester (p<0.05).

Functional disorders during pregnancy increased in both groups; there was a difference in BASFI scores between the groups only in the third trimester: 3.5±2.8 and 1.7±1.2, respectively (p<0.05).

***Conclusion**. Back pain and functional disorders increase in AS patients during gestation. Night back pain, morning stiffness, and enthesitis reflect the inflammatory activity of AS during pregnancy. Mechanical back pain joins in 40% of women with AS in the third trimester. The criteria for inflammatory back pain and BASFI require adaptation when used in pregnant women.*

***Keywords:** ankylosing spondylitis; pregnancy; back pain; enthesitis; BASFI.*
Contact:** Olga Arkadievna Krichevskaya; **o.krichevskaya@mail.ru
***For reference:** Krichevskaya OA, Gandaloeva ZM, Demina AB, et al. Back pain and functional status in patients with ankylosing spondylitis during pregnancy. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2019;13(4):26–35.*
***DOI:** 10.14412/1996-7012-2019-4-26-35*

Inflammatory back pain is one of the main clinical manifestations of ankylosing spondylitis (AS) that determine the activity of the disease. During pregnancy, in most women with AS, back pain intensity is increased in the second trimester [1]. Consensus on the AS course in the third trimester of pregnancy is not reached yet. However, all investigators agree on the need for differential diagnosis of back pain nature in the second half of gestation due to the high risk of the addition of mechanical pain associated with pregnancy itself. At the same time, it is not specified whether the parameters of inflammatory back pain can be observed in healthy pregnant women, thereby losing their significance as markers of AS activity. In the second half of preg-

nancy in female patients with AS, cases of mixed back pain not accompanied with other signs of inflammation, such as morning stiffness, night pains and elevated CRP, are particularly challenging. The need to clarify the nature of pain in pregnant women with AS is relevant due to limitation of therapeutic options in the third trimester of gestation because of contraindications for non-steroidal anti-inflammatory drugs (NSAID) among other factors.

In the general population, back pain during pregnancy occurs in 20–90% of women, and its frequency is increased with duration of gestation [2]. Data scattering is mainly due to the variety of terminological, classification and diagnostic definitions. Pregnancy-related pelvic girdle pain (PGP), localized between the iliac crest and the gluteal fold, including the sacroiliac joint area, and/or in the symphysis [3], which are typical locations of back pain and entheses associated with AS, is considered separately. Pain associated with PGP can radiate to the inguinal region, the inner and outer thighs, be associated with clicking or gritting in the pelvic region. Clinical manifestations are very diverse, which complicates differential diagnosis. On the one hand, the pain is often unstable, subsides at rest, intensifies with certain movements; on the other hand, it can occur during prolonged sitting, lying down, subside after warming up [4], mimicking inflammatory rhythm. S. Morino et al. [5] identified 16 types of movements associated with everyday activities, which can intensify or cause lower back pain during pregnancy in healthy women. Difficulty in performing some of these movements (standing up from a chair/bed, body turning, walking upstairs, etc.) reflect the functional capabilities evaluated using BASFI index in female patients with AS, which indeed raises the question of whether it is correct to use this questionnaire to determine the functional status of pregnant women with AS.

Some authors consider PGP a specific type of lower back pain [3], however, most of them agree that this syndrome should not be equated with lumbodynia [6, 7], and various functional tests and questionnaires are proposed to be used for differential diagnosis [8]. However, none of these tests was checked in pregnant women with AS, and therefore cannot be used to clarify the nature of pain. During pregnancy, at least 20% of healthy women experience pain in the pelvic girdle only and more than a half of them in combination with back pain of different location. [3, 9]. According to G. Dunn et al. [10], of 288 surveyed pregnant women, 42% had upper back pain, 77% in the lower back pain and 74% pain in the pelvic girdle in various combinations.

The causes of PGP during pregnancy are not completely elucidated. A combination of several causative factors is being considered, with most attention to hormonal and biomechanical factors [8]. The previous prevailing theory of the relaxin and progesterone effect on the relaxation of the pelvic ligaments as the main mechanism of pain is subject to some criticism due to the fact that in at least 7% of women the symptoms persist up to 3 months after delivery, when hormonal status returns to normal. At the same time, the question on abnormal hormonal status before pregnancy remains open; in particular, relationship between the early onset of menarche and pelvic girdle pain during gestation has been revealed. It is supposed that pain in the first trimester of pregnancy is most likely associated with hormonal effects. Starting from the second trimester, there is a combination of hormonal and biomechanical factors. Muscular imbalance (decreased strength of the abdominal muscles, lumbar spine, pelvic floor, gluteal muscle spasm), as well as a change in posture and body's center of mass shift lead to dysfunction and pain in the sacroiliac joint area. Metabolic (hypocalcemia, hyperglucosemia), genetic (associated with relaxin activity) and parity-dependent (parity equal to or higher than 3) causes are also being discussed. Moreover, risk factors for pain during gestation include history of pelvic trauma, lumbosacral back pain during previous pregnancies, similar pains experienced by mother and/or sister, occupational stress [4]. It can be assumed that during gestation, all above-mentioned factors can have an additional effect on back pain manifestation in women with AS, therefore detailed obstetric, gynecological and family history collection can help to clarify its causes. **The aim of the study:** to study time course of back pain, enthesis pain, inguinal pain and functional status of female patients with AS during pregnancy and identify clinical signs most accurately reflecting inflammatory activity during gestation.

Materials and methods

To achieve this aim, two groups of pregnant women were formed. In the study group for prospective observation at the Research Institute of Rheumatology n.a. V.A. Nasonova 36 pregnant women with a proven diagnosis of AS according to modified New York criteria, 1984 were included. Mean age of female patients was 31.6±4.8 years, age at the time of disease onset – 21.8±10.9 years, duration of the disease – 134.9±89.3 months. HLA-B27-positive female patients were predominating (n-28; 77.8%). The clinical stage of AS was determined based on the latest X-ray scans performed before pregnancy: advanced stage was determined in the vast majority of female patients – 34 (94.4%), late stage – only in 2 female patients. Bilateral sacroiliitis, stage II, was determined in 8 (22.2%) woman, sacroiliitis, stage II–III – in 24 (66.7%), sacroiliitis, stage IV – in 4 (11.1%) women.

100% of subjects included in the study had history of inflammatory back pain, 16 (44.4%) had history of coxitis, 18 (50%) – history of enthesitis. In the month of conception, 23 (63.8%) women experienced back pain; its average intensity according to NRS was 3.1±2.7; morning stiffness was observed in 26 (72.2%), with average duration of 30±26.3 min; enthesites were observed in 9 (25%) female patients with AS.

In the month of conception, 5 (13.9%) women received NSAID. During pregnancy, ibuprofen was the drug of choice: 11 (30.6%) female patients received it at daily dose of 800 [600; 800] mg in the 1st trimester; 23 female patients (65.7%) – at daily dose of 800 [400; 1200] mg in the 2nd trimester; 16 female patients (47.1%) at daily dose of 1200 [800; 1200] mg in the 3rd trimester up to 32d week of gestation. At the same time intervals, genetically engineered biological drugs (GEBD) were taken by 4 (11.1%) – 4 (11.4%) – 1 (2.9%) female patients, glucocorticoids by 6 (16.7%) – 6 (17.1%) – 8 (23.5%) women, respectively.

15 (41.6%) female patients had first pregnancy, 21 (58.3%) had previous pregnancies. The first delivery was expected in 20 (55.5%) female patients enrolled in the study. Two cases of unfavorable pregnancy outcome in the 2nd trimester were reported: intrauterine fetal death at 18th week of gestation; and in another case, at week 23, surgical abortion due to critical condition of the fetus (stage 3 impaired fetopla-

cental blood flow) according to dopplerometry, fetal growth retardation, absolute oligohydramnios (fetus weighing 250 g died on the first day). 34 pregnancies resulted in delivery at week 38.8±1.2 of gestation: normal delivery was reported in 18 (52,9%) women, surgical – in 16 (47.1%) women. One twin pregnancy was reported, other cases were singleton pregnancies. Mean body weight of 35 newborns was 3384.9±382.0 g, height – 51.5±2.0 cm, Apgar score 1 min after birth was 8.0±0.4; 5 min after birth – 8.4±0.4.

The control group included 30 pregnant women without rheumatic diseases and diseases that could be manifested by back pain as well as without history of back pain or arthritis, regardless of their cause. Due to the absence of significant concomitant disorders in women from the control group, they will be subsequently referred as "healthy pregnant women". Recruitment, examination and questionnaire survey of pregnant women were carried out in the antenatal clinic of Vidnoye Perinatal Center under the cooperation agreement between this medical institution and Research Institute of Rheumatology n.a. V.A. Nasonova. Mean age of the pregnant women was 28.2±4.5 years. 10 (33.3%) women had first pregnancy, 20 (66.7%) women had previous pregnancies, 14 (46.7%) women were primiparous. All pregnancies resulted in delivery on average at 38.7±1.4 weeks of gestation: normal delivery were reported in 26 (86.7%), surgical aid was required for 4 (13.3%) women. 30 neonates were born, mean weight was 3362.0±442.6 g, height – 51.8±2.3 cm, Apgar score 1 min after birth was 7.8±0.5, 5 min after birth – 8.8±0.5.

Pregnant women of both groups were comparable by parity (average number of pregnancies in female patients with AS was 2.3±1.4, in healthy pregnant women – 2.0±0.9; p>0.05).

Examinations were conducted on 10–11, 20–21 and 31–32 weeks of pregnancy. In order to clarify the presence of specific AS symptoms in healthy women during gestation, pregnant women of both groups underwent standard clinical examination in accordance with Russian Guidelines for the Assessment of Disease Activity and Functional Status in Female patients with AS [11].

Back pain intensity was evaluated according to numerical rating scale (NRS). MASES score (Maastricht Ankylosing Spondylitis Enthesitis Score) was used for evaluation of enthesites [11]. Additionally, pain at the site of plantar aponeurosis attachment to the calcaneal tuber and greater trochanter area was evaluated. Functional status was evaluated according to the BASFI (Bath Ankylosing Spondylitis Functional Index) [11]. The inflammatory nature of back pain was evaluated according to the Assessment of SpondyloArthritis International Society [12].

Hip joint ultrasonography (US) was performed only in female patients with AS: all pregnant women in the 3rd trimester; in the 1st and 2nd trimesters – in case of complaints of pain in the hip joint area. Coxites were determined based on ultrasonography results evidencing cervicocapsular distance (CCD) >7 mm or asymmetry of CCD >1.5 mm.

The study was approved by the Ethics Committee of Research Institute of Rheumatology n.a. V.A. Nasonova. Pregnant women of both groups signed informed consent before enrollment in the study.

Statistical computation of the data was performed by STATISTICA software (Data analysis software system, StatSoft, Inc. 2014) version 12.0 under WINDOWS using standard methods of parametric and nonparametric analysis. Data are presented as mean and standard deviation (M±SD) or median and 25th and 75th percentiles (Me [Q1; Q3]). Comparison of two independent groups by quantitative criteria was performed using Student's t-test or Mann–Whitney U-test. Correlations between variables was revealed by calculating correlation major coefficients. The differences were regarded as statistically significant if p-value is p<0,05.

Results and discussion.

1. Characteristics of back pain and morning stiffness during pregnancy

Pain intensity. During pregnancy, almost all women with AS (94% in all trimesters) had back pain; moreover, there was a trend towards increased intensity in the 2nd trimester (4 [3; 5.5]) compared with the 1st trimester (3 [2; 4]). At weeks 10–11 of pregnancy, 7 (20.6%) female patients evaluated pain above 4 points according to NRS, in 2nd trimester their number increased to 12 (36.4%), while in the 3rd trimester the number was 13 (40.1%); however, differences in back pain severity over the entire gestation period were non-significant.

Back pain in the 1st trimester was reported by one third of healthy pregnant women (n=10, 33.3%), it was of mild intensity (0 [0; 1]), only 1 woman complained of severe pain (7 according to NRS) in the lumbar spine. In the 2nd trimester, the pain was reported by 6 (20%) pregnant women in the control group, its intensity was 0 [0; 0] (maximum – 9) according to NRS. In trimester there was a trend towards increased number of women with back pain – 15 (50%) as well as pain intensity – 1 [0; 4] according to NRS. At the same time, the number of pregnant women with moderate and severe pain increased at 30–31st weeks of pregnancy – 7 (46.7% of women

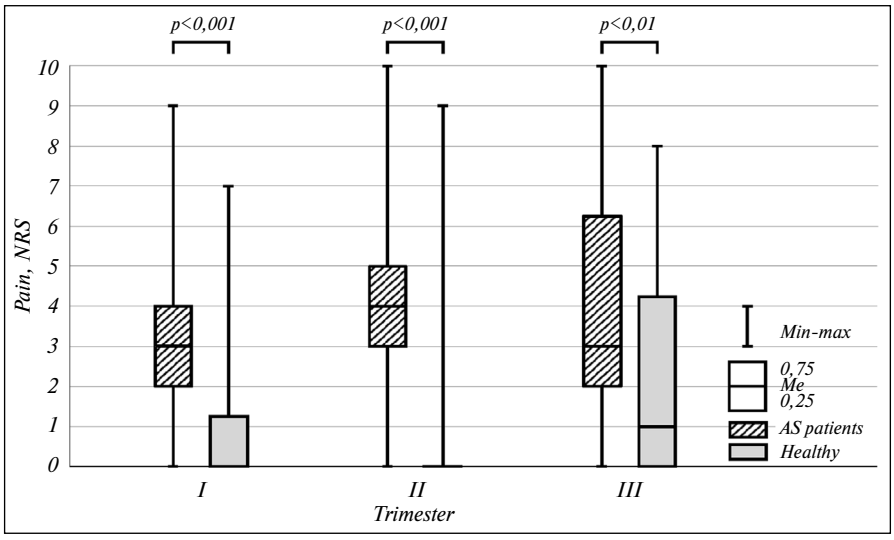

Fig. 1. *Intensity of back pain during pregnancy in female patients with AS and healthy women*

Table **4**. *Incidence of inflammatory back pain parameters in female patients with AS and in healthy women during pregnancy*

	1st trimester		2nd trimester		3rd trimester	
	AS female patients (N=36) n (%)	healthy women (N=30) n (%)	AS female patients (N=35) n (%)	healthy women (N=30) n (%)	AS female patients (N=34) n (%)	healthy women (N=30) n (%)
Back pain	34 (94.5%)$^{\Delta}$	10 (33.3%)	33 (94.3%)$^{\Delta}$	6 (20%)	32 (94.1%)	15 (50%)
Night pain	28 (82.3%)$^{\Delta}$	1 (10%)*	23 (69.7%)	3 (50%)	28 (87.5%)$^{\Delta}$	2 (13.3%)
Morning stiffness	29 (80.6%)$^{\Delta}$	1 (3.3%)	30 (85.7%)$^{\Delta}$	1 (3.3%)	28 (82.4%)$^{\Delta}$	1 (3.3%)
Lack of improvement at rest	30 (88.2%)*, **, $^{\Delta}$	1 (10%)	22 (66.7%)$^{\Delta}$	0	18 (56.3%)$^{\Delta}$	0
Pain reduction after physical exercises	29 (85.3%)*, **, $^{\Delta}$	2 (20%)**	23 (69.7%)	3 (50%)	20 (62.5%)	10 (66.7%)

Note: *p<0.05 compared to the 2nd trimester; **p<0.05 compared to the 3rd trimester; $^{\Delta}$p<0.001 compared to healthy pregnant women; percentages are calculated based on the number of women experiencing pain, except raws «back pain» and «morning stiffness», where percentages calculated based on the total number of women in the group.

with pain). Pain i7 according to NRS throughout the gestation was reported by only one woman; at the phone contact in a month after delivery, she reported that the pain was alleviated the day after natural delivery.

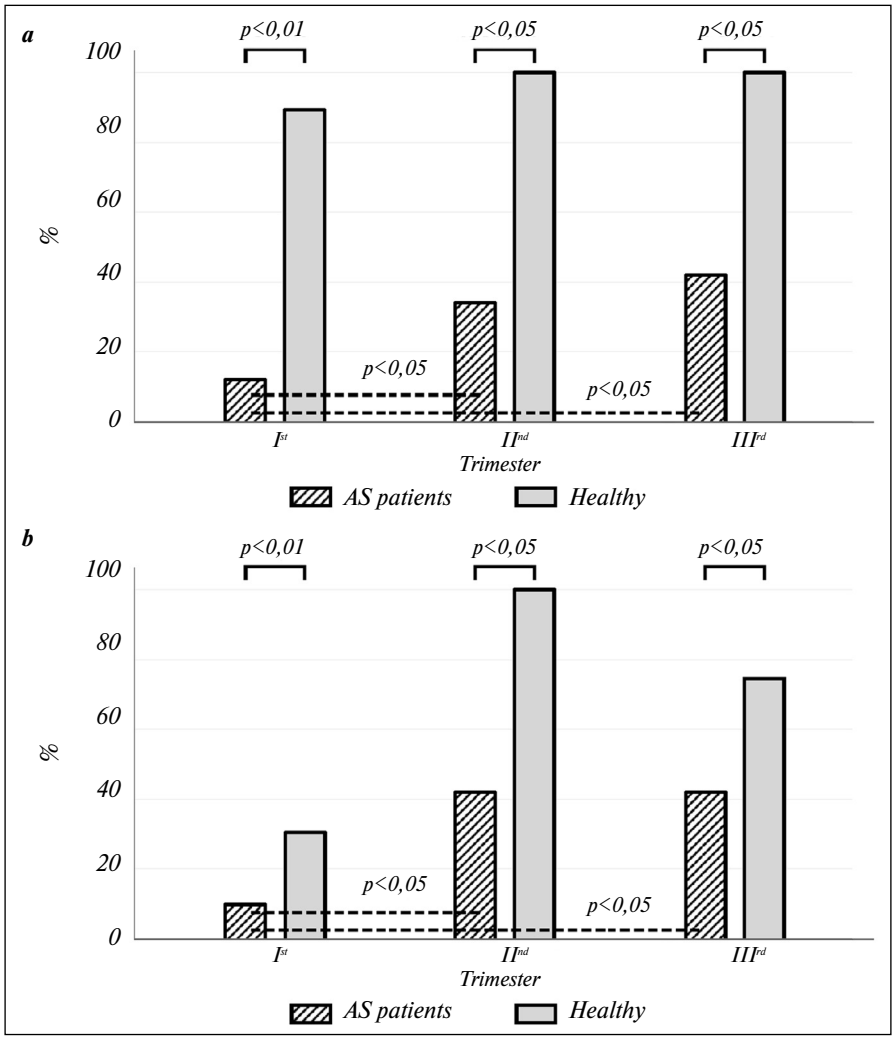

Fig. 2. *a – incidence of mechanical pain elements during pregnancy in female patients with AS and healthy women suffering from back pain. Improvement at rest. b– incidence of mechanical pain elements during pregnancy in female patients with AS and healthy women suffering from back pain. Pain aggravation at physical activity*

Throughout pregnancy, pain intensity in women in the control group was lower than in female patients with AS (p<0.0001), Fig. 1.

Pain type. Analysis of pain parameters reflecting its inflammatory nature in women with AS revealed increased night pain intensity in the 2nd (3 [0; 5]) and 3rd (3 [1; 6]) trimesters compared with the 1st trimester (2 [1; 4]; p<0.05 in both cases) and a trend towards increased duration of morning stiffness in the second half of pregnancy (1st trimester – 10 [5; 20] min, 2nd – 15 [10; 55] min, 3rd – 15 [5; 60] min). Night back pain during pregnancy was observed in 70–88% of female patients, morning stiffness – in 81–86%; differences by trimesters were not statistically significant. At the same time, there were fewer pregnant women who reported decreased back pain intensity after exercise (63–85%) and lack of improvement at rest (56–88%) in the 2nd and 3rd trimesters than at the beginning of gestation (p<0.05 in all cases), Table 1.

As for healthy pregnant women, only 1 woman noted morning stiffness throughout pregnancy with a maximum duration of 10 minutes in the 3rd trimester. Night pain in the control group was less common than in pregnant women with AS (p<0.01 in all trimesters): in the 1st trimester – in 1 (3.3% from the total number of women and 10% from those with pain), in the 2nd trimester – in 3 (10% and 50%, respectively), in the 3rd trimester – in 2 (6.7% and 13.3%, respectively), its intensity was also lower compared to

female patients with AS ($p<0.01$ in all trimesters): in the 1st trimester – 0 [0; 2], in the 2nd trimester – 0 [0; 0], maximum – 5; in the 3rd trimester – 0 [0; 0], maximum – 5. It is interesting that healthy pregnant women reported decreased back pain after exercising more often in the 3rd trimester (n=10; 33.3% and 66.7%, respectively), $p<0.05$ compared with the 1st trimester (n=2; 6.7% and 20%, respectively); only one pregnant woman in the 1st trimester complained of lack of improvement at rest; in the second half of pregnancy this symptom was not observed in women from the control group (Table 1).

At the same time, the proportion of women who noted elements of mechanical back pain increased in both groups during pregnancy ($p<0.05$ between 1st and 2nd, 1st and 3rd trimesters, Fig. 2, a, b). Pregnant women from the control group in the 1st and 3rd trimester more often reported both pain alleviation at rest and pain aggravation towards evening and/or after physical activity compared to women with AS ($p<0.05$ in both cases). Indeed, 11.7% (n=4) of female patients with AS reported decreased pain at rest in the 1st trimester, 43.7% (n=14) of female patients in the 3rd trimester; whereas healthy pregnant women reported that in 90% (n=9) and 100% (n=15) of cases, respectively. Pain aggravation at physical activity in the 1st trimester was noted by 3 (8.8%) female patients with AS and 3 (30%) healthy pregnant women, in the 3rd trimester – by 14 (42.4%) and 11 (73.3%), respectively.

We clarified whether female patients with AS had suffered from back pain during previous pregnancies before AS onset. It turned out that all women with mechanical pain during this gestation experienced back pain in the second half of pregnancies, which developed before the onset of AS symptoms. No differences in the frequency of mechanical pain in female patients with AS with early and normal age of menarche were identified ($p>0.05$).

Pain location. At the beginning of pregnancy, women with AS had the same frequency of thoracic (50%) and lumbar (52.9%) back pain, and slightly less often – sacral (35.2%) and cervical (29.4%) back pain. In the 2nd trimester, number of female patients complaining on lumbar back pain increased up to 72.7% and remained at stable level in the 3rd trimester (Fig. 3, a–c). Trend towards increased incidence of lumbar back pain was based both on increased proportion of female patients with isolated pain lumbar back pain syndrome (20.6% in the 1st trimester and 31.2% at the end of pregnancy) and on combination with pain of other locations (32.4% and 43.8% in the 1st and 3rd trimesters, respectively). Frequency of isolated pain in the thoracic spine region decreased from 20.6% at 10th week of pregnancy to 9.3% in the 3rd trimester. Pain in all regions of spine was noted by 3 (8.8%) women with AS in the 1st trimester and by 2 (6.0%) in the 2nd and 3rd trimesters.

In the 1st trimester of pregnancy, out of 10 women in the control group with complaints of back pain, 3 (30%) had pain in the cervical spine, 4 (40%) in the lumbar spine; 1 (10%) woman had combined pain in the lumbar and cervical spine, and 1 (10%) pregnant woman reported pain in the sacral and thoracic spine. However, starting from week 21 of gestation, all women without AS who had spine aches reported only lower back pain (Fig. 3, a–c). In the 3rd trimester, 9 (60%) pregnant women complained on isolated lumbar back pain, 1 (6.6%) – on back pain in sacral region, 5 (33.3%) – on back pain in sacral and and lumbar regions.

Thus, more than 90% of women with AS during pregnancy experienced back pain with a trend towards increased pain intensity in the second half of gestation. Pregnant women without concomitant rheumatic conditions reported back pain in 33–20% of cases in the 1st and 2nd trimesters with increased frequency of pain to 50% in the 3rd trimester. There was also a trend towards increased back pain intensity in healthy women by week 31–32 of gestation. Throughout pregnancy, the pain intensity in pregnant women without AS was lower than in female patients

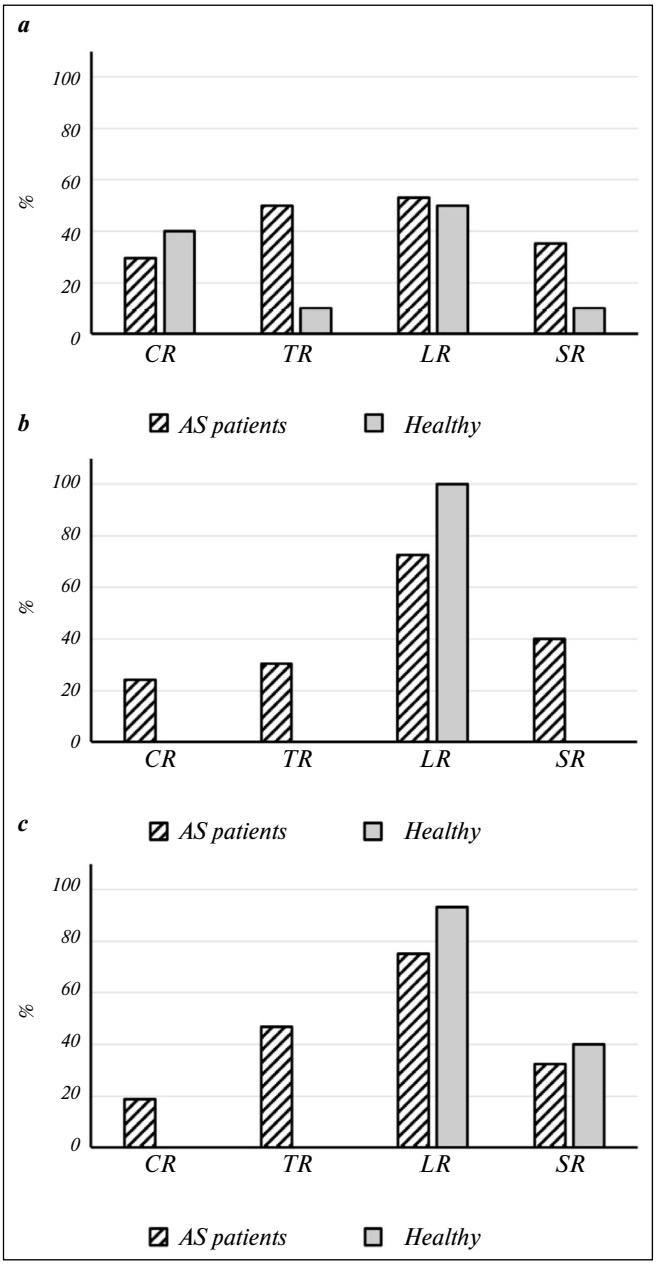

Fig. 3. *a – location of back pain in the 1st trimester of pregnancy in female patients with AS and healthy women. b – location of back pain in the 2nd trimester of pregnancy in female patients with AS and healthy women. c – location of back pain in the 3rd trimester of pregnancy in female patients with AS and healthy women. CR – cervical region, TR – thoracis region, LR – lumbar region, SR – sacral region.*

with AS. Pain associated with pregnancy was most often localized in the lumbar and sacral spine regions. Signs characteristic of inflammation (night pain, morning stiffness) were present only in isolated cases in pregnant women from the control group, night pain intensity in all trimesters was lower than in female patients with AS. However, in the 3rd trimester, 67% of women without AS reported pain alleviation after physical exercises, one of the criteria of inflammatory back pain. This fact requires further study in order to clarify the correct use of this symptom as an indicator of inflammatory pain in female patients with AS at the end of pregnancy. Starting from week 20 of pregnancy, back pain in almost 50% of women with AS changed due to the addition of mechanical components. In 90% of healthy women who complained of back pain during gestation, pain had mechanical nature throughout pregnancy, starting from the 1st trimester (isolated reduction of back pain in healthy pregnant women after physical exercises in the absence of other inflammatory pain criteria, in particular the absence of improvement at rest, does not justify considering this pain syndrome as inflammatory).

2. Pain in the inguinal areas

In female patients with AS, inguinal pain (in inguinal regions), along with restricted range of movements in the hip joint, is a characteristic clinical sign of coxitis. Moreover, enthesites in places of attachment of tendons to the pelvic bones and the greater and lesser trochanter of the femur can be manifested by pain in the groin [13]. However, during pregnancy, with pain in the pelvic girdle, even women without rheumatic diseases experience lower abdomen and inguinal pain [3]. Clarification of pain origin is of fundamental importance for the choice of therapeutic strategy for pregnant women with AS.

Pain in the hip joint area during pregnancy was reported by 9 (25%) women with AS in the 1st trimester and up to 12 (35.3%) female patients by the end of gestation. There was a trend towards increased pain intensity during pregnancy, however the differences were non-significant (2.4±1.9; 3.3±2.4; 4.3±3.0 according to NRS by trimester; $p>0.05$). When comparing maximum distance between medial ankles (MDMA) in female patients with (94.9±14.5 cm) and without (97.2±14.4 cm) groin pain in the 3rd trimester, no differences were identified ($p>0.05$).

No relationship between pain intensity and presence of coxitis according to US and US-signs of enthesopathy was observed. In the 3rd trimester, 5 out of 12 pregnant women with pain in the inguinal regions were diagnosed with coxitis, mean CCD was 8.7±2.2 mm (maximum – 12.6 mm); inguinal pain intensity (2.8±2.2 according to NRS) and MDMA (103.6±3.1 cm) were similar to these parameters in women with inguinal pain not associated with coxitis (5.4±3.3 according to NRS and 87.3±14.7 cm, respectively) $p>0.05$).

In total, in the 3rd trimester, coxitis was revealed in 7 female patients according to ultrasonography data (CCD – 8.4±1.9 mm). It turned out that in pregnant women with coxitis groin pain intensity (1 [0; 4]) and MDMA (104.7±3.5 cm) were similar to those in female patients without coxitis (0 [0; 1] and 94.3±15.3 cm, respectively; $p>0.05$).

Moreover, no differences in intensity of pain in inguinal regions in women with (n=18 (60%); 0 [0; 4] according to NRS) and without US-signs of enthesopathy of greater trochanters (0 [0; 0], maximum – 6 according to NRS; $p>0.05$). As for enthesites in the area of pelvic bones, as determined on palpation, in the group of pregnant women with AS there were no female patients with enthesites in the area of anterior superior spine illiac spines, which could have been manifested by groin pain.

7 (19.4%) pregnant women with AS had history of destructive coxitis. Of them, during gestation, groin pain was reported by 2 female patients with intensity of 2 and 4 according to NRS.

Healthy women reported pain in the inguinal areas only in the 3rd trimester (n=7; 23.3%); in all pregnant women it was combined with lower back pain. Pain intensity was mild, 1.4±0.5 according to NRS and lower than that in female patients with AS ($p<0.05$). In this subgroup of healthy pregnant women, MDMA was 90.4±4.4 cm which was lower than that in women from the control group without groin pain (101.1±4.7 cm; $p<0.01$) and similar to MDMA in pregnant women with AS.

Thus, in our female patients with AS, during pregnancy, intensity of pain in the inguinal area was not related to the presence of coxitis and enthesites in the pelvic area and greater trochanter area, and hip joint destruction. Further studies are required to clarify the effect of both manifestations associated with AS and pregnancy itself on groin pain during gestation. Decreased MDMA in healthy pregnant women with groin pain may be due to a fear of increased pain during this test.

3. Enthesites

Enthesites are the most common extra-axial manifestation of AS, observed in 40–60% of female patients, according to various authors [14]. It is common for enthesites to manifest as pain with possible irradiation along the tendinous-ligamentous and muscle fibers involved, as well as local pain in the area of enthesis, which requires more intensive therapy. According to our previous data [15], the number of affected entheses, determined according to MASES index, increases with gestation age. Most of the areas, evaluated by MASES index, are places of tendons and ligaments attachment to the pelvic bones, an area most often associated with painful sensations in healthy women in the second half of pregnancy. Considering the biomechanical theory of pelvic girdle pain development in healthy pregnant women, associated with muscle imbalance and overload of several pelvic muscles, non-inflammatory enthesopathy development during pregnancy cannot be ruled out. Moreover, increased frequency of pain in the sterno-costal joints in women with AS in the 3rd trimester [15] required ruling out the effect of breast changes on unpleasant sensations in the area under examination. In order to clarify the question of possible association of pain in the area of entheses with normal pregnancy course and not only AS activity, we evaluated MASES index, pain at the site of attachment of plantar aponeurosis to the calcaneal tuber and greater trochanter area in both groups of pregnant women.

Number of AS female patients with enthesites increased during gestation: in the 1st trimester, enthesites were observed in 13 (36.1%) pregnant women, in the 2nd trimester – in 20 (57.1%), in the 3rd trimester – in 21 (61.8%). In the second half of pregnancy, there was increased frequency of enthesites in I and VII costochondral joints, crests, and posterior superior

Table **2**. *Frequency of pain in the area of entheses in female patients with AS and healthy women by trimester of pregnancy*

	1st trimester		2nd trimester		3rd trimester	
	AS female patients (N=36) n (%)	healthy women (N=30) n (%)	AS female patients (N=35) n (%)	healthy women (N=30) n (%)	AS female patients (N=34) n (%)	healthy women (N=30) n (%)
I costochondral joints	2 (5.6%)*,**	0	7 (20%)	1 (3.3%)**	8 (23.5%)	4 (13.3%)
VII costochondral joints	5 (13.9%)*,**	0	12 (34.3%)	0	10 (29.4%)	2 (6.6%)
Iliac crests	2 (5.5%)**	0	2 (5.7%)**	1 (3.3%)	3 (8.8%)	1 (3.3%)
Posterior superior iliac spines	3 (8.3%)*,**	0	10 (28.6%)	0	10 (29.4%)	0
Anterior superior iliac spines	0	0	0	0	0	0
V lumbar spinous process	5 (13.9%)	0	8 (22.9%)	1 (3.3%)	9 (26.5%)	2 (6.7%)
Proximal insertion of Achilles tendon	3 (8.3%)	0	3 (8.3%)	0	3 (8.6%)	0
Attachment of the plantar aponeurosis to the calcaneus	1 (2.8%)	0	2 (5.7%)	0	2 (5.9%)	0
Greater trochanter	1 (2.8%)*,**	0	4 (11.4%)	0	19 (55.9%)	0

Note: * – $p<0.05$ compared to the 2nd trimester; ** – $p<0.05$ compared to the 3rd trimester

iliac spines and in the region of the greater trochanter of the femur ($p<0.05$ compared with the 1st trimester in all cases). Moreover, there was a trend towards increased frequency of entheses inflammation in the area of the V lumbar spinous process (Table 2).

Number of inflamed entheses in pregnant women with AS in the 1st trimester was low, MASES index was 0 [0; 1], max – 7, however it was increased in the second half of pregnancy: at 21st week of gestation it was 1 [0;], max – 5 and at 31st week – 2 [0;3], max – 9 ($p<0.01$ between the 1st and 2nd, 1st and 3rd trimesters). In the 2nd trimester of gestation, correlation between MASES index and night back pain severity was identified (r=0.5).

Pregnant women in the control group reported pain on palpation in the entheses area less often than female patients with AS ($p<0.05$) and only in the second half of gestation: in the 2nd trimester – 3 (10%) women, in the 3rd trimester – 6 (20%) women. In isolated cases, healthy pregnant women reported unpleasant sensations in the area of I and VII costochondral joints, iliac crests and of the V lumbar spinous process with increased frequency of these symptoms in the 3rd trimester. It is interesting that pregnant women from the control group with pain in the spinous process of the V lumbar spinous process did not suffer from lumbar back pain, while women with pain in the sterno-costal joints did not report thoracic back pain.

Throughout gestation, MASES index in healthy pregnant women (0 [0; 0], max – 2 in the 2nd trimester and 4 in the 3rd trimester) was lower than in the study group ($p<0.01$). No correlation of MASES index with indicators characterizing inflammation was detected. Pain in the entheses area in the control group was also less severe than in female patients with AS ($p<0.0001$ in all trimesters): in the 2nd trimester – 0 [0; 0] according to NRS in healthy pregnant women and 2 [0; 4] according to NRS in female patients with AS; in the 3rd trimester – 0 [0; 0] and 2 [0; 6] according to NRS, respectively.

Thus, taking into account low frequency and low intensity of pain in the entheses area in healthy pregnant women, lack of correlation with other manifestations of inflammation, it can be assumed that enthesites reflect the activity of AS and are not associated with pregnancy-related changes.

4. Functional status

Functional disorders according to BASFI in female patients with AS increased with gestational age: index values by trimester were 1.9±2.1 (1.2 [0.2; 3.1]); 2.3±2.1 (1.6 [0.4; 3.9] and 3.5±2.8 (2.4; [1.0; 5.6]) ($p<0.01$ between 1st and 2nd, 1st and 3rd trimesters). In healthy pregnant women, there was also increased restriction of functional abilities during gestation: 0.8±1.1 (0.5 [0.2; 1.0]); 1.1±1.0 (1.0 [0.5; 1,4] and 1.7±1.2 (1.6; [1.0; 1.8] ($p<0.05$ between 1st and 2nd, 1st and 3rd, 2nd and 3rd trimesters).

Only in the 3rd trimester the value of the functional BASFI index was significantly higher in female patients with AS compared with women in the control group ($p<0.05$). However, individual components of the index had statistically significant differences in each trimester, with the exception of questions 9 and 10 (doing physically demanding activities and doing a full day activities) throughout gestation, question 7 (ability to climb 12–15 steps without aid) in the 2nd and 3rd trimesters and question 4 (ability to get up from a chair without using hands) in the 1st trimester. Thus, the results obtained put in doubt the ability of items 9 and 10, and, possibly, 7 to reflect decreased functional capacity associated with AS, and not with physiological course of pregnancy.

To answer the question which components of BASFI contribute the most to the value of index in each trimester, correlation analysis was performed between the BASFI index value and its individual components in both groups of pregnant women (Table 3). It turned out that in female patients with AS there was high (rs>0.7) and very high (rs>0.9) correlation of all BASFI components with index itself in each trimester of pregnancy. In

Table 3. *Statistically significant correlations between values of BASFI index and its components in female patients with AS and healthy pregnant women*

No	1st trimester		2nd trimester		3rd trimester	
	AS female patients (N=36) n (%)	healthy women (N=30) n (%)	AS female patients (N=35) n (%)	healthy women (N=30) n (%)	AS female patients (N=34) n (%)	healthy women (N=30) n (%)
1 Put on socks/tights	0.87		0.76		0.91	
2 Bend forward to pick up an object from the floor	0.81		0.77		0.92	0.69
3 Reach up to a high shelf	0.88	0.40	0.81	0.43	0.87	
4 Get up out of a chair without using hands	0.83		0.83	0.40	0.91	0.53
5 Getting up off the floor from lying on the back	0.82		0.90	0.68	0.86	0.52
6 Stand unsupported for 10 minutes	0.89	0.42	0.87	0.77	0.84	0.61
7 Climb 12 – 15 steps without aid	0.87	0.47	0.85	0.63	0.85	0.77
8 Turn head and look over shoulder	0.74	0.45	0.71	0.41	0.87	0.52
9 Do physically demanding activities	0.88	0.87	0.84	0.76	0.88	0.68
10 Do a full day activities	0.86	0.84	0.78	0.84	0.84	0.59

healthy women, high correlation was observed between BASFI index and questions assessing the doing everyday activities (questions 9 and 10), in the first two trimesters, as well as the ability to stand unsupported for 10 minutes (question 6) in the 2nd trimester and climb 12–15 steps without aid (question 7) in the 3rd trimester.

Increased BASFI index in the 2nd trimester of pregnancy compared with the 1st trimester in the group of AS female patients correlated significantly with decreased ability to get off the floor from lying position (question 5, rs=0.41), to climb steps without aid (question 7, rs=0, 38), doing physically demanding activities (question 9, rs=0.55) and doing a full day activities (question 10, rs=0.45). Increased BASFI index in the 2nd trimester in healthy women correlated with increased difficulty standing unsupported (question 6, rs=0.39) and doing a full day activities (question 10, rs=0.38). Increased BASFI index in the 3rd trimester compared to 2nd trimester in the study group has shown correlation with all index components (rs=0.46–0.66), while in the control group only with the ability to climb steps without aid (question 7, rs=0.40), doing physically demanding activities (question 9, rs=0.50) and doing a full day activities (question 10, rs=0.37).

Thus, components of the BASFI index, which is designed for global evaluation of the ability of AS female patients to do daily activities (questions 9 and 10), reflect functional disorders during pregnancy in non-specific manner. Considering high correlation of these components with BASFI value, incorrect interpretation of the values of BASFI index itself and overdiagnosing of functional disorders associated with AS during gestation are possible. Reliability of questions 6 (standing unsupported) and 7 (climbing steps without aid) in pregnant women with AS requires further clarification.

In conclusion, it should be repeated that, according to our study data, night back pain, morning stiffness and enthesites reflect inflammatory activity of AS during pregnancy. During gestation, back pain and enthesis pain as well as functional disorders in pregnant women with AS are intensified. The nature of back pain in the second half of pregnancy changes: on the one hand, the intensity of some inflammatory pain components is increased (night pain, morning stiffness), on the other hand, there is additional joint pain of mechanical nature and decreased frequency of other inflammatory pain components (lack of improvement at rest and pain alleviation after physical exercises). Thorough collection of medical history and analysis of complaints is necessary to clarify pain origin and choose correct treatment strategy. If healthy pregnant women have one of the inflammatory pain criteria – pain alleviation after physical exercises C it should be clarified in large control groups and possibly criteria of inflammatory pain for pregnant women with AS should be reconsidered. BASFI functional deficiency index also requires modification when used during pregnancy in women with AS.

Study transparency

The study was conducted within the framework of scientific topic No. 398 "Pathogenetic aspects and personalized therapy of ankylosing spondylitis and psoriatic arthritis", approved by the Academic Council of Federal State Scientific Institution TResearch Institute of Rheumatology n.a. V.A. NasonovaУ. Authors are solely responsible for submitting the final version of the manuscript for printing.

Declaration of financial and other relationships

The study was not sponsored. All authors participated in the development of the study concept and design and in the manuscript writing. Final version of the manuscript was approved by all authors. The authors did not receive any fees for the article.

BIBLIOGRAPHY

1. Кричевская ОА, Гандалоева ЗМ, Дубинина ТВ. Анкилозирующий спондилит и беременность: современный взгляд на проблему. Современная ревматология. 2018;12(3):19-28. [Krichevskaya OA, Gandaloeva ZM, Dubinina TV. Ankylosing spondylitis and pregnancy: a current view on the problem. *Sovremennaya revmatologiya = Modern Rheumatology Journal*. 2018;12(3): 19-28. (In Russ.)]. doi: 10.14412/1996-7012-2018-3-19-28

2. Casagrande D, Gugala Z, Clark SM, et al. Low back pain and pelvic girdle pain in pregnancy. *J Am Acad Orthop Surg*. 2015 Sep; 23(9):539-49. doi: 10.5435/JAAOS-D-14-00248. Epub 2015 Aug 13.

3. Wu WH, Meijer OG, Uegaki K, et al. Pregnancy-related pelvic girdle pain: terminology, clinical presentation, and prevalence. *Eur Spine J*. 2004 Nov;13(7):575-89. Epub 2004 Aug 27. doi: 10.1007/s00586-003-0615-y

4. Malmqvist S, Kjaermann I, Andersen K, et al. The association between pelvic girdle pain and sick leave during pregnancy; a retrospective study of a Norwegian population. *BMC Pregnancy Childbirth*. 2015; Oct 5; 15:237. doi: 10.1186/s12884-015-0667-0.

5. Morino S, Ishihara M, Umezaki F, et al. Low back pain and causative movements in pregnancy: a prospective cohort study. *BMC Musculoskelet Disord*. 2017; Oct 16; 18(1): 416. doi: 10.1186/s12891-017-1776-x.

6. Vleeming A, Albert HB, Ostgaard HC, et al. European guidelines for the diagnosis and treatment of pelvic girdle pain. *Eur Spine J*. 2008 Jun;17(6):794-819. doi: 10.1007/s00586-008-0602-4

7. Bhardwaj A, Nagandla K. Musculoskeletal symptoms and orthopaedic complications in pregnancy: pathophysiology, diagnostic approaches and modern management. *Postgrad Med J*. 2014 Aug;90(1066):450-60. doi: 10.1136/postgradmedj-2013-132377. Epub 2014 Jun 5.

8. Verstraete EH, Vanderstraeten G, Parewijck W. Pelvic Girdle Pain during or after Pregnancy: a review of recent evidence and a clinical care path proposal. *Facts Views Vis Obgyn*. 2013;5(1):33-43.

9. Mahovic D, Laktasic-Zerjavic N, Tudor KI, et al. Pregnancy-related severe pelvic girdle pain caused by unilateral noninfectious sacroiliitis. A case report and literature review. *Z Rheumatol*. 2014 Sep; 73(7):665-8. doi: 10.1007/s00393-013-1323-6

10. Dunn G, Egger MJ, Shaw JM, et al. Trajectories of lower back, upper back, and pelvic girdle pain during pregnancy and early postpartum in primiparous women. *Womens Health (Lond)*. 2019 Jan-Dec; 15:1745506519842757. doi: 10.1177/1745506519842757.

11. Дубинина ТВ, Гайдукова ИЗ, Годзенко АА и др. Рекомендации по оценке активности болезни и функционального состояния больных анкилозирующим спондилитом в клинической практике. Научно-практическая ревматология. 2017;55(4): 344-50. [Dubinina TV, Gaidukova IZ, Godzenko AA, et al. Guidelines for the assessment of disease activity and functional status in patients with ankylosing spondylitis in clinical practice. *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2017;55(4):344-50. (In Russ.)]. doi: 10.14412/1995-4484-2017-344-350

12. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009 Jun;68 Suppl 2:ii1-44. doi: 10.1136/ard.2008.104018.

13. Дубинина ТВ, Дёмина АБ, Смирнов АВ и др. Диагностика коксита при анкилозирующем спондилите. Научно-практическая ревматология. 2015;53(6):624–31. [Dubinina TV, Demina AB, Smirnov AV, et al. Diagnosis of coxitis in ankylosing spondylosis. *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2015;53(6):624–31. (In Russ.)]. doi: 10.14412/1995-4484-2015-624-631

14. Rudwaleit M, van der Heijde D, Landewe R, et al. The assessment of spondyloarthritis international society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis*. 2011 Jan;70(1):25-31. doi: 10.1136/ard.2010.133645. Epub 2010 Nov 24.

15. Кричевская ОА, Гандалоева ЗМ, Демина АБ и др. Течение анкилозирующего спондилита на фоне беременности: промежуточные данные проспективного наблюдения. Современная ревматология. 2019;13(2):61-72. [Krichevskaya OA, Gandaloeva ZM, Demina AB, et al. The course of ankylosing spondylitis during pregnancy: intermediate data of a prospective follow-up. *Sovremennaya revmatologiya = Modern Rheumatology Journal*. 2019;13(2): 61-72. (In Russ.)]. doi: 10.14412/1996-7012-2019-2-61-72

Article received 23.08.2019