

Pregnancy in rheumatoid arthritis in Romania

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ABSTRACT

Background. The new therapies have enforced another approach regarding the success of a pregnancy in rheumatoid arthritis, in a sense of a decrease in the number of complications which may interfere with the fetal or maternal outcome.

Aims. The study aim is to evaluate fertility among female patients with rheumatoid arthritis, in Romania, having as secondary objectives to appraise the pregnancy outcome, in parallel with monitoring the activity of the disease, the relation with the postpartum flare, as well as following up on the evolution status of the fetuses.

Material and method. We have analysed a number of 38 female patients diagnosed with rheumatoid arthritis that have had at least one post-diagnosis obstetrical episode, for 23 of the patients we have done it retrospectively, and for 15 patients, prospectively. The study is multicentric and has been carried out between October 2012 and July 2015. The patient evaluation criteria include: the activity of the disease and the treatment management in the pre-conceptual stage; monitoring of the disease every trimester and adequate therapeutic intervention; postpartum reactivation of the rheumatoid arthritis in connection with the breast feeding and the control of the disease during pregnancy; teratogenicity and autoimmunity bearing risks over the product of conception; outcome of pregnancies and fetuses.

Results. The 38 women have had an average age at conception of 31.02 years, at almost 6 years from diagnose and we have obtained a number of 67 pregnancies with the following outcome: 31 births at term, 3 premature births, 12 elective abortions and 21 spontaneous abortions. The pregnancy has been planned in 47.77% of cases. Patients have been exposed during preconception as well as during pregnancy at synthetic and biological disease-modifying antirheumatic drugs.

During preconception, the activity of the disease was controlled for half of the patients, status that has been kept or improved during pregnancy and only 3 cases have shown a minimal reactivation.

The length of the pregnancies was about 34.94 weeks, the average weight at birth was of 2,668 grams. No foetal anomalies have been identified.

The postpartum flare has occurred after 9.7 weeks and in 9 of the patients we have not recorded an increase in the degree of activity of the disease.

Conclusions. The rheumatoid arthritis is not a contraindication to pregnancy, as the activity of the disease is controlled or partially controlled during the pregnancy with or without antirheumatic therapies, but the risk of an early postpartum relapse remain possible, the majority of pregnancies have a positive outcome.

Discussion. The data obtained in our country are in general superposable to the data found in the specialized literature. Giving good pre-conceptual counselling and having an efficient interdisciplinary management of pregnancies are the key elements for successfully covering this chapter in the life of our female patients.

Keywords: rheumatoid arthritis, pregnancy, fetal outcome, disease activity

INTRODUCTION

Rheumatoid Arthritis (RA) is a complex pathologic entity, especially due to complications that may be debilitating, to treatment that requires a high degree of compliance from patients, as well as to a large number of adverse effects that occur as a result of administering it. The long term results are satis-

factory, most of the times a favourable and sustainable therapeutic response is obtained.

Due to the fact that the onset of the RA is frequent in female patients during their fertile period, the association of this medical condition to pregnancy represents an important aspect and at the same time it is difficult to manage.

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If 20 years ago the rheumatology was first and foremost confronted with the issue of controlling autoimmune diseases, along with the occurrence of targeted therapies there was an increasing shift of focus towards the quality of life of these female patients and their family life and most of all their fertility have become one of the priority areas. The female patients benefit more and more from social and family lives close to the ones of the general population, as they may have a quasi-normal pregnancy outcome.

Although the pregnancies in RA seems to be easier to control, in some medical environments it is still maintained like a sensitive, taboo subject, because of the fear of possible complications difficult to manage.

In Romania or from Romania there are few published data on the pregnancy or fertility of female patients diagnosed with rheumatoid arthritis.

The success of a pregnancy first of all comes from planning: choosing the right moment of pregnancy, the disease has to be in remission or at a low level of activity over a period of at least 6 months, and the medication with a teratogen risk has been discontinued at the right time (1).

The pregnancies of patients with RA is considered at risk (2).

The issues are multiple, starting with the pre-pregnancy counselling and therapeutic preparation, fertility issues, possible complications of the pregnancy, the therapy during pregnancy, reactivation of the disease during pregnancy, the treatment during pregnancy, the birth, the postpartum relapse and the control of the disease's activity, the therapy during breast feeding (3).

For the duration of the pregnancy, as well as the breastfeeding, there are multiple therapeutic choices - for instance the use of approved synthetic as well as biologic DMARDs. Some medication cannot be administered, due to a lack of data rather than a proven teratogenicity.

Since now, it is considered that female patients with RA may give birth to healthy foetuses, as the disease may be kept under control in most cases. (3)

AIMS

The main purpose of the analysis is to evaluate the fertility of female patients with RA in Romania, having as secondary objectives the pregnancy and fetal outcome, in parallel with monitoring the activity of the disease during the pregnancy and postpartum.

Another important issue is to recommend the right moment for conception as a result interdisciplinary evaluation, with the purpose of minimizing the occurrence of potential peripartum and postpartum complications.

Another objective of the study is to quantify the improvement of the activity during the pregnancy. It is known from the literature to have had a decrease from 90% down to 48%, probably due to the good control of the disease in preconception and also using validated scores (4).

As far as the postpartum flare is concerned, the objective is to evaluate its correlation to the breastfeeding, as well as to the activity of the disease in the preconception stage, and in the first trimester of pregnancy.

Regarding the possible associated autoimmune pathology with risk on the pregnancy outcome, testing the antibodies anti-Ro(SSa), anti-La(SSb), antiphospholipidic, serum homocysteine, ATPO, TSH, free T4, are important objectives of the analysis, but with a secondary character.

The fetal outcome essential, especially in the context of unplanned pregnancies, with exposure to teratogenic medication.

MATERIAL AND METHODS

The analysed group was made up of 38 female patients diagnosed with RA (in accordance to the ACR modified criteria) that have had at least one post-diagnosis obstetrical episode. The study has been prospective for 15 patients and retrospective for 23 patients. The evaluation has been done multicentrically and has been carried out between October 2012 and July 2015. The patient evaluation criteria include:

- Preconceptional planning
- The activity of RA and the treatment management in preconception
- Monitoring of the disease activity every trimester and therapeutic approach
- Postpartum relapse in connection with breastfeeding and the control of the disease during pregnancy
- Teratogenicity and autoimmunity bearing risks over the product of conception;
- Pregnancy and fetal outcome;

In view of making a thorough and efficient analysis of the group, we have drafted a questionnaire that includes 42 items which represent, in detail, the parameters that start from the basic ideas of this study:

Age at inclusion in study, at diagnose, at conception, comportamental habits (smoker/alcohol consumption), the reproductive status before the diagnose, associated autoimmunity (Anti Ro and Anti La positivity), mother's comorbidities, the level of the activity of RA in preconception, during the pregnancy, in each trimester and postpartum, seropositive or negative status of the disease, the planning of the pregnancy, the medication in 12 weeks before conception, during the pregnancy and postpartum, during the breastfeeding, the biological therapy and the pregnancy, the outcome of the pregnancy: birth at term, premature birth, spontaneous abortion, elective abortion, intrauterine growth deficit, dead foetus, cesarian section or natural birth, the fetal anomalies, the direct teratogenicity, the birthweight, the length of pregnancy, the duration of breastfeeding, etc.

RESULTS

At the moment of being included into the group, the female patients had an age (average (interval)) of 39.51 years (26...60 years), at the moment of diagnosis of 24.91 years (14...39 years), while at the time of conception the age average was of 31.02 years (23...42 years). Therefore at approximately 6 years after the arthritis diagnosis, they have had at least one pregnancy.

The 38 analysed patients have had the rheumatic disease for a long time, with negative prognostic factors present and associated moderate disability: 35 of 38 (95.53%) have been seropositive (positivity of Rheumatoid Factor (RF) and/or Anti-citrullinated protein antibodies (ACPAs)); 7 patients were diagnosed with juvenile idiopathic arthritis; 31 of 38 have been considered to belong in the functional stages II- III, at the time of conception.

A percentage of 81.57% (representing 31 of 38) of the patients in the study were nulliparous at the time of diagnose, the majority of them were having a normal weight (BMI 21.11 kg/m²), with an average weight during preconception of 57.61 kg, for an average height of 165.18 cm.

The analysis of the personal behaviours of the patients has yielded that 10.44% (7 patients out of 38) smoke, the entire lot has denied any alcohol consumption and the majority of patients come from an urban environment 92.1% (35 out of 38 patients).

Although the number of patients with RA from Romania identified as having a history of obstetrical post-diagnostic is still low as an absolute value, the

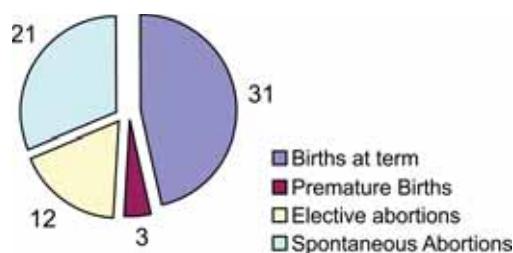


FIGURE 1. The pregnancies outcome in RA

number of associated comorbidities that may negatively influence fertility and the pregnancy outcome is significant, thus mentioning: 1 anti-phospholipidic syndrome, 1 secondary Sjogren Syndrome, 2 thrombophilia (heterozygote mutation with a normal serum homocysteine), 3 total arthroplasty of the hip (2 with bilateral prosthesis), 1 embolized uterine leiomyoma – with a time to pregnancy of 1 year), 2 Toxoplasmosis gondii, one minor talasemia, one autoimmune thyroiditis.

As a result of centralizing the results, we have obtained a number of 67 pregnancies: 31 births at term, 3 premature births, 12 elective abortions and 21 spontaneous abortions.

33 of 67 pregnancies have been unplanned (49.25%), this value thus explains the large number of abortions on demand related to the entire lot, accounting for 17.91%, motivated by the fact that the planned number of children was already reached, by fear of transmitting the disease and by the fact that the medication has a teratogenic potential. Other important factors that have contributed to the decision to give-up the pregnancy have been the disability and the increased activity of the disease at conception.

For the spontaneous abortions, we were able to identify a part of the elements with causative potential:

TABLE 1. Conditions with abortive potential

Toxoplasmosis Gondii
Thrombophilia
Associated anti-phospholipidic syndrome
Exposure in utero to abortive and teratogenic medication – Methotrexate, Leflunomide

Prematurity is present in a low percentage, of 4.47%, one of the three cases having a twin pregnancy with exposure to Leflunomide, up until the 16th week of pregnancy.

In case of the planned pregnancies, the synthetic medication has been discontinued in time, for the Methotrexate the recommendation being of at least

12 weeks, in the studied lot, this medication has been stopped with 42.85 weeks before conception (between 3 months and 3 years).

Regarding the Leflunomide, another drug with an insufficiently proven teratogenic effect, a wash-out period of up to 2 years is recommended, with serum monitoring of the concentration of Leflunomide, in the analysed patients the preconception interruption period has been ranging between 36 week and 9 months. The Sulfasalazine and Azathioprine are treatments compatible with the pregnancy, we have noted 2 cases with preconception discontinuation – 30 weeks for Sulfasalazine, and 12 weeks for Azathioprine, respectively.

In case of the biological therapies, for planned pregnancies a discontinuation has been done 2 years before the pregnancy for Etanercept (1 case) and 6 months before for Adalimumab. The recommendation for the anti TNF-alpha therapies is to stop the treatment when pregnancy is diagnosed (2 cases however have followed a treatment with Etanercept up until the second/third week of the pregnancy). As far as the Rituximab is concerned, the treatment has been discontinued 12 months before the planned pregnancy, in accordance with the recommendations of the EULAR Task Force on Pregnancy.

Due to the fact that only half of the analysed group have had a planned pregnancy, we shall describe the cases of exposure in utero to synthetic and/or biological medication less recommended:

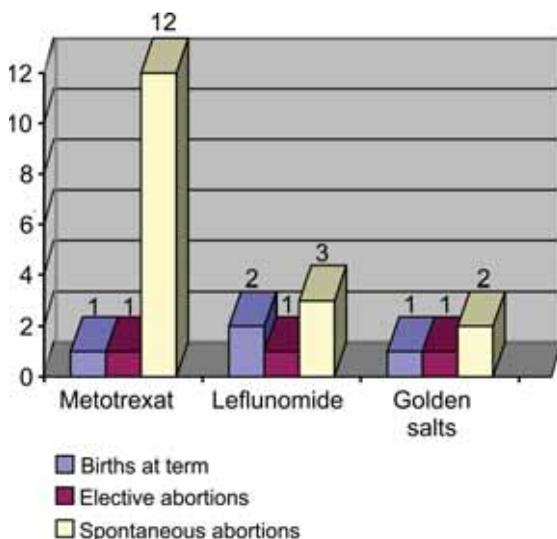


FIGURE 2. Unplanned pregnancies in patients with terathogenic risk medication

We have found for Methotrexate a high rate of spontaneous abortions however, 11 of the 12 spontaneous abortions with exposure to Methotrexate dur-

ing the first trimester of pregnancy have shown a cumulus of abortive factors (Toxoplasmosis gondii, Thrombophilia, insufficient control of the RA). At the same time, we must mention that the birth at term with preconceptional and gestational exposure of up to four weeks into the pregnancy to Methotrexate (10 mg/week) did not associate anomalies of the foetus.

In case of the Leflunomide, the two pregnancies with live foetuses have not associated fetal complications, one patient was the recipient of Leflunomide up until the seventh week of pregnancy (with birth at term), while for the second case the exposure has been done up to the 16th week (twin premature pregnancy).

TABLE 2. The outcome of unplanned pregnancies in patients treated with Rituximab

RITUXIMAB	
Moment of treatment – preconception	Evolution of the pregnancy
1 month	Birth at term
1 month	Spontaneous Abortion
5 months	Full Term Birth
6 months	Premature Birth

During pregnancy and preconception, 6 patients have been exposed to treatment with Sulfasalazine of which one has evolved into a spontaneous abortion, while the other 5 have had a positive outcome, the Sulfasalazine was administered up until the third trimester.

The second synthetic drug compatible with the pregnancy is Hydroxyclozoquine, 2 patients received it in preconception and up until the 20th week of pregnancy, with no fetal or maternal abnormalities detected.

Moreover, we need to mention that a part of the patients, especially from the retrospective group, have benefited at preconception only from steroidal or Nonsteroidal anti-inflammatory drugs, in some cases they have been continued into the pregnancy, without negative outcomes.

As we have described, the patients have several important comorbidities, so they received any treatment during the pregnancy. The both patients with Trombophilia (heterozygote mutations) and the patient with Associated Anti-Phospholipidic Syndrome were treated with Low Dose Aspirin (LDA) and Low Molecular Weight Heparin. The obstetrician recommended LDA starting with the 14th week of pregnancy to prevent the preeclampsia or eclampsia to one patient with low uterine artery and vein blood velocity and flow rate. The patient known with Autoimmune Thyroiditis received Levothyroxine.

The patient diagnosed with Secondary Sjogren Syndrome needed small dose Prednisone during the entire pregnancy in order to keep the disease under control (MDA) and to prevent the atrioventricular block (normal fetal cardiac ultrasound examination).

The activity of the RA improves in pregnancy, starting with the first trimester of gestation under the influence of hormonal factors, of the lymphocyte switch and transplacental fetal antigen passage.

In patients in remission or with a low activity of the disease (DAS28 CRP) the evolution has been to preserve the same status, except for 3 cases: one patient the remission has become Low Disease Activity (LDA), and for the other 2 patients the LDA has become MDA (Moderate Disease Activity). In patients with active disease (moderate or high) the trend is towards improvement to the clinical and biological parameters, but with a significant latency, the amelioration could be quantified starting with the second trimester of pregnancy.

A percentage of 29.41% (10 out of 34 patients) have shown a sustained amelioration of the activity of the disease during the pregnancy. The analyse was made only for the giving birth pregnancies.

Regarding the fertility of the patients, the time to pregnancy was in average of 17.91 weeks, the value is satisfactory, one of the patients participating in the study needed a repeated ovarian stimulation for a period of 2 years until conception.

In the context of the existence of 3 twin pregnancies identified in this analysis, we have had a total of 37 children, 34 parturitions for 32 women with RA that have given birth to live foetuses, 2 of the patients have had 2 pregnancies post diagnose.

The average pregnancy length was 34.94 weeks, with a minimum of 30 weeks and a maximum of 40 weeks and the mean birthweight was 2,668 grams, value ranging between 1,100 grams – the premature twin pregnancy and maximum 3,900 grams.

The RA activity ameliorates during pregnancy, however it may relapse early postpartum. We have identified 25 flares in the 34 parturitions (73.52%) with an average duration of disease reactivation of 9.7 weeks, a value correlated with the activity of the disease in preconception and during the pregnancy.

In some cases it was necessary to start Hydroxychloroquine or Prednisone during the lactation or to discontinue the breastfeeding in order to take Methotrexate, Leflunomide or biological therapies.

Of the 34 parturitions, 21 have been natural births, while for 13 of the patients the indication was

to have a Cesarean section, due to the associated comorbidities and mother's choice.

25 patients breastfed, in average for 22.72 weeks, with a minimum of 4 weeks and a maximum of 2 years. The mean duration of lactation for the entire lot was 16.7 weeks (approximately 4 months postpartum).

Due to the limited homogeneity of the lot, the foreseen result would be that the foetuses maintain this evolution pattern with an associated autoimmunity and malformations. Until the time of the study we did not identify any foetal anomaly linked to the treatment or to the disease, in any of the 37 live foetuses.

CONCLUSIONS

The results of the analysed group composed of 38 patients from Romania diagnosed with RA, support the conclusion that the pregnancy is allowed, that it associates with a small number of complications, that the disease has a tendency towards clinical and biological improvement during pregnancy, but, subsequently the patients relapse postpartum, in a variable duration or intensity.

Choosing the optimal moment for the pregnancy during the low activity or remission period of the disease is associated with a higher success of the pregnancies, with the recommendation to discontinue at the right time any potentially teratogenic medication. In conclusion, a good preconception planning is needed, ideally done after carrying out an interdisciplinary evaluation.

Identifying and treating associated comorbidities that may negatively influence the pregnancy and fetal outcome requires special attention for patients with RA or any other autoimmune pathologies.

No unfavourable outcome of pregnancies have been described, as there was a low percentage of prematurity. No fetal malformations was identified, even in the cases exposed to teratogenic medication periconceptionally.

DISCUSSION

The data obtained as a result of the study are in general lines superposable to the data found in the specialized literature.

In relation to the fertility and most of all the fecundity of the analysed patients, only 2 of the 38 women (5.26%) have had a prolonged time to pregnancy (one year), while according to a prospective study carried out in Holland on 245 women with RA planning a pregnancy, a subfertility of up to a year has

been noted in 42% of cases, being correlated to the activity of the disease and to medication. We have to mention that the analysed lot (in Romania) includes only patients with almost one obstetrical event (4).

The number of children is reduced in rheumatic diseases by comparison to the general population (5). Particularly, for this analysis, there is a high percentage of elective abortions, due to a lack of information regarding the contraception during the treatment with teratogenic risk or due to the fact that the proposed number of children was achieved

A percentage of 29.41% of the patients participating in the study (10 out of 34 patients) have shown a sustained amelioration of the RA activity during the pregnancy and the value is slightly lower than the internationally accepted actual percentage, of 48% (in the prospective PARA study) (6).

A percentage of 73.52% of the parturitions have had a new flare in postpartum, with an average duration of reactivation of the disease of 9.7 weeks (2 months and a half). The recent prospective studies have shown that the RA reactivates in a percentage of 49-62% during the first 6 months, the most cases occurring in the first 3-4 months in postpartum (7).

Identifying the associated autoimmunity is part of a good management of pregnancy in rheumatic diseases. The atrioventricular blocks appear in a percentage of 1-2% in foetuses exposed in utero to antibodies anti Ro, but echocardiographic monitoring and prophylactic medication decrease this percentage up to 0.3-0.6%, one third (8).

Regarding the biological therapies, the TNF-alpha inhibitors are recommended to be discontinued when the pregnancy test becomes positive. These medications have been classified as therapies with some risks over foetuses and they are not contraindicated in pregnancies (some of these not even in the third trimester), if they are necessary for the control of RA (9).

The preconceptual planning remains an essential first step to have a normal pregnancy and a controlled disease intrapartum and postpartum.

If the disease is active in preconception, it will require to treat aggressive and to postpone the pregnancy until at least 6 months of low activity or remission have passed. If the patient is treated with potentially teratogenic medication it will be necessary to replace it with drugs of the type Sulfasalazine, Hydroxychloroquine, corticotherapy, Azathioprine, drugs which are compatible with pregnancy. Once modified, the new therapeutic approach must be maintained for a minimum period of 2-3 months, in order to be able to prove the sustained remission until conception and during pregnancy (10).

The limits of the study are due to the small number of cases, once again we state that it has a national character and it is still in progress, to the lack of homogeneity – retrospectively and prospectively, to the variable ages of the patients at the time of their inclusion and/or at the time of conception, to the different therapeutic approaches of the Rheumatology and Obstetrics Gynaecology clinics in which they have been evaluated and treated.

This study aims to bring a new approach with regarding the pregnancy in patients with RA from Romania and to highlight the idea according to which pregnancy does not represent a contraindication among these patients.

The results obtained through this study support this hypothesis, according to which a good management of the disease prepartum and intrapartum, as well as a sustained interdisciplinary evaluation may lead to an increase in the success rate of pregnancy for patients with rheumatoid arthritis.

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