RHEUMATOID ARTHRITIS AND PREGNANCY

Khusainova Munira Alisherovna
Assistant of Samarkand State Medical University

Abstract *In more recent prospective studies, it was shown that only 48-66% of pregnant women have clinical improvement during gestation, and postpartum exacerbation of RA is noted in 70% of patients, while most patients require drug therapy. In the first observation, described about 80 years ago, a decrease in the activity of the disease was noted in the absolute majority of pregnant women. Rheumatoid arthritis (RA) often affects women of childbearing age, which determines a long-standing interest in studying the mutual effects of pregnancy and RA.*

The aim of the study was to evaluate the dynamics of RA activity according to DAS28–CRP during pregnancy and after childbirth; to clarify the effect of RA activity at the beginning of gestation on the further course of the disease. To determine the need for drug therapy in pregnant women with RA.

Material and methods. Prospectively, in each trimester of gestation and for 12 months after delivery, it was followed

32 pregnancies in 29 women with reliable RA (ACR criteria of 1987) examined.

Results and discussion. During pregnancy, 46% of RA patients had a decrease in disease activity. Within 12 months, on average 1.5 months after delivery, 75% of patients had an exacerbation of RA. In patients with remission and low disease activity at the beginning of pregnancy, RA activity during the entire gestation period and 1 month after delivery remained significantly lower than in patients with moderate and high activity in the first trimester (p=0.0008–0.04). A similar trend was observed in patients with no arthritis at the time of conception (according to the survey). 23 (71.9%) in patients with signs of disease activity during pregnancy, anti-inflammatory therapy was intensified, against which DAS28-CRP decreased (p=0.008), while in the remaining 9 (28.9%), with low activity without drug intervention, it tended to increase. After childbirth, patients with high and moderate activity improved earlier (p=0.008), since they resumed therapy with basic anti-inflammatory (HDL) and genetically engineered drugs earlier biological drugs (GIBP) than in patients with remission and low activity during pregnancy. In the latter, the tendency to increase activity persisted until 3 months after childbirth. In 12 (37.5%) patients who became pregnant while taking HDL or GIBP and urgently canceled them due to pregnancy, the disease activity in the I–III trimesters was significantly higher than in 20 (62.5%) cases when HDL and/or GIBP were not used or canceled in advance when planning pregnancy (p<0.04).

Conclusions. *Remission or low activity of RA at the beginning of pregnancy is a predictor of low activity of the disease and minimization of drug therapy up to complete rejection of it throughout pregnancy. Without medical intervention, RA activity may tend to*

increase. Postpartum exacerbation of RA is also noted in patients who had remission and low RA activity before childbirth. The abrupt cancellation of HDL or GIBP in connection with the onset of unplanned pregnancy contributes to an increase in the activity of RA already from the first trimester of gestation. Pregnancy should be planned by choosing stable anti-inflammatory therapy in advance.

Keywords: *rheumatoid arthritis; pregnancy; rheumatoid arthritis activity; DAS28-CRP; anti-inflammatory therapy.*

INTRODUCTION

The authors report that the frequency of clinical improvement during gestation ranged from 66 to 91%, and exacerbation after childbirth was observed in 60-91% of patients. J.L. Nelson et al. in a study of 57 pregnancies in 41 women, remission of the disease was noted only in 39% of cases, and a decrease in activity in 21%. It should be emphasized that the activity of RA during pregnancy can also be influenced by ongoing therapy. Rheumatoid arthritis (RA) often affects women of childbearing age, which determines a long-standing interest in studying the mutual effects of pregnancy and RA. The first description of pregnancy in RA dates back to 1935, P.S. Hench in a prospective study observed a decrease in disease activity in 20 patients with RA during 33 of 34 pregnancies. In 2011, a large review on pregnancy in RA was published.

The goal is to trace the dynamics of RA activity during during pregnancy and after childbirth, using DAS28-CRP; to clarify the effect of RA activity at the beginning of gestation on the further course of the disease, to determine the need for drug therapy in pregnant women with RA.

MATERIALS AND METHODS OF RESEARCH

The work is based on the results of a prospective follow–up of 32 pregnancies in 29 women with reliable RA (ACR criteria 1987), 11 of them (38%) with juvenile RA (JURA). The patients were examined at 10-12, 20-22, 30-32 weeks of gestation, as well as 1, 3, 6 and 12 months after delivery. Most of the patients (n=25, or 78.1%) were included in the study starting from the first trimester of pregnancy, 3 more (9.4%) – from the second and 4 (12.5%) – from the third trimester. During the follow-up period, three women had repeated pregnancies (one of them is two repeat pregnancies), three of which were also included in this

study. In the case of a new pregnancy within 12 months after the previous birth, the observation of the previous case was considered completed. A new pregnancy was considered as a new case of pregnancy at the same control dates as the rest of the pregnancies. At the time of inclusion in the study, the median age of patients was 29 [27; 31] years, the duration of the disease was 8 [4; 16] years, the age of onset of the disease was 19 [13; 25] years. Seropositive for rheumatoid factor (RF) – n=18 (62.1%) and antibodies to cyclic citrullinated peptide (ADCP) – n=17 (58.6%) variants of RA prevailed, II and III radiological stages – n=21 (72.4%), I and II functional classes – n=25 (86.2%). 5 (17.2%)

patients had a history of extra-articular manifestations of the disease: pericarditis (n=4), rheumatoid nodules (n=2) and polyneuropathy (n=1). One patient had amyloidosis of the internal organs. At the time of inclusion in the study, 15 (51.7%) patients were pre-pregnant; 18 (62.1%) of the surveyed were expected to have the first birth, 11 (37.9%) had the second. Nonsteroidal anti-inflammatory drugs (NSAIDs) were taken in anamnesis by 27 (93.1%) patients, 3 (9.4%) – including at the time of conception. In order to minimize the adverse effects on the fetus and the course of labor, NSAIDs were canceled no later than 30-32 weeks of pregnancy. Basic anti-inflammatory drugs (HDL) in the anamnesis was received by 26 (89.7%) patients. In 24 (75%) cases, they were canceled before pregnancy the interval from the moment of withdrawal to conception was 18 [10; 30] months, in 8 (25%) patients pregnancy occurred against the background of taking HDL, which were canceled immediately after the fact of pregnancy was established.

THE RESULTS AND THEIR DISCUSSION

The median DAS28-CRP significantly decreased during pregnancy (p=0.005), and increased after childbirth (p=0.05), then, by the 12th month after childbirth, it tended to decrease, but without statistical reliability. Remission or low activity of RA in the first trimester had in 13 (52%) patients, 12 (48%) had moderate or high activity. By the third trimester, the number of patients who had remission or low activity increased to 20 (62.6%), and the number of patients with moderate or high activity decreased to 12 (37.4%). 1 month after delivery, remission or minimal RA activity was determined in 14 (43.7%) cases, and the number of patients with high and moderate disease activity was maximum – n=18 (56.3%). Then, by the 12th month after delivery, the number of patients with low RA activity and remission increased to 15 (57.7%), the number of patients with moderate activity decreased to 11 (42.3%), and high activity was not observed. In the first month after childbirth, the maximum number of exacerbations was observed: 10 (31.3%) moderate and 2 (6.3%) significant ones. Upon further observation, the decrease and increase in RA activity were observed in approximately the same proportions.

A decrease in DAS28-CRP from the beginning of follow-up (I/II trimester) to the third trimester of gestation was observed in 13 (46.4%) patients, of whom 7 (25%) had a pronounced decrease. Moderate exacerbation of the disease during gestation was noted only in 3 (10.7%) cases. After the maximum exacerbation during the 1st month after childbirth (n=12, or 37.6%), then from the 1st to the 12th month, a decrease in disease activity was observed in 12 (46.2%), and moderate exacerbation occurred in 8 (30.8%) patients. When analyzing the postpartum activity of RA in each patient, it was noted separately that only 8 (25%) patients did not have episodes of exacerbation for all 12 months after childbirth, while 24

(75%) had at least during one postpartum visit. The median period from childbirth to the appearance of the first clinical signs of an exacerbation of RA was 1.5 [0.75; 2.5] months. Interestingly, in patients with seronegative RF variant of RA [of which 9 (81.8%) were from JURA] in the first trimester DAS28-CRP was significantly higher (p=0.03). At the

same time CHBS, CHPS and the duration of morning stiffness in their joints were longer than in patients with seropositive RA, not only in the first but also in the third trimester of pregnancy (p=0.006–0.02).

The effect of rheumatoid arthritis activity at the beginning of pregnancy on the subsequent course of the disease In order to assess the effect of disease activity

at the beginning of pregnancy on the further course of RA, the patients observed from the first trimester (n=25) were divided into two groups. The first group included 13 (52%) patients with remission (n=10) or low activity (n=3) in the first trimester; in the second – 12 (48%) patients with moderate (n=8) and high (n=4) disease activity. The selected groups were comparable in age and duration of RA. During the entire observation, the activity of the wound Group 2 remained higher than in group 1: significantly up to 1 month after delivery (p=0.0008-0.04), then without statistical reliability. In group 1, DAS28–CRP fluctuated slightly during pregnancy with a tendency to increase in the second trimester, and in group 2, it progressively decreased throughout the gestational period . The decrease in disease activity in group 2 during pregnancy was more pronounced (p=0.0008). In the third trimester in group 1, remission was determined in 10 (76.9%), and in the 2nd – only in 3 (25%) cases, low activity in group 2 was observed in 4 (33.3%) patients; moderate activity in group 1 was observed in 3 (23.1%) cases, in group 2 - also in 3 (25%), and high activity was observed only in group 2 – in 2 (16.7%) of patients.

During the 1st month after delivery, DAS28-CRP increased in both groups. By this time, most patients with RA exacerbation were suppressed lactation and active antirheumatic therapy resumed (see below); thus, the further dynamics of the disease activity was primarily due to the therapy. Therefore, by the 3rd month after childbirth, activity decreased in the 2nd group, and in the 1st, where active therapy began later, it increased slightly (p= 0.008). In the future, the dynamics of DAS28-CRP in both groups was similar, and by the 12^{th} month after delivery, the index values practically did not differ. The absence of arthritis at the time of conception according to the data Anamnesis was observed in 15 (46.9%) cases. The duration of the period of absence of arthritis before pregnancy was determined from the words of patients, and its median was 12 [6; 12] months (from 6 to 84 months). In these patients, DAS28-CRP throughout pregnancy and 1 month after delivery was significantly lower than in patients with arthritis at the time of conception (p=0.0007–0.04). At the same time, in patients who became pregnant against the background of arthritis, activity decreased, and in patients with no arthritis at the time after conception, the activity of RA increased. This may be due to the increased attention of the doctor to patients with arthritis at the beginning of pregnancy and the appointment of adequate therapy immediately after childbirth, while the exacerbation of the disease in patients without arthritis at the beginning of pregnancy was less expected, and therapy after childbirth was prescribed to them later. Therapy during the observation period Only 6 (18.8%) patients conceived against the background of the absence of drug therapy, in 5 (15.6%) cases there was no need to prescribe it during the entire pregnancy and only in 1 (3.2%) – and within 12

months after childbirth. In 7 (28%) patients with low RA activity or remission of the 25 patients observed from the first trimester of gestation, therapy did not change during pregnancy, while all 12 (48%) patients with moderate and high activity had increased anti-inflammatory therapy (p=0.01).

The main drugs for activity control RA during pregnancy were NSAIDs (n=20; 62.5%) and GC (n=23; 71.9%). At the same time, the dose of HA increased in 9 (28.1%) patients during pregnancy, and 4 (12.5%)they were appointed for the first time. In addition, during gestation, 16 (50%) patients required intra–articular

and 6 (18.8%) - intravenous drip of HA. During childbirth, 20 (62.5%) patients with signs of RA activity were additionally parenterally injected with GC. After childbirth, due to increased disease activity, the need for HA (n=24; 75%) and NSAIDs (n=27; 84.4%) increased. If necessary, HDL therapy was resumed (n=28; 87.5%) and/or GIBP was added (n=8; 25%), and therefore intraarticular (n=12; 37.5%) and intravenous (n=3; 9.4%) administration of HA was required less often than during pregnancy. To clarify the contribution of drug therapy to changes in RA activity during and after pregnancy, we compared the dynamics of DAS28-CRP in patients whose treatment regimen did not change during gestation (n=9; 28.9%) with patients whose anti-inflammatory therapy increased during pregnancy

(n=23; 71.9%). In the gestational period in group 2, the median DAS28-CRP was expected to decrease, while as in the 1st group, there was some increase in it.

Thus, without medical intervention (Group 1) RA activity increased during pregnancy. After childbirth, an increase in disease activity was noted in both groups, requiring the addition of appropriate therapy, against which, by the time the observation was completed, the median DAS28-CRP decreased. To assess the effect of previous pregnancy therapy, we identified 12 (37.5%) patients who had an unplanned pregnancy while taking HDL (n=8; 25%) or GIBP (n=4; 12.5%; 5 (41.7%) of them had no children at the time of conception arthritis. After the withdrawal of these drugs due to pregnancy, the disease activity from the first to the third trimester was significantly higher in them than in 20 (62.5%) cases when HDL and/or GIBP were not used or were canceled in advance when planning pregnancy ($p<0.04$). In addition, the dose of HA was increased in these patients during pregnancy, as a result of which by the third trimester it was significantly higher than in patients with planned pregnancy (p=0.04). After childbirth, due to the exacerbation of RA in most patients, the difference in disease activity between these groups was minimal.

CONCLUSIONS

1. During pregnancy, 46% of RA patients have a decrease in disease activity. After childbirth, 75% of patients experience an exacerbation of RA, on average after 1.5 months.

2. Anti-inflammatory therapy during pregnancy makes a significant contribution to reducing the activity of RA during this period. Without medical intervention, RA activity may tend to increase.

3. Remission or low activity of RA at the beginning of pregnancy is a predictor of low activity of the disease and minimization of drug therapy up to complete rejection of it throughout pregnancy.

4. Postpartum exacerbation of RA is noted, including in patients who had remission and low RA activity before childbirth. Such patients also need the increased attention of a doctor for the timely appointment of adequate therapy.

5. The abrupt cancellation of HDL or GIBP in connection with the onset of unplanned pregnancy contributes to an increase in the activity of RA already from the first trimester. Pregnancy should be planned by choosing stable anti-inflammatory therapy in advance.

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