ORIGINAL INVESTIGATIONS

Pregnancy in ankylosing spondylitis: the view of a female patient and a physician

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

Objective: *to study the impact of the diagnosis of ankylosing spondylitis (AS) on the planning of pregnancy by patients and their attitude towards the use of drugs during gestation and to assess the competency of physicians in the issues relating to pregnancy in AS.*
Patients and methods. *The data of three studies based on the questionnaire surveys of female AS patients and rheumatologists.*
Results and discussion. *The questionnaire survey revealed a decline in the number of pregnancies per woman after the onset of AS. Having learned about their diagnosis, 70% of patients reported a change in their maternity plans; however, most (80%) women said that they were still going to become pregnant, but they would constantly feel discomfort and fear for their own health and the health of their future child. Pregnancy was rejected due to AS development by 13.9% of patients, regardless of the presence or absence of children born in the healthy period of their life. Only 50% of women discussed the issues relating to pregnancy with a rheumatologist, and one third of them did not obtain the necessary information. Only one fourth of patients were ready to continue treatment for AS in the period of preparation for conception and during gestation.*
On the whole, Russian rheumatologists have enough knowledge about pregnancy outcomes in AS, and, in particular, about the factors which may influence the favorable outcome and about the fundamentals of follow-up for pregnant women. At the same time, 18% of rheumatologists expect increased AS activity during gestation, more than two thirds consider sacroiliitis to be an indication for surgical delivery, and 30% are ready to discontinue the drugs which are permitted for use before pregnancy.
Conclusion. *Lack of information about the planning and course of pregnancy in AS, the risk of disease exacerbation and the safety of therapy during gestation is noted in both patients and rheumatologists. It is necessary to implement educational measures on the problem of pregnancy in AS for rheumatologists and women of fertile age and their family members.*

Keywords: *ankylosing spondylitis; pregnancy; disease activity; questionnaire survey; drug therapy.*
Contact: *Zuleikhan Mikailovna Gandaloeva;* ***gzm92@bk.ru***
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The attitude to pregnancy in patients with chronic immunoinflammatory rheumatic diseases (IIRDs) has changed in recent decades both among physicians and patients. In comparison with 1970s, the beginning of XXI one witnessed a more than four-time increase in deliveries in patients with IIRDs, including those with ankylosing spondylitis (AS) [1]. Yet families with members suffering from AS still have fewer children as compared with general population [2]. Lack of awareness about interrelation between AS and pregnancy, therapy options in pregnancy planning and during gestation and/or lack of time are the factors making it hard for rheumatologists to discuss the issues with their patients. With no information provided by her physician, not knowing about her incompetence, a patient with AS has to make decisions concerning future pregnancy on her own.

This work summarizes the findings of three studies carried out by questioning rheumatologists and patients with AS. The study also estimates the impact of AS diagnosis on pregnancy planning, the patients' adherence to medication therapy prior to and during pregnancy, and physicians' competence in managing of pregnancies in patients with AS.

Statistical analysis of the data was performed by Statistica (Data analysis software system, StatSoft 10, Inc. 2011) under Windows, using standard methods of parametric and nonparametric analysis.

An analysis of correlation tables using a Pearson's chi-square test was done to assess qualitative data in groups. Correlation between variables was revealed by calculating correlation major coefficients using Spearman's Rank correlation coefficient technique. The differences were regarded as statistically significant if p- value was $p<0,05$. The data we presented as mean (M)± standard deviation of a median (Me) [25th; 75th percentile].

1. A survey of female patients with AS: changing pregnancy plans after AS diagnosis; attitude to medication therapy while planning and during pregnancy.

The goal was to survey the impact of AS diagnosis on a woman's intention to have children as well on her attitude to proceed with AS therapy prior to and during pregnancy.

Patients and Methods. From May to November 2018 a questioning survey among women with AS was done. Inclusion criteria were the AS diagnosis, confirmed by rheumatologist; age of the respondents between 18–45 at the onset of the study; voluntary agreement to participate in the questioning.

The questionnaire included 18 questions concerning age, education, marital status, duration of AS, number of pregnancies and deliveries, pregnancy readiness in women with the disease, experience of interaction with a rheumatologist while planning and during pregnancy, AS patient's attitude to continuation of AS therapy during this time.

The survey involved 302 women aged 32,4±6,0 years with an average AS duration of 10,2±7,4 years. The level of respondents' education placed them in the following way: 224 (74,2%) had higher education, 68 (22,5%) had secondary specialized education and 10 (3,3%) had only secondary education. At the moment of questioning 215 (71,2%) of women lived in a registered mar-

riage, 25 (8,3%) lived in a common-law marriage, 21 (6,9%) women were divorced and 41 (13,6%) were single.

214 (70,9%) respondents had 492 pregnancies, with 278 prior to AS onset, and 214 after it. Regarding the total number of respondents, the average number of pregnancies in one woman was 1,6±1,6; with 0,9±1,3 before AS onset, Me 0 [0; 1] and was 0,7± 0,9, Me 0 [0; 1] during the disease.

Results. As soon as AS diagnosis was made, the majority of the respondents changed their attitude to a possible pregnancy. The responses of 206 (68,2%) women, who reported their wish to reconsider their maternity plans due to AS, were ranked as follows: 12 (5,8%) patients were firm in their decision to interrupt an unplanned pregnancy; 21 (10,2%) women made a decision to cancel their pregnancy plans as they had already had children before AS diagnosis was made; 9 (4,4%) patients said they would avoid pregnancy despite absence of children; 164 (79,6%) women admitted the possibility of pregnancy, yet they pointed out that they would feel constant discomfort and fear for their own health and the health of their future child. Thus, 42 (13,9%) respondents flatly refused the idea of pregnancy due to AS development.

An weak inverse correlation was revealed between AS duration and changing patients' attitude to pregnancy (R= 0,14; p<0,05). No association between age, education level, marital status and pregnancy readiness in patients with AS was found.

150 (49,7%) patients discussed pregnancy planning with their rheumatologist. Herewith women with higher education more often discussed their future pregnancy with their rheumatologist as compared with patients with secondary specialized and secondary education (55,5; 35,3 and 40%, respectively; the chi square statistic «2; p=0,002). Apart from that, women who were in registered and common-law marriages more often sought their rheumatologist's opinion, concerning that issue, as compared to the divorced ones and single women (54; 56; 28,6 and 34,2% respectively; square statistic «2; p=0,002). Among 150 patients with AS, who visited a rheumatologist during pregnancy, 97 (64%) were satisfied with the physician's advice, 53 (35%) did not get an exhaustive answer to their questions; 4 patients were recommended not to plan pregnancy due to AS.

Patients' attitude to continuation of AS therapy during pregnancy planning and conception was as follows: 107 (35,4%) women claimed that all medications should be stopped, 75 (24,8%) admitted taking medications, 120 (39,8%) were uncertain. In patients' opinion, it was possible to continue nonsteroidal anti-inflammatory drugs (NSAIDs;) 46 patients (15,2% out of the total number of respondents and 61% of those who admitted continuation of medication therapy)), glucocorticoids (GC; 20 patients (6,6 and 26%, respectively)), sulphasalazine (SSZ; 20 patients (6,6 and 26%, respectively), biological agents (21 patients), and 1 patient voted for methotrexate (MTX). Among those who admitted medical treatment prior to conception 46 patients (61.3%) discussed that with their rheumatologist. Patients with higher education more often admitted continuation of MT at conception than those with secondary specialized and secondary education ((29% vs 11.8%), and less frequently insisted on discontinuation of all MT (32.6% vs 45.6%), though the difference was not statistically significant in both cases. Patients with only secondary education more often found it hard to answer this question as compared to those with higher education (50 and 38.4%, respectively; p<0.05). The patients' attitude to the continuation of therapy during pregnancy planning and at conception was independent of age, AS duration, and marital status.

Of 137 pregnant women with AS only 91 (66,4%) saw a rheumatologist regularly during that time. The average number of visits to a rheumatologist during pregnancy amounted to 3,1±2,3, which meets the recommended number of 3,1±2,5 visits. A rheumatologist's opinion of AS therapy matched that of an obstetrician only in 56 (61,5%) women. 68 (74,7%) pregnant women discussed 'rheumatological' grounds for surgical delivery with their rheumatologist and 24 patients (35,3%) got similar recommendation from their obstetricians. 229 (75,8%) AS patients considered vaginal delivery as an option.

Regarding the AS therapy during gestation 302 respondents answered in the following way: 112 (37.1%) women insisted on discontinuation of all drugs, 69 (22.8%) allowed for the possibility of medication therapy, 121 (40.1%) were uncertain. Similar distribution of answers was observed among the patient group who saw their rheumatologist during pregnancy (n=91): 38 (41.7%), 26 (28.6%) and 27 (29.7%) respectively. According to 41 respondents (13,6% of all respondents and 59,4% of those in favor of MT) NSAIDs could be administered during gestation, 23 patients (7,6 and 33,3% respectively) admitted continuation of GC, 15 patients (5,0 and 21,7% respectively) admitted continuation of SSZ, 13 (4,3 and 18,8% respectively) admitted continuation of biological agents, and 1 patient (0,3 and 1,4% respectively) mentioned MTX.

Patients with higher education more often considered proceeding with AS therapy during pregnancy an option, as compared to women with secondary specialized education (27,2 and 8,8% accordingly; p=0,002). No link between age, duration of AS, marital status and attitude to the possibility of medication therapy during gestation was observed.

198 respondents left their comments regarding actual problems they faced up to when planning and during pregnancy. These problems can be subdivided into four main groups:

1. Difficulty in obtaining reliable information about the probability of AS inheritance, the effects of AS on maternal and fetal outcomes, safety of MT during pregnancy for mother and baby, and AS dynamics during pregnancy.

On one hand, this issue can result from the lack of available specialized rheumatological care in small towns and remote regions, and also from physicians' lack of time for a comprehensive conversation with their patients. On the other hand, (and patients consider it the primary cause) that can be accounted for by rheumatologists' insufficient competence in question of pregnancy planning and management in AS patients and appropriate therapeutic options during gestation.

2. No cooperation between rheumatologists and obstetricians as well as the latter's lack of knowledge of AS.

3. Physicians' lack of empathy, sympathy, attention and respect for their patients, as well as lack of support by their family members.

4. No professional psychological counselling.

Results. Most women with a confirmed AS diagnosis changed their views on pregnancy, but only 14% of them were ready to cancel their pregnancy plans due to AS. Less than a half of all AS patients saw their rheumatologist when planning pregnancy, with one third of them being unsatisfied with the recommendations. Only one in four patients admitted continuation of AS therapy while preparing for conception and during gestation. Their supervision by a rheumatologist did not impact their opinion of therapy options during this time. Higher education is a factor, that makes women adopt a more positive attitude to MT when planning and during pregnancy. The main problems women with

AS are facing at this time are difficulty in obtaining information and no interaction between rheumatologists and obstetricians.

2. A survey of female patients with AS: medication therapy during pregnancy in real clinical practice.

The aim was to assess the frequency of different types of medication therapy prior to and during pregnancy; the impact of discontinuation or changing NSAIDs administration on back pain management during gestation.

Patients and Methods. 86 pregnant women with AS who then had a delivery no early than 2015 took part in a questioning survey which was on from November 2016 up to September 2017. The time gap between delivery and participation in the survey was no more than 2 years, which helped to minimize the loss of information by the respondents. The survey form listed questions pertaining to the subjective evaluation of patient's health during pregnancy as well as to the medication therapy used 3 months prior to conception, during gestation by trimester and separately in the month of conception. Greater back pain intensity, relapse or beginning of arthritis, enthesitis, uveitis was viewed as worse health.

The respondents filled in the form during a visit or hospitalization to V.A. Nasonova Research Institute of Rheumatology or at the internet sites of public charitable disability organization 'The Society for Mutual Assistance in Bekhterev's disease'. The average respondent age was 34,0±5,8 years, an average AS duration was 120±73,5 months. The median of delivery date was 39 [38;40] weeks, an average body mass of newborns was 3241,1±484,6 gr., an average Apgar's score at 1 minute after birth was 7,6± 1.

Results. During pregnancy 58 (67,4%) women reported worsening of health at least during one of the three trimesters, with the 1st trimester accounting for 15 (17,4%), 2nd for 26 (30,2%), and 3d for 36 (41,8%) cases.

Increased back pain in the 1st trimester was reported by 10 patients (66,7% of those pointing out growing AS clinical activity), in the 2nd trimester by 22 (84,6%) patients, and in the 3d one by 26 (72,2%) respondents.

3 months ahead of pregnancy NSAIDs were taken by more women (63,4%) as compared with the month of conception (37,2%) and gestation (by trimester: 25,6; 34,8 and 9,3% accordingly; $p<0,05$ in both cases). At conception NSAIDs were discontinued by 41,8% of respondents, 60 % in the 1st trimester (as compared with treatment prior to pregnancy). Depending on the NSAIDs plan all patients were divided into two groups (Table 1): drug therapy 'on demand' (1st group) and continuous therapy (2nd group). Changes in frequency of NSAIDs regime were not revealed (3d trimester was removed from the analysis due to NSAIDs contraindication after 32d week of gestation.

Back pain tended to increase in pregnant women who discontinued NSAIDs or switched to an 'on demand' regime (65%) one month prior to conception, as compared to those who took NSAIDs on a daily basis. Patients, who took NSAIDs 'on demand' in the 1st trimester, were more likely to report worsening of health in the 2nd trimester (34,6%) as compared to those taking NSAIDs on a constant basis (18,2%). Besides, patients in the 1st group, as well as women, who did not take NSAIDs in the 1st trimester, more often complained of a back pain (54,6 and 53,1%) during gestation in comparison with patients in the 2nd group (36,4%). Those patients, who took NSAIDs 'on demand' in the 2nd trimester reported worsening backache during pregnancy in 83,3% of cases, and in 58,3% ($p<0,01$) of cases among those on a constant NSAIDs regime.

GC were mostly administered during pregnancy (16,3%; 20,9 and 22,1% in 1st, 2nd, and 3d trimester respectively), rather than prior to it (7%) and at conception (9,3%, $p<0,001$ in both cases).

Prior to pregnancy SSZ was taken by 14 (16%) women, at conception by 7 (8%) patients and during pregnancy by 3 patients (3,5%; $p<0,01$ in both cases). At conception SSZ was discontinued by 50% of respondents, by 85,7% in the 1st trimester (as compared to its use before pregnancy). Among those, who stopped taking the drug, only 1 (9%) woman registered more severe symptoms or new forms of arthritis during gestation.

Prior to gestation biological agents were administered to 11 (12,85) women, at conception (adalimumab – ADA, Etanercept – ETC) to 6 (6,9%) women, in the 1st and 2nd trimester to 2 patients (2,3%; $p<0,01$ in between the month of conception and the 1st and 2nd trimesters). At conception biological agents were discontinued in 45,5% of patients, and in the 1st trimester in the 81,8% of them (as compared to the treatment prior to pregnancy). After discontinuation of TNFα (tumor necrosis factor inhibitors α) during pregnancy planning or shortly after conception 81,8% of respondents reported worsening of health during gestation, with 100% of respondents in the 1st trimester, 63,6% in the 2nd, and 54,5% in the 3d. AS flaring included increased back pain (in all patients with worsening health), arthritis (27,3%) and uveitis (27,3) relapses.

Results. During pregnancy and the month of conception the number of women who took NSAIDs, SSZ, biological agents was lower as compared with the number before pregnancy. GC are more often administered when planning pregnancy and during gestation, rather than before gestation. NSAIDs discontinuation or switching to a 'on demand' plan in the 1st trimester was often

Table 1. NSAIDs regime in patients with AS prior to and during pregnancy (in %)

Regime	3 months prior to pregnancy	On the date of conception	I	II	III
Continuous therapy	23 (41,8)	12 (37,5)	11 (50)	12 (40)	2 (25)
'On demand'	32 (58,2)	20 (62,5)	11 (50)	18 (60)	6 (75)

associated with a higher frequency of back pain during pregnancy, yet on account of controversial data pertaining to the safety of non-stop NSAIDs regimen in the 1st trimester, changes to the therapy and administration of drugs with higher safety profile are needed.

3. A survey of rheumatologists: rheumatologists' competence in pregnancy planning and management of patients with AS.

The aim was to estimate the rheumatologists' awareness of AS effect on pregnancy duration and outcome, indications for surgical delivery and therapeutic options compatible with conception and pregnancy in AS patients.

Material and Methods. The study is based on the data collected by questioning survey of rheumatologists. The survey form contained 20 questions, pertaining to physicians' vision of the problem of AS impact on pregnancy duration and outcome, some aspects of delivery management in AS patients and factors requiring cesarean delivery, knowledge of the principles of medication therapy administration before and during pregnancy, personal experience in management of AS patients during pregnancy. 214 rheumatologists took part in an anonymous survey, which was conducted from May to December 2018, during educational activities held in different Russian regions. An average professional experience was 13,3±9,3 years. 115 (53,7%) physicians worked in clinical and diagnostic centers, 93 (43,5%) were hospital physicians, 6 (2,8%) respondents worked in educational and research institutions, with 18 (8,4%) respondents working part-time in different organizations.

Results. 76 (35,5%) respondents had their own experience of AS pregnancies management. Nearly all respondents – 209 (97,7%) answered positively to the question of chances of a safe gestation outcome in patients with AS.

According to the respondents, factors that determine a safe pregnancy outcome were ranked as follows:

1) Low AS activity at conception (weighted average is 4,9);
2) AS activity monitoring during gestation (3,6);
3) Regular visits to a rheumatologist (3,0);
4) Absence of comorbidity (2,9);
5) NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), biological agents (2,2) discontinuation and absence of evident changes in sacroiliac joints and the spine (2,2).

According to the physicians-respondents, spontaneous abortion (27 responses, 12,6%), premature birth (7 responses, 3,3%) and congenital abnormality (22 responses, 10,3%) are the most frequent negative outcomes for mother and baby.

18,2% of rheumatologists expected increase of AS activity during pregnancy.

According to the respondents, an AS patient must visit her rheumatologist 5,2±3,1 times on average during pregnancy. But actually, according to 76 physicians, with AS patients management experience, these patients see their rheumatologist 2,9±4,2 (Me 3 [1; 3]) times. 50 (65,8%) respondents happened to cooperate with an obstetrician on curation of pregnant AS patients. Most respondents (63,1%) assumed that their patients did not have an opportunity visit obstetrician and gynecologist with enough experience in management of pregnancy in AS patients.

When discussing issues relating to delivery details, the majority of respondents (82,7%) allowed for a possibility that women with AS may have vaginal delivery. According to physicians, 'rheumatological' indications for a surgical delivery include:

1) Sacroiliitis on X-rays –155 (71,5%) respondents
2) Active sacroiliitis on MRI – 69 (32,2%) respondents
3) Coxitis – 51 (23,8%) respondents
4) Extraarticular manifestations, including uveitis, – 15 (7,0%) respondents
5) Symphysitis – 12 (5,6%) respondents;
6) Endoprosthesis replacement, aseptic necrosis of hip joints – 9 (3,3%) respondents;
7) High AS activity – 4 (1,9%) respondents.

Regarding the grade of sacroiliitis that was a contraindication to vaginal delivery, rheumatologists' responses were as follows: 26,1% of physicians thought it could be any grade, 59,5% believed it to be grades III–IV, 14,4% of them mentioned only grade IV.

Therapy in pregnancy planning.

Most rheumatologists believed there was no need in therapy discontinuation (ranging from 45% to 63% depending on medication), except MTX, while planning pregnancy; 15–23% of physicians found it hard to answer if medication therapy may be continued when planning pregnancy. Nevertheless, 42 (19,6%) physicians thought it necessary to discontinue COX-2[1] nonselective NSAIDs (n- NSAIDs) 8,4±9,5 weeks prior to conception on average; 70 (32,7%) physicians thought COX-2 selective NSAIDs (s- NSAIDs) had to be discontinued 5,9±6,6 weeks prior to conception; 48 (22,4%) physicians thought so about SSZ 14,9±8,8 weeks before conception; 69 (32,2%) physicians insisted on discontinuation of biological agents 15,9±9,7 weeks prior to conception. 36 (16,8%) physicians allowed for MTX to be administered before conception, 45 (21%) physicians found it difficult to answer the question.

Depending on their professional experience, rheumatologists' answers showed that physicians who had been in the profession for more than 5 years were more likely to discontinue therapy when planning pregnancy, unlike those, whose professional experience was less than 5 years ($p<0,005$ in all groups of medications; Table 2). Moreover, physicians with greater experience were less undecided about medication therapy before pregnancy unlike their 'young' colleagues ($p< 0,05$). No discrepancy concerning time difference in medications discontinuation before conception in these physicians' group were observed.

Therapy during pregnancy

Physicians' opinion concerning therapy options in pregnant patients with AS during pregnancy is shown in Table 3.

On average 17,7% of rheumatologists were not sure about compatibility of MT, most doubts were concerning GC (33,7%) and SSZ (25,7%).

When comparing two groups of rheumatologists depending on their professional experience, no differences in their knowledge of necessity to discontinue or proceed with MT was observed.

Results. The survey showed physicians were aware of the factors that influenced optimal pregnancy outcome, of most common gestational complications in patients with AS and the basics of follow-up management of pregnant women. At the same time most of the respondents (72%), who allowed for a possibility of

[1]COX - cyclooxygenase

Table 2. Opinion of rheumatologists with different level of professional experience on medical treatment compatible with conception and pregnancy in patients with AS, n (%)

Drug	Professional experience <5 years (n=66)			Professional experience ≥5 years (n=148)		
	Therapy discontinuation	Continuous therapy	Not sure	Therapy discontinuation	Continuous therapy	Not sure
N- NSAIDs	6 (9,2)	43 (66,2)	16 (24,6)	34 (24,1)	87 (61,7)	20 (14,2)
S- NSAIDs	13 (20)	36 (55,4)	16 (24,6)	55 (39)	63 (44,7)	23 (16,3)
SSZ	8 (12,3)	45 (69,2)	12 (18,5)	38 (27)	89 (63,1)	14 (9,9)
MTX	29 (44,6)	17 (26,2)	19 (29,2)	102 (72,3)	18 (12,8)	21 (14,9)
Biological agents	11 (16,9)	36 (55,4)	18 (27,7)	56 (39,7)	59 (41,8)	26 (18,4)

Note. N- NSAIDs – non-selective non-steroidal anti-inflammatory drugs; S- NSAIDs – selective non-steroidal anti-inflammatory drugs; SSZ – sulphasalazine; MTX – methotrexate

vaginal delivery in women with AS, thought sacroiliitis could require surgical delivery. Low awareness of drugs administration during pregnancy planning among rheumatologists is evident: nearly one fifth of physicians do not see any need in drugs discontinuation prior to conception. Yet 20–32% of specialists are ready to discontinue drugs, that are compatible with pregnancy. No more than a half of rheumatologists are informed about therapy options during gestation: only 10–50% of physicians (depending on the type of medication therapy) consider administration of the medications, which are classified as relatively safe in Russian clinical guidelines [3] and EULAR guidelines. What is more, 4–13% of physicians are ready to continue medication therapy despite contraindication or lack of sufficient evidence base.

Discussion. Fertility in patients with AS does not differ from that of healthy women [1], though the number of pregnancies in women after the onset of AS decreases significantly, as compared with a period before the disease and with general population [2]. In our research we specified how AS diagnosis could change maternity plans (of note, some women were ready to get pregnant despite the disease symptoms manifestation but before the diagnosis was confirmed and a regular therapy started). Seventy percent of respondents said they would reconsider their pregnancy plans, with the majority (80%) allowing for a possibility of getting pregnant amid fears about their own health and the health of their child. 13,9% of respondents did not want to get pregnant because of the AS diagnosis irrespectively of already having children, born during a healthy life period, or absence of the latter. B. Mills et al have reported similar findings [5] in 154 women with AS in the USA: after AS diagnosis 11% of them refused to get pregnant, and 46% took a negative stance on their pregnancy plans.

Pregnancy outcomes and course of IIRDs during gestation are to a greater extent determined by the disease activity and the administered therapy, which means that pregnancy of such patients must be planned [3]. Yet, according to our data, only 50% of women discuss their pregnancy plans with their rheumatologist, with one third of them not getting enough information. We believe, the reasons for such incomprehensive interaction with a rheumatologist might result from poor family planning culture in Russia (no more than 60% of women [6] plan their pregnancy) and from limited availability of qualified rheumatological care and physicians' incompetence in questions of pregnancy management. All this undoubtedly enhances patients' doubts and their unmet need for knowledge about the course of pregnancy in AS and compatibility of medication therapy with pregnancy. Women try to find answers turning to other sources (Internet, other patients' opinion, physicians, not specializing in the disease, etc.). As a result, some patients decide to cancel maternity plans, and the majority of patients plan their pregnancy on their own, often discontinuing the all MT.

As the survey shows that only one fourth of patients consider proceeding with MT when preparing for conception and during gestation. Notably, among those, who admitted continuation of MT at conception, more than 60% consulted with their rheumatologist about pregnancy planning, but the fact of seeing a rheumatologist during pregnancy did not affect patients' knowledge about therapy options during this time.

Table 3. Rheumatologists' opinion of MT administration during pregnancy in AS patients.

Drug	Possibility of therapy		Necessity for discontinuation	Undecided
	n (%)	Pregnancy , week	n (%)	n (%)
N-NSAIDs	84 (39,4)	26,8 ±8,6	99 (44,4)	35 (16,3)
S- NSAIDs	28 (13,1)	25,9±9,9	153 (71,5)	33 (15,4)
GC	106 (49,5)	38,0±4,8	36 (16,8)	72 (33,7)
SSZ	61 (28,5)	38,1±4,0	98 (45,8)	55 (25,7)
MTX	4 (1,9)	25,5+13,4	187 (87,4)	23 (10,7)
INF	27 (12,6)	21,4±8,3	159 (74,3)	28 (13,1)
ETA	29 (13,5)	25,0±7,7	151 (70,6)	34 (15,9)
ADA	21 (9,8)	22,9±10,0	164 (76,7)	29 (13,5)
CZP	54 (25,2)	37,8±5,9	118 (55,2)	42 (19,6)
GLM	8 (3,7)	27,5±13,0	177 (82,7)	29 (13,6)
SEK	1 (0,5)	40,0±0	184 (86,0)	29 (13,6)
Paracetamol	41 (19,2)	36,7±7,5	133 (62,1)	40 (18,7)

Note. N- NSAIDs – non-selective non-steroidal anti-inflammatory drugs; S- NSAIDs – selective non-steroidal anti-inflammatory drugs; GC – glucocorticoids; SSZ – sulphasalazine; MTX – methotrexate; INF – Infliximab; ETA – etanercept; ADA – adalimumab; CZP – certolizumab pegol; GLM – golimumab; SEK – secukinumab.

Only 66% of patients saw a rheumatologist during pregnancy, and 42% of rheumatologists advised to discontinue all MT, which did not differ from the patient's view (37%). A lack of information about MT in patients, who saw a rheumatologist during gestation, indicates low patients' confidence in rheumatologists or their poor advice. Higher education was a factor which determined women's adherence to therapy before conception and during pregnancy, besides more educated patients often discussed pregnancy planning issues with their rheumatologist.

In real-world clinical practice the number of patients on medication therapy during pregnancy planning and gestation is somewhat higher than one expected after the first round of survey. Yet 41% of women discontinued NSAIDs prior to pregnancy, 60% did so in the 1st trimester (compared to NSAIDs regimen 3 months before pregnancy), 50 patients and 86% discontinued SSZ, and 46 and 86% did so with biological agents. According to the respondents, NSAIDs discontinuation or switching to an 'on demand' regimen in the 1st trimester and at conception was associated with increased acute back pain during pregnancy, biological agents discontinuation – with more acute back pain, arthritis relapses and uveitis. But drug administration during gestation is still a difficult decision both for physicians and patients. According to T. Haroun et al. [7], 50% of US patients with joint syndrome discontinue MT during pregnancy on their own or following their physician's advice, though the disease remains active in some women.

One of the main problems that pregnant AS patients have to face and that then diminishes their adherence to therapy is a lack of cooperation between rheumatologists and obstetricians, and as a result, their contradictory advice. Concerning AS treatment plan during gestation, the opinion of rheumatologist and obstetrician concurred only in 62% of cases. An absence of such approach of rheumatologists and obstetricians to MT before and during pregnancy is also reported in other countries. Thus, in 2013 in UK only 59% of rheumatologists and 70% of obstetricians were ready to continue SSZ therapy, and 7 and 15% were in favor of TNFα, and 0 and 3% approved MTX [8].

The problem of poor therapy adherence, and that is patient's compliance (drug regimen, diet and other life-changing measures) with physician's advice, is quite crucial in many chronic diseases, including IIRDs [9, 10]. Adherence requires cooperation of physician and patient based on the patient's awareness of their health and therapy benefits. Adherence to medication therapy is evaluated by the ratio of standard and administered dozes; 80% adherence is usually seen as an acceptable borderline. Currently more than 250 parameters that influence adherence are revealed, they can be classified into five main groups relating to [11]:

– Patient (age, education, social status, relations in the family, personal traits, etc.);
– Physicians (qualification, an ability to establish physician–patient relations based on trust, to spell out some details of condition and the necessity/safety of medications therapy);
– Health care system organization (available medical care and drug provision);
– Disease (severity, comorbidity, psychological reaction to the disease);
– Therapy administered (complex dosage regimen, adverse effects, large number of prescribed drugs).

According to E. Vangeli et al. [12], the main parameters, that determine adherence to therapy in IIRDs are psychosocial factors, which include relations of trust between a physician and a patient, a belief in the necessity of medication therapy, psychoemotional status, and availability of medical treatment. According to P. Arturi et al. [13], a decrease in adherence in AS and rheumatological arthritis (RA) did not depend on age, level of education, duration and progression of disease, what is more, therapy adherence in AS was lower than in RA. Similar findings were presented by P. Michetti et al. [14]: adherence to AS therapy was proved to be the lowest in comparison with a number of other IIRDs. Thus, adherence of AS patients to NSAIDs and biological agents was 28,7% (53% in RA patients and 49% in patients with psoriatic arthritis); adherence to TNFα inhibitors was 65% (no less than 70% in AS and PsA), which might result from underestimation of the severity of the disease by AS patients.

During pregnancy, with lack of confidence on a patient's part, regarding safety of medication therapy for fetus, one can expect even low compliance with rheumatologist's advice. It is noteworthy, that during pregnancy the main problems, listed by the respondents, matched those factors that decreased therapy adherence. That was poor access to relevant information about mutual influence of AS, pregnancy and therapy options in gestation, limited availability of qualified rheumatological care, lack of trust between patient and physician, low physicians' competence.

The revealed lack of trust in physicians served as one of the reasons for carrying out a survey among rheumatologists to verify their competence in pregnancy planning and management.

As our figures show, Russian rheumatologists have enough knowledge of pregnancy outcomes in AS, namely of factors that influence its optimal outcome, and about the basics of follow-up treatment and management of pregnant patients. Yet only 18% of respondents expect greater AS activity during gestation, though currently it is a common belief, that AS activity persists or grows in the II trimester. Unfortunately, more than 2/3 of physicians still adhere to an unproved viewpoint that X-rays confirmed sacroiliitis requires surgical delivery. Bearing in mind, that frequency of caesarian delivery in women with AS is higher than during healthy life period [2], a more serious discussion about 'rheumatological' reasons for surgical delivery in coordination with obstetricians is needed.

Despite EULAR Guidelines [4] published in 2016 and Russian clinical guidelines, published in 2017, medications therapy issues, when planning and during pregnancy, become a challenge for rheumatologists. Up to 30% of respondents are ready to discontinue medication therapy, allowed for pre-gestation period, when planning pregnancy. Moreover, physicians with more than 5-year professional experience more often recommend unreasonable discontinuation of MT. Hence, 22% of rheumatologist believe it is necessary to discontinue SSZ therapy 20 weeks prior to conception, on average, discontinue biological agents 16 weeks prior to conception. It is of interest, that according to 2013 data, 41 and 54% of British rheumatologists discontinued these drugs therapy when planning pregnancy [8].

The survey data analysis puzzled by a surprisingly low level of knowledge about MTX therapy in planning gestation, as nearly one-fifth of physicians does not see any reasons to discontinue therapy with this drug before conception. According to S. Panchal et al. [8] 100% of English rheumatologists discontinue MTX at that time.

No more than a half of all rheumatologists are informed about therapeutic options during gestation, with 18% of physicians finding it hard to answer the questions, the rest were confident in their knowledge. We want to stress, that physicians were not much informed about both 'new' medications and MT which was practiced in rheumatology for decades and was based on enough evidence to use it in pregnancy planning. 55–74% of respondents admitted the necessity of TNFα discontinuation during gestation, and only 10–25% of the respondents allowed for a possibility to proceed with therapy. Low awareness about biological agents is more likely down to the instruction to these drugs, except that for certolizumab, that says pregnancy is a contraindication to therapy, which is against clinical guidelines [3, 4]. It is of importance that only 40% of physicians are ready to administer N-NSAIDs, 45% of them are more likely to discontinue them, depriving AS pregnant women of therapy.

The respondents' opinion of SSZ is also a point of interest, as it is considered relatively safe during pregnancy, less than one-third of the physicians recommend its administration, and nearly half of them find its discontinuation compulsory. An approach to treatment with SSZ in real practice is controversial in different countries. Having analyzed the data of 12 years, concerning the tendencies in MT administration in patients with RD in the USA, 3 months prior to conception R. J. Desai et al. [15] revealed that the number of cases of basic NSAIDs administration decreases with more frequent use of biological agents, besides SSZ is discontinued during pregnancy in 65% of patients. Along with it, according to S. Van den Brandt et al. [16], who looked into the risk factors leading to acute spondylarthritis, all patients participating in the trial, who took SSZ at conception, proceeded with it during gestation.

Thus, the results of the study revealed that both AS patients and rheumatologists lack information about planning and course of pregnancy in AS, and about safety of medication therapy. To raise the standards of medical care, eliminate unjustified MT discontinuation by physicians and patients, to support patients of childbearing age in pregnancy planning and to increase the number of pregnancies monitored and managed by rheumatologists, we recommend to:

– pay more attention to pregnancy planning and management issues, to therapeutic options during gestation for AS patients at all stages of rheumatologists' education and training;
– develop leaflets and guidelines for physicians on how to deal with the issue;
– increase patients' awareness by organizing patients and family-members schools, publishing booklets on AS and pregnancy;

– Provide better access to specialized rheumatological care;
– Build trustful relations between physician and patients by means of competent, informative visits, allowing sufficient time for that [11];
– Put more effort in educating patients on such issues as AS duration in gestation, reasons for drug administration and its safety for woman and fetus;
– Raise effectiveness of multidisciplinary cooperation of rheumatologists, obstetricians and other medical specialists.

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