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MONITORING OF IMMUNOBIOLOGICAL PARAMETERS IN PREGNANT WOMEN WITH AUTOIMMUNE DISEASE AND THEIR CORRELATION WITH NEONATAL DISORDERS

PHD THESIS SUMMARY

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GENERAL PART

Achieving pregnancy in patients with chronic autoimmune inflammatory pathology has always been a challenging topic for rheumatologists, gastroenterologists, internal medicine doctors, obstetricians, neonatologists, and the patients themselves. Being limited by the therapeutic options, until recently, these patients were advised to avoid getting pregnant due to the high risks of complications, either of the underlying disease induced by the state of pregnancy or of the pregnancy-induced by the autoimmune disease. With the advent of new innovative therapeutic molecules and the advancement of medicine and interdisciplinarity, pregnancy has become a reality in patients with chronic autoimmune inflammatory disease [1]. However, pregnancy associated with autoimmune pathology represents a pregnancy with risk both from the obstetrical and fetal point of view, as well as from the point of view of the evolution of the disease, considering that reactivations or exacerbations of the disease can occur during pregnancy and in labor [2]. Also, maternal illness's impact on the newborn and maternal immunosuppressive medication on it is a separate topic, incompletely addressed in the specialized literature [3].

Predominantly affecting women of childbearing age, inflammatory autoimmune diseases bring with them the concern of affecting fertility in these patients [4]. Fertility can be influenced by the medication administered in order to control the underlying disease (for example, chronic treatment with non-steroidal anti-inflammatory drugs - NSAIDs is associated with the inhibition of ovulation by inhibiting cyclooxygenase 2 with the inhibition of the production of prostaglandins involved in breaking the ovulatory bridge; treatment with high-dose cortisone inhibits the hypothalami-pituitary-ovarian axis; cyclophosphamide in a cumulative dose of more than 7g causes ovarian toxicity), by the decreased sexual appetite due to chronic pain, dyspareunia, the feeling of vaginal dryness, and on the other hand due to the patient's fear of procreating because of the toxicity of the treatment, the risk of complications, the risk of affecting the child - a new concept used in the specialized literature as "voluntary infertility"[1,5]. Compared to the general population, patients with inflammatory autoimmune diseases tend to postpone the moment of pregnancy most of the time due to the instability of the disease or fears; on the other hand, with advancing age, the productive potential also decreases [6]. Another important aspect is the alteration of the uterine environment that these patients can associate thus, the appearance of an inflammatory environment at the level of the endometrium can negatively affect decidualization, implantation, and placentation, increasing the risk of abortion, preeclampsia, intrauterine growth restriction, premature birth [7].

Interdisciplinary preconception counseling aims to assess disease activity at least six months before conception (a high activity score is associated with complications), dosage of specific antibodies, assessment of the complete state of health on devices and systems, adaptation of the therapeutic protocol with replacement potentially teratogenic medication with medication compatible with pregnancy, training and informing the patient about potential complications, some life-threatening [5]. The direct involvement of sex hormones in the modulation of the immune response and autoimmune reactivity correlates with the onset of the disease and its stages of activity. Estrogens are the promoters of the inflammatory response, and androgens tend to have anti-inflammatory effects. Progesterone antagonizes the effects of estrogens having immunomodulatory and anti-inflammatory effects, causing an immune response mediated by TH2 lymphocytes and inhibiting the signaling pathway of interleukin 2, decreasing the TH1 immune response [8].

So, considering the hormonal involvement in the generation of the immune response and the fact that pregnancy behaves like a hormonal and immunological storm, knowing and understanding the immunological and physiological adaptations in pregnancy are fundamental to understanding the possible complications induced by inflammatory autoimmune disease. Thus, the increased hormonal levels during pregnancy can lead to an increase in the risk of disease relapse during pregnancy (for example, reactivations of lupus and inflammatory bowel diseases); on some diseases instead, pregnancy can have a protective role - in rheumatoid arthritis in most cases there is an improvement in symptoms [2,9]. Also, autoantibodies specific to autoimmune diseases can have effects on the product of conception by crossing the placental barrier: antiphospholipid antibodies are directly involved in the pathogenesis of recurrent pregnancy loss, fetal death in utero, are involved in the pathogenesis of preeclampsia; anti-Ro and anti-La antibodies can have devastating effects on the fetus by affecting the atrioventricular node and the occurrence of conduction disorders creating various degrees of atrioventricular block, they can induce the occurrence of neonatal lupus or fetal hydrops and even fetal death [9–14]. The pro-coagulant status induced by pregnancy in conjunction with the mechanical prothrombotic factors associated with pregnancy (compression given by the pregnant uterus, venous stasis, reduction of physical activity with increased rest in clinostatism) increases the thromboembolic risk in the pregnant patient; in this context and adding prothrombotic factors induced by autoimmune diseases (nephrotic syndrome, presence of antiphospholipid antibodies) this risk is exacerbated. At the same time, we must not lose sight of the risk of bone demineralization and osteopenia that occurs during pregnancy and which, added to an already

installed osteoporosis in a patient with chronic steroid treatment, can have serious consequences such as bone fractures and vertebral subsidence.

The new immunosuppressive medication shows its benefit in improving maternal-fetal prognosis and disease control [15]. The choice of the opportune moment of conception is the primary reference of the interdisciplinary approach to pregnancy in a patient with autoimmune diseases. Achieving pregnancy after stabilizing the disease and adjusting the medication by replacing the teratogenic medication with molecules allowed in pregnancy and breastfeeding leads to a quasi-normal maternal-fetal prognosis, similar to the general population[1,16,17]. Therefore, the customization of pregnancy planning and the multidisciplinary management of patients with the autoimmune inflammatory disease following the recommendations formulated by international experts and the strict monitoring of the pregnancy in experienced centers leads to a significant reduction of maternal-fetal complications while also improving the vital prognosis.

However, pregnancy in these patients remains a challenging subject burdened by possible maternal-fetal complications such as premature birth, intrauterine growth restriction, preeclampsia, and risk of fetal death in utero. The short- and long-term effects of newborns born to mothers with autoimmune diseases on specific immunosuppressive therapies are significant to autoimmune disease specialists, obstetricians, and neonatologists. In this sense, this paper wants to pioneer this field by bringing new, eloquent data and laying the foundations for the Romanian documentation of maternal-fetal effects and the neonatal impact of autoimmune diseases, correlating the maternal-fetal and neonatal prognosis with the activity scores of the included diseases in the study.

The main objective of this doctoral thesis is to identify the main risk factors for the occurrence of maternal-fetal complications and to correlate the status of the maternal disease with the evolution and possible complications of the newborn. The central working hypothesis is based on the confirmation of data from the specialized literature regarding the bidirectional impact between pregnancy and autoimmune disease.

The general part of this doctoral thesis is based on the presentation of the current state of knowledge of the included autoimmune diseases; this part is structured in an introductory part, with general information and the outline of the problem in the field and seven chapters in which the included pathologies are described in part from the point of view of epidemiological data, etiopathogenetic, the theme of fertility, preconception counseling, the clinical picture in pregnancy, description of the activity score, particularities of treatment, evolution and possible complications in pregnancy.

SPECIAL PART

The purpose and objectives of the study

This doctoral study aims to evaluate the mutual influences between autoimmune pathologies and pregnancy and determine their neonatal impact.

In order to achieve the proposed goal, a series of specific objectives were formulated:

1. Preparation of the study group with the registration of patients in an electronic database that includes all the parameters necessary for the research
2. Evaluation of the impact of pregnancy on autoimmune disease
3. Evaluation of the impact of autoimmune disease on pregnancy
4. Processing descriptive statistics data in the control group and making correlations with the study group, identifying risk factors of maternal and neonatal damage
5. Making clinical-biological correlations useful in diagnosis and critical data processing
6. Identifying and suggesting possible evolutionary patterns of the disease during pregnancy, peripartum, postpartum, pregnancy, and lactation
7. Correlation of disease activity in the preconceptual period and during pregnancy with the frequency of complications: premature births, intrauterine growth restriction, pregnancy-induced hypertension, preeclampsia, gestational diabetes, fetal death in utero/peripartum/intrapartum and such as and with neonatal complications.

General methodology

The present work was based on the anamnestic, clinical, and paraclinical data identified in the observation sheets of the patients from the Obstetrics, Gynecology, and Neonatology Clinic of the ELIAS Bucharest Emergency University Hospital, as well as on the analysis of the pregnancy medical records of patients with autoimmune diseases followed and treated in several Rheumatology Clinics in Bucharest (“Sf. Maria” Clinical Hospital, "Dr. I. Cantacuzino" Clinical Hospital) and the Gastroenterology Clinic of the ELIAS University Emergency Hospital during 2013-2019. We thus totaled a number of 70 cases that will be analyzed in this paper.

The methodological characteristics of the study based on which the research design was

established were:

- *Unicentric:* within the Obstetrics, Gynecology, and Neonatology Clinic of the ELIAS University Emergency Hospital, Bucharest
- *Retrospective:* data were collected in the period 2020-2021 for patients who were followed up between January 1, 2013, and December 31, 2019
- *Non-experimental:* it has not influenced either the therapeutic management of the autoimmune disease or the management of pregnancy
- *Descriptive:* described the study group following the proposed objectives
- *Correlational:* determined correlations between various parameters based on statistical analysis

The study group was established by querying the ELIAS University Emergency Hospital database and identifying patients who cumulatively meet the eligibility criteria, as well as by involving colleagues from the Rheumatology specialty from the following hospitals in Bucharest: Sf. Maria Clinical Hospital, Clinical Hospital " Dr. I. Cantacuzino" and from the Gastroenterology specialty at the ELIAS University Emergency Hospital with the provision of complete medical records of patients who met the eligibility criteria.

In addition to the study group that contains patients diagnosed with rheumatological autoimmune disease or inflammatory bowel disease before pregnancy, a control group was created that contained 995 patients with ongoing pregnancy, without autoimmune disease, and patients who were monitored in the department of Maternal-Fetal Medicine of the Obstetrics, Gynecology and Neonatology Clinic of the ELIAS University Emergency Hospital and who fulfilled similar characteristics to the study group in terms of demographics, anthropometrics, associated comorbidities, risk factors, and risk behaviors.

Based on the proposed purpose and the specific objectives established, the eligibility criteria were identified:

- Patients with rheumatological autoimmune disease or inflammatory bowel disease diagnosed before pregnancy according to the national guidelines in force
- Patients monitored in the Obstetrics Gynecology and Neonatology Clinic of the ELIAS University Emergency Hospital throughout pregnancy and postpartum evolution, or eligible patients who did not give birth in our maternity hospital but expressed their desire to participate in this study and made available the entire medical file: of the primary disease, of pregnancy, the maternity and neonatology discharge notes, as well as the medical documents

of the newborns from their first year of life

- Patients monitored in terms of the evolution of autoimmune rheumatological or inflammatory bowel disease throughout pregnancy
- The presence in the observation sheets or the medical files of all the necessary anamnestic, clinical and paraclinical information

In order to comply with the current regulations regarding the confidentiality of personal data, the collection of data, the creation of the database, and the presentation of the results were made anonymously.

Data collected included:

- DEMOGRAPHIC CHARACTERISTICS (age, education level, background)
- PERSONAL PHYSIOLOGICAL AND PATHOLOGICAL HISTORY (menarche, menstrual cycle, comorbidities)
- RISK BEHAVIORS (smoking, alcohol consumption)
- CLINICAL EXAMINATION (anthropometric indicators)
- CHARACTERISTICS OF AUTOIMMUNE DISEASE (diagnosis, evolution, staging of disease activity - was performed by the attending rheumatologist or gastroenterologist based on the activity scores specific to each pathology and was coded in the doctoral thesis as follows: 0 - remission, 1- low activity, 2- moderate activity and 3- set of increased activity of the disease, whereas for the antiphospholipid syndrome there is no activity score, patients with pure SAFL and ongoing pregnancy were assimilated to the 0 activity score assuming control of the disease; patients with SAFL associated with other pathologies were classified in activity scores specific to the associated pathology; treatment)
- CHARACTERISTICS AND EVOLUTION OF PREGNANCY (occurrence of complications: intrauterine fetal growth restriction, pregnancy-induced hypertension, preeclampsia, gestational diabetes, oligohydramnios, fetal distress, premature birth)
- THE RESULTS OF THE SCREENING ULTRASOUND ASSESSMENT FOR PREGNANCY ANOMALIES IN THE I AND III TRIMESTER
- DATA REGARDING THE BIRTH (gestational age at which it occurred, route of delivery, degree of urgency, intrapartum and postpartum evolution of the mother)
- DATA REGARDING THE EVOLUTION OF THE NEWBORN (immediate adaptation, admission to neonatal intensive care, need for ventilatory support, need for antibiotic therapy, the average duration of hospitalization, neonatal complications)

The study was carried out by complying with the rules in force regarding scientific research valid at the national level (updated Law 206/2004), as well as at the European level (The European Code Of Conduct For Research Integrity[18] as well as the Declaration of Helsinki[19]). The collection, manipulation, storage, and analysis of data, as well as the presentation of the results, were done in compliance with all regulations regarding the use of personal data (Law no. 190/2018, General Data Protection Regulation). The Grant of the Institutional Ethics Committee of the ELIAS University Emergency Hospital registered with the number 4491/23.06.2021 was obtained.

The statistical analysis that generated the statistical data, tables, and figures in the results section was carried out using the applications JAPS version 0.16.1 (JASP Team, 2021, https://jasp-stats.org), MedCalc version 20.022 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) and IBM SPSS Statistics version 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp, https://www .ibm.com/products/spss-statistics).

Results

Considering the purpose and aims of the study, it is appropriate to divide the results into two studies:

1. Descriptive presentation of the study group with follow-up during pregnancy, as well as in the postpartum period by creating statistical correlations between the activity of the autoimmune disease, preconception and pregnancy, and materno-fetal/ neonatal prognosis
2. Evaluation of the autoimmune disease impact on pregnancy complications risks and newborn follow-up by comparing the study group with a control group using anthropometric data, associated risk behavior, first and third-trimester screening from the point of pregnancy, and the newborn progress.

The central element of the study was the underlying autoimmune disease (rheumatological/ inflammatory) diagnosed with antepartum according to international diagnostic guidelines. The autoimmune diseases included in the study were: Crohn’s disease (7 cases-10%), systemic lupus (11 cases-14.28%), rheumatoid arthritis (25 cases-35.71%), Sjögren’s syndrome (6 cases-8.57%), ulcer-hemorrhagic colitis (9 cases-12.85%), antiphospholipid syndrome (2 cases-2.86%), ankylosing spondylitis (8 cases-11.43%), Sjögren’s syndrome associated with antiphospholipid syndrome (2 cases-2.86%) or with systemic lupus (1 case-1.43%). The selection of the pathology included was based on similarities in terms of disease, progression pattern, underlying treatment, and pregnancy

impact. The disease evaluation was performed according to the activity scores of each disease and later translated into a common scoring system, as follows: 0 activity score- remission, one activity score- the low activity of the disease, two activity score - the moderate activity of the disease, three activity score- the high activity of the disease. Since there is no activity score for antiphospholipid syndrome, patients with primary antiphospholipid syndrome and ongoing pregnancy were assimilated to a 0-activity score, while patients with antiphospholipid syndrome associated with other pathologies were noted according to associated pathology activity scores.

Study 1

In the first study, descriptive analysis was performed on the study group, and the bidirectional impact of pregnancy on the autoimmune disease was investigated. The analyzed data were: demographic data, anthropometric data, associated risk behaviors, autoimmune disease follow-up, and treatment data, follow-up pregnancy according to first and third-trimester screening data, occurred complications, birth options, and newborn development.

Regarding the age of autoimmune disease diagnosis, *Table 1* and *Figure 1* show the age of diagnosis between 12 and 32 years, with a mean of 23.73 years and a deviation standard of 5.09 years. Most patients were diagnosed after age 20; during the fertile window, the distribution curve deviated to the right.

Table 1- Descriptive statistics regarding the age of diagnosis of the underlying autoimmune disease

Descriptive statistics

	Age of diagnosis
Valid	70
Absent	0
Medium	23.73
Median	25.00
Standard deviation	5.09
Minimum	12.00
Maximum	32.00

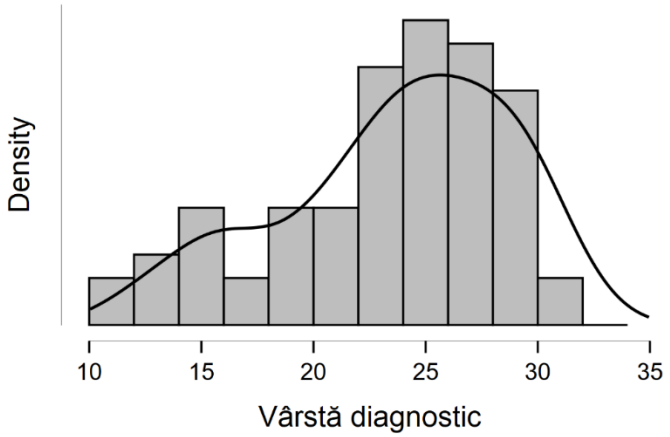

Figure 1- Patients' distribution according to the age of autoimmune disease diagnosis

At the time of delivery, the patient's age ranged from 19 to 43, with a median of 32 years. The maximum number of cases was between 30-35 years range with a number of 35 cases *(Figure 2).*

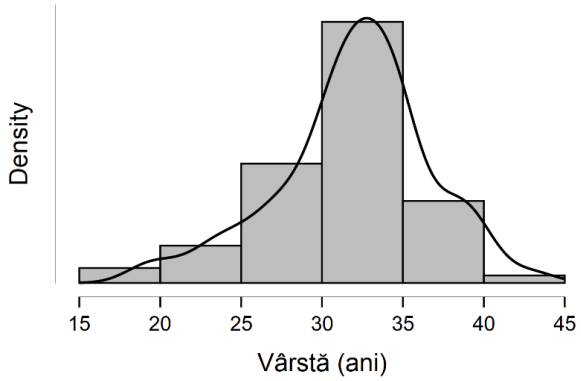

Figure 2- Case distribution by age

Most of the patients included in the study had a high degree of schooling: 6 completed only the high school cycle, 39 completed university studies, and 25 completed postgraduate studies (*Figure 3*). Analyzing patients' distribution according to BMI, a maximum number of cases was found between the BMI value of 20-25 (41 cases) (*Figure 4*).

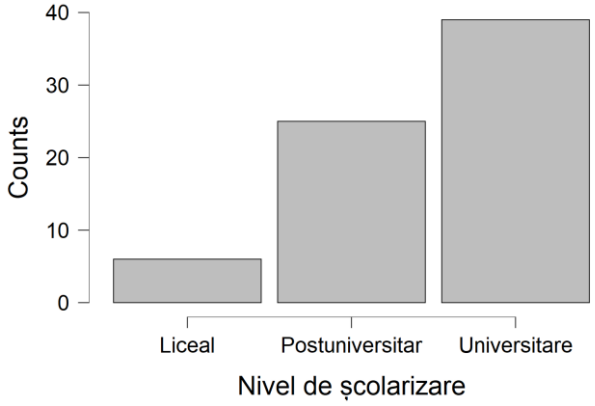

Figure 3- Case distribution according to schooling level

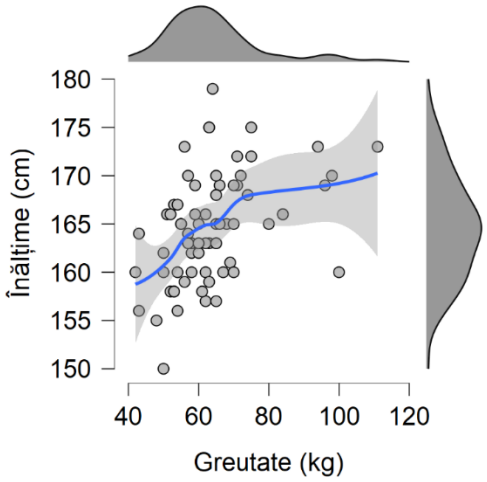

Figure 4- Patients' distribution according to height (cm) and weight (kg)

Spontaneous pregnancy was obtained in most cases (78/ 80 cases) (97.14%), while a small proportion- 2 out of 70 required an assisted human reproduction technique. Another essential element is pregnancy planning; 54 of 70 cases (77.14%) carefully planned the pregnancy at a time of remission.

During pregnancy, included patients had a weight gain between 5 and 30 kg with an average of 12.4 kg.

The period from autoimmune disease diagnosis moment to pregnancy was with a mean value of 8.05 years, with a range of 1 to 19 years and a standard deviation of 4.84 years. From the last autoimmune disease relapse perspective, the mean value was 13.84 months with a standard deviation of 13.49 months and a range between 0-84 months (*Figure 5*).

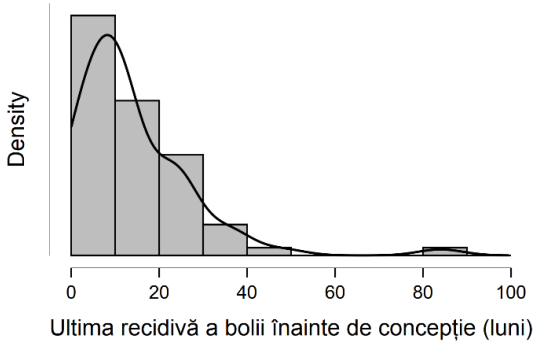

Figure 5- Patients' distribution according to last autoimmune disease relapse

Regarding the treatment used to control the disease in patients included in the study, it can be observed a tendency toward new, innovative medication which can have a high safety profile according to disease progression, but most importantly, in terms of safety during preconception and

in pregnancy. Therefore, in addition to classical synthetic antirheumatic molecules (DMARS) and corticosteroids, biological therapies are increasingly common (*Table 2* and *Table 3)* both in preconception and during pregnancy. The new biological molecules with unique features which do not cross the placental barrier ensure reasonable disease control in the third trimester because, until recently, there was no option to continue treatment after the second trimester (*Table 4).*

Table 2- Cases' distribution according to followed treatment

Medication	Preconcepțion	I Trimester	II Trimester	III Trimester	Postpartum	Total number of pacients
DMARS	34	23	22	24	10	70
Biological treatment	35	26	21	8	28	70
Corticotherapy	9	10	9	17	5	70
Anticoagulant therapy	4	6	6	6	5	70

Tabele3- Used DMARS treatment options

DMARS	Preconcepțion	I Trimester	II Trimester	III Trimester	Postpartum
Plaquenil	15	16	15	15	7
Sulfsalasine	9	7	7	9	2
Methotrexate	7				1
Plaquenil+Methotrexate	3				
Total	34/70	23/70	22/70	24/70	10/70

Table 4. Types of biological medications used by patients included in study

Biological medications	Preconcepțion	I Trimester	II Trimester	III Trimester	Postpartum
Etanercept	10	4	-	-	6
Adalimumab	7	7	8	1	7
Infliximab	7	7	6	1	6
Certolizumab pegol	6	8	7	6	8
Golimumab	1	-	-	-	-
Rituximab	2	-	-	-	1
Tocilizumab	2	-	-	-	-
Total	35/70	26/70	21/70	8/70	28/70

During pregnancy, a series of complications occurred: pregnancy-induced hypertension (16/70 cases) (22.85%) diagnosed between week 25 and 34 of gestation (*Tables 5 and 6*), gestational diabetes (4/70 cases representing 5.71%), preeclampsia (4/70 representing 5.71%). Intrauterine fetal

growth restriction was identified in 21.42% of patients (*Tables 7 and 8*), 17.1% of cases developing a tardive form diagnosed after 32 weeks of gestation (Figure 6), and oligohydramnios was seen in 6 patients (8.57%).

Table 5- Cases distribution according to pregnancy induced hypertension

		Frequency	Percentage	Valid percentage	Cummulative percentage
Valid	No	54	77.1	77.1	77.1
	Yes	16	22.9	22.9	100.0
	Total	70	100.0	100.0	

Table 6- Cases distribution according to presence of pregnancy induced high blood pressure and moment of diagnosis gestational age (weeks)

No	54	77.14%
25 weeks of pregnancy	4	5.71%
26 weeks of pregnancy	1	1.42%
28 weeks of pregnancy	6	8.57%
30 weeks of pregnancy	2	2.85%
32 weeks of pregnancy	1	1.42%
33 weeks of pregnancy	1	1.42%
34 weeks of pregnancy	1	1.42%
Total	70	100.0%

Table 7- Cases' distribution according to intrauterine growth restriction

		Frecquency	Percentage	Valid percentage	Cummulative percentage
Valid	No	55	78.57	78.57	78.57
	Yes	15	21.42	21.42	100.0
	Total	70	100.0	100.0	

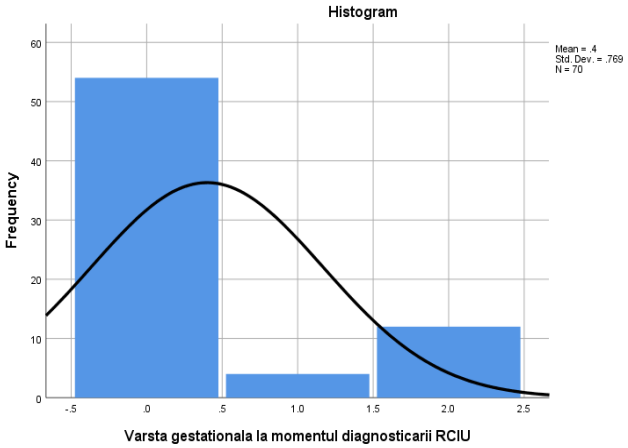

Figure 6- Graphic representation of cases' distribution (intrauterine growth restriction) according to diagnostic moment

There were 23 cases of autoimmune disease relapse during pregnancy; table 8 shows the percentage of cases according to the activity score of the underlying disease in 5 moments of pregnancy evolution: preconception, the three trimesters, the postpartum period. Most patients were in remission or had a low activity disease at the time of conception (64/70 cases representing 91.42%) and in the first trimester (65 cases). However, later in the pregnancy, the number of patients in remission decreased, suggesting a new relapse: 57 cases in the second trimester, 53 cases in the third trimester, respectively 36 cases in the postpartum period (*Table 9 and Figure 7*).

Table 8- Cases' distribution according to recurrence of underlying autoimmune disease during pregnancy

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no	47	67.1	67.1	67.1
	yes	23	32.9	32.9	100.0
	Total	70	100.0	100.0	

Table 9- Cases' distribution according to underlying autoimmune disease activity score

	Remission	Low	Moderate	High
Preconception	40	24	5	1
T1	37	28	5	0
T2	35	22	11	2
T3	33	20	10	7
Postpartum period	19	17	20	14

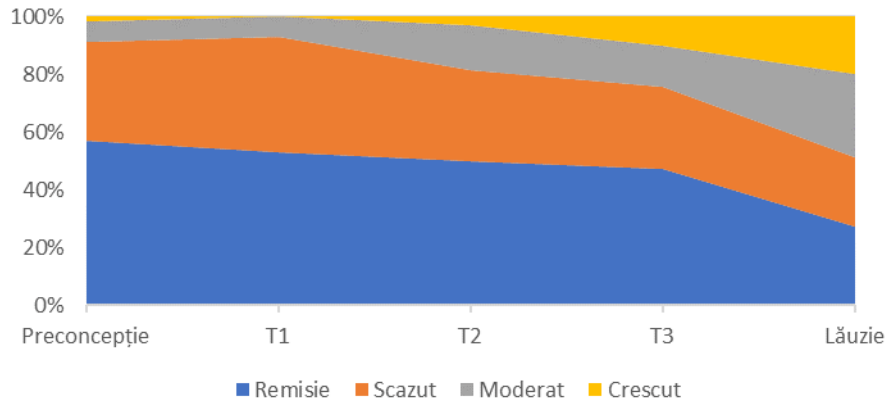

Figure 7- Worsening process of underlying autoimmune disease during pregnancy

Correlating the occurrence of fetal distress at birth, it was observed that it occurs more frequently in cases where underlying autoimmune disease worsened during pregnancy (7/8 cases); only one case of fetal distress occurred in a patient in remission. In the case of patients who gave birth to newborns without fetal distress, a number of 34/62 cases worsened during pregnancy. Thus, women whose newborns presented fetal distress at the time of birth had a risk of worsening the disease five times higher; however, the statistical significance is modest (OR 5.76, p=0.111) (*Figure 8*).

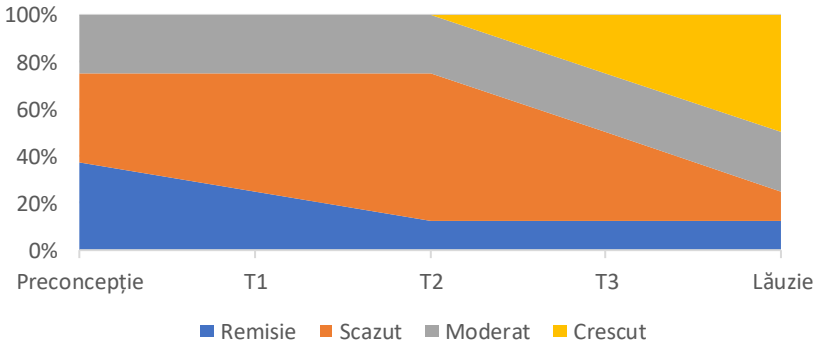

Figure 8. Dynamic percentual distribution of cases based on immune disease activity score in patients with fetal distress

Analyzing the cases from the perspective of the gestational age at which the birth occurred, we can observe the association of preterm birth (defined as birth before 37 full weeks of gestation) with an aggravation of the underlying autoimmune disease in 6 out of 9 cases (66, 66%), thereby in the group of patients who gave birth on term, the ratio of patients in whom the underlying disease relapsed during pregnancy was 27/61 cases (44.26%). Therefore, women who gave birth prematurely presented a more than 2.5 higher risk of aggravating form of the disease; however, this observation has no statistical significance (OR 2.51, p=0.219) (Figure 9).

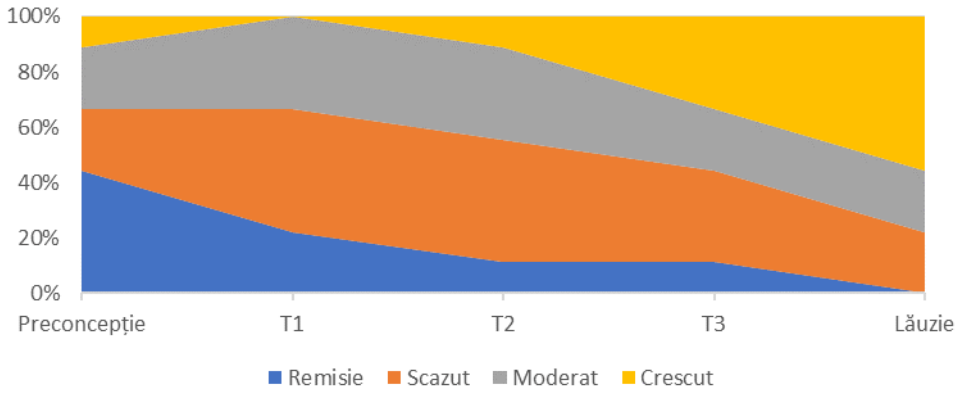

Figure 9. Dynamic percentage distribution of cases in correlation to the activity score of the underlying autoimmune disease for patients who gave birth prematurely

Furthermore, when analyzing the impact of the underlying autoimmune disease measured by the activity score in preconception, during the three trimesters of pregnancy, and in the postpartum period, the following statistical correlations were established. A disease activity score > 1 in preconception increases the risk of recurrence during pregnancy by 2.967 times (OR=12.778, CI95% = 1.395-117.074; RR= 2.967, CI95% = 2.829 – 3.105), in the second trimester this risk increases by 2.257 times (OR=17.333, CI95% = 1.902 -157.999; RR = 2.257, CI95%= 2.076 – 2.438), similar risk being identified for the third trimester (OR=11.25, CI95%=2.004-63.168; RR=0.453, CI95%=2.013-2.403). Moreover, a score = 1 or the lack of disease activity before conception has a beneficial, protective role, as these patients will not relapse during pregnancy (RR = 4.313, 95%CI = 0.716 – 25.978). An activity score = 1 during the second trimester of pregnancy is associated with the absence of acute recurrences of autoimmune diseases for the remaining period of the pregnancy (RR = 7.682, 95% CI = 1.132 – 2.131); the degree of this association decreases if the activity score = 1 is recorded during the third trimester (RR = 5.100; 95% CI = 1.322 – 19.675). Patients with an activity score > 1 compared to those with an activity score = 1 in the second trimester have a 2.257 (95% CI = 2.076 – 2.438) higher risk of disease recurrence during pregnancy. Moving on to the analysis of the impact of the activity score at the beginning of the third trimester of pregnancy on the risk of relapse (OR = 11.250 95% CI = 2.004 - 63.168), a value of 1 is associated with the absence of relapses (RR = 5.100 95% CI = 1.322 – 19.675) compared to a score > 1. However, the activity score > 1 at the beginning of the third trimester of pregnancy is associated with a risk of recurrence in the last part of the pregnancy (RR = 2.208 95% CI = 2.013 – 2.403).

The risk of adverse events during pregnancy is correlated with the disease activity score in preconception, first trimester, second trimester, and third trimester. Therefore, an activity score in

preconception with a score > 1 increases almost 6 times the risk of pregnancy complications (OR = 11,000 CI95% = 1,271-95,178; RR = 5,988, CI95% = 5,856 - 6,120), and a score ≤ 1 in this period has a slight protective role against adverse events during pregnancy (RR = 1.833 CI95% = 0.816 – 4.118). An activity score > 1 in the first trimester will increase the risk approximately 8 times (OR = 19.500, CI95% = 1.964-193.639; RR = 8.403, CI95% = 8.310 – 8.496), while values ≤ 1 of this score have been associated (RR = 2.321 CI95% = 0.790 – 6.825) with the absence of adverse events during pregnancy. Starting from the second trimester, the relevant threshold value of the activity score is 2. Activity score values > 2 in the second trimester are associated (OR = 7.250 CI95% = 0.375 – 140.245) with adverse events in pregnancy (RR = 4.132 CI95% = 3.936 – 4.328), there still being an association between scores ≤ 2 and the absence of such events, but the intensity of this association is beginning to decrease (RR = 1.758 CI95% = 0.437 - 7.068). The association between the score > 2 becomes stronger (OR = 10.500 CI95% = 1.321 – 83.490) if such scores are registered in the third trimester, when the risk of adverse events increases (RR = 6.410 CI95% = 6.286 – 6.534), and the risk value associated with scores ≤ 2 decreases (RR = 1.633 CI95% = 0.854 – 3.124).

Comparing the disease activity score in preconception, first, second and third trimesters, the highest risk of emergency delivery identified in the study batch was in the patients who had a disease activity score > 1 in the first trimester, followed by those who had the same score in preconception (OR=13.778, CI95%=1.635-116.122; RR=0.115 versus OR=5.464, CI95%=0.839-35.968; RR=0.214); the patients with an activity score > 2 in preconception were associated with 17.24 times higher risk of emergency delivery (RR=0.058). An activity score > 2 in the third trimester increases the risk of preterm birth and/or emergency delivery by 4.5 times (OR=13.250, CI95%=2.249-78.069; RR=0.222, CI95%= 0.106-0.464%).

Out of the 70 patients included in the research, 50 (71.43%) gave birth by Caesarean section, and the remaining 20 (28.57%) had a vaginal delivery (*Figure 10*). From the perspective of gestational age, the delivery occurred for all patients between the 34th and 40th week, with a median value of 38 weeks. Among the 15 cases of premature births (under 37 weeks of gestation), 10 cases were iatrogenic premature births, the birth being indicated by a maternal indication (*Table 10*).

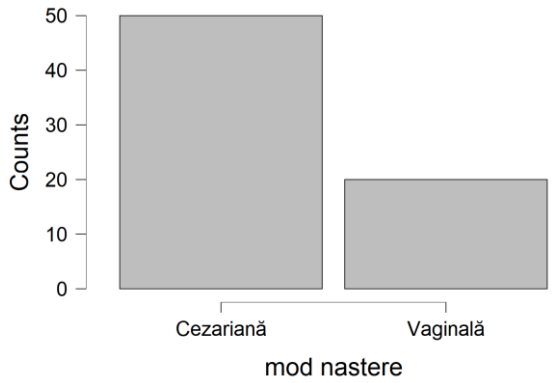

Figure 10. Type of birth

Table 10. Reasons of preterm birth

		Frequency	Percent	Valid Percent	Cumulative percent
Valid	NA	55	78.6	78.6	78.6
	Mother related	10	14.3	14.3	92.9
	Fetal related	5	7.1	7.1	100.0
	Total	70	100.0	100.0	

The evaluation of immediate adaptation to extrauterine life was performed using Apgar Score with possible values between 6 and 10 points, with a maximum number of cases obtaining Apgar 9 – 47 cases (67.14%), followed by the cases which obtained Apgar 10 – 14 cases (20%). Among the total 70 cases, a number of 8 cases exhibited fetal distress during delivery representing 11.4%, obtaining Apgar ≤8 and a fetus who was born dead, the death occurring a couple of days before based on the skin desquamation, in this case, the Apgar score is 0.

The Apgar score, which indicates the immediate adaptation to extrauterine life, was correlated in this study with disease activity during preconception and the first trimester. Thereby, a score higher than 1 in the first trimester, raises the risk of an Apgar Score <8 by 12.8 times (OR=20,667, CI95% =2,121-201,410; RR=12,821, CI95% = 12.757 - 12.885), while a score higher than 1 during preconception has a weaker association (OR=15,250, CI95%=1,680-138,408) with a lower risk than the predecessor; RR=10.526, CI95% = 10,447 – 10,605).

An objective parameter of newborn evolution is the need for admission into the neonatal intensive care unit (NICU) and the time they spend in this department. Thus, from the total of 69 live newborns, 12 cases (17.39%) required hospitalization in the INC unit, from which 2 cases (2.89%) required orotracheal intubation with mechanical ventilation. The two newborns required respiratory support for 3 and 5 days. The number of days spent by the neonates in the NIC unit varied from 1 to

11 days, with an average of 2.58 days, with a maximum number of cases – 9, spending only one day in NICU (*Table 11*).

Table 11. Cases distribution related to the period spent in the intensive neonatal care unit

NICU days	Frequency	Percent	Valid percent	Cumulative percent
0	57	82.61	82.61	82.61
1	9	13.04	13.04	95.65
4	1	1.45	1.45	97.10
7	1	1.45	1.45	98.55
11	1	1.45	1.45	100.00
Total	69	100.00		

Admission into the intensive neonatal care unit was also correlated with disease activity during the first trimester and preconception. Thereby a score higher than 1 before conception is associated (OR=13,750 CI95%=2,157-87,651) with a risk of admission into intensive neonatal care unit for at least 24 hours (RR = 5.263 CI95% = 5,154 – 5,372). Higher than 1 scores during the first trimester raise the association with admission risk into neonatal intensive care unit (RR = 6,410 CI95% = 6,325 – 6,495).

From the perspective of hospitalization days, most cases – 34 from 69 (49.27%), were hospitalized for three days after birth. During hospitalization, 21 neonates (30.44%) needed antibiotic therapy, while for the rest of the 48 cases, antibiotic therapy was not necessary (*Figure 11*).

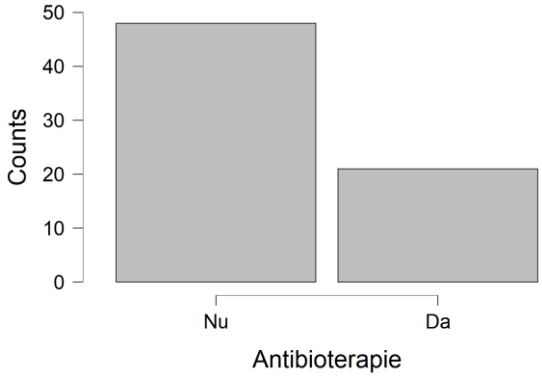

Figure 11. Distribution of cases concerning antibiotic therapy during hospitalization

Statistic correlations were also identified between activity scores during the first trimester and newborn hospitalization period or the necessity of antibiotic therapy. Thus, during the first trimester (OR=11,059, CI95%=1,154-106,023), a disease activity score higher than 1 is associated

with antibiotic therapy (RR = 3,012 CI95% = 2,863 – 3,161), while a disease activity score lower than 1 is associated with the lack of necessity for antibiotic therapy (RR = 3.672 CI95% = 0.632 – 21,326). Scores higher than 1 during the third trimester is associated (OR=4,900, CI95%=0,747-32,123) with a hospitalization period longer than 5 days (RR = 3,012 CI95% = 2,863 – 3,161).

Of the total of 69 newborns, 8 (11.59%) had to be hospitalized during the first six months, 7 (10.14%) of them presented respiratory infection (2-2.89%) or urinary infection (5-7.24%), and 1 of them presented anemia (1-1.44%). Of 7 neonates who needed hospitalization for various infections during the first six months postpartum, six had repeated infections. They needed at least one more hospitalization during the first year of life. (*Tabel 12*).

Table 12. Distribution of cases based on hospitalization during the first six months

Hospitalization during the first 6 months	Frequency	Percent	Valid percent	Cumulative percent
No	61	88.41	88.41	88.41
Yes	8	11.59	11.59	100.00
Lack	0	0.00		
Total	69	100.00		

According to neonate growth charts, the distribution of cases showed a number of 4 cases (5.8%) with a development below the 50th percentile. In contrast, the rest of the cases – 65 (94.20%), presented an average growth during the first six months of life (*Tabel 13*).

Table 13. Distribution of cases according to neonate growth charts during the first six months of life

Growth chart during the first 6 months	Frequency	Percent	Valid percent	Cumulative percent
Normal	65	94.20	94.20	94.20
Below 50^{th} percentile	4	5.8	5.8	100.00
Lack	0	0.00		
Total	69	100.00		

The first study included, evaluated, and described screening evaluations for fetal anomalies in the first and third trimesters; these were further used in the second study for comparative analysis with the control group.

Study 2

In the second study, we evaluated the impact of the autoimmune disease over pregnancy and the evolution of the fetus and newborn through comparison between the study group and control group based on anthropometrical dates, associated risk behaviors, screening evaluations during the first and third trimester, pregnancy complications and evolution of newborn.

Comparative analysis of the two groups from a patient age perspective showed similar average values – 31.02 years in the control group, respectively 31.95 years in the study group, without a statistically significant difference in averages. (*Figure 12*)

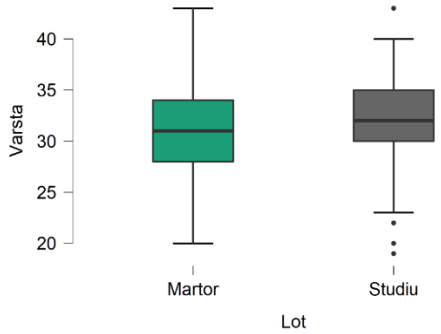

Figure 12. Descriptive chart comparing age between the two groups

Statistic data for the two groups regarding body mass index showed similar values regarding their averages (23.09 vs. 23.50) without a statistically significant difference, the two groups being comparable from the perspective of case distribution. (*Figure 13)*.

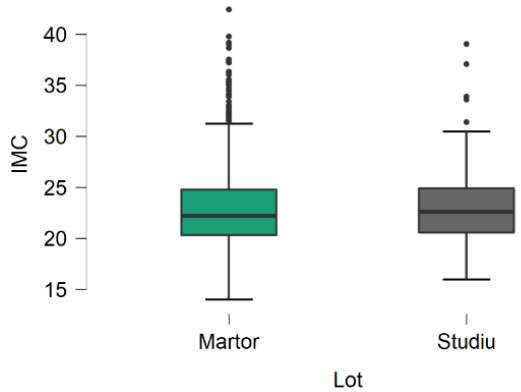

Figure 13. Descriptive stats showing the average body mass index of the two groups

In the study and control groups, natural conception represented the majority standing at 97.14% and 94.87%, without a significant statistical difference. Mean blood pressure, which was evaluated during the first trimester, showed comparable average values between the two groups (86.13 mmHg in the control group vs. 87.24mmHg in the study group and a standard deviation of 7.05mmHg for the control group and 7.27 mmHg for the study group), the difference bearing no significant statistical difference which as a result showed similarity between the two groups. (*Figure 14*).

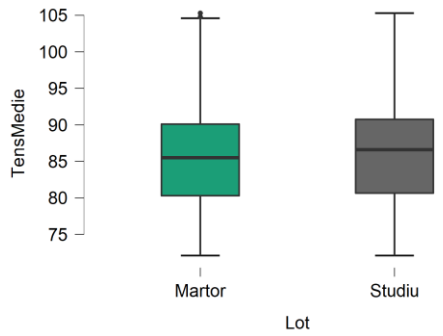

Figure 14. Descriptive chart comparing mean blood pressure between the two groups

Screening evaluation during the first trimester was based on combined screening, and maternofetal practitioners only performed it. The trisomy 13th risk (T13), calculated based on first trimester combined screening, had a higher average value of 0.643 in the study group than the control group (0.723/10.000 against 0.080/10.000), which is a statistically significant difference – $p<0.001$ (*Figure 15*).

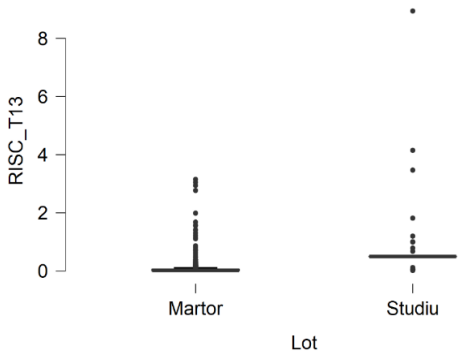

Figure 15. Descriptive chart regarding trisomy 13th risk in the two groups

The average risk of developing Trisomy 18 (T18) was also higher for the study group, with a value of 0,765/10.000, compared to the control group – 0,123/10.000. The value of the subtraction of means of 0,641 in our research represented a value of the level of statistical significance

p<0.001*(Figure 16).*

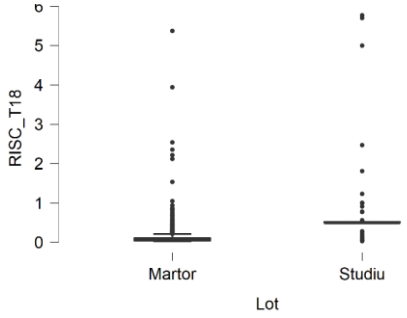

Figure 16. Descriptive statistics regarding to the risk of developing Trisomy 18 in the two groups

The risk of developing Trisomy 21 (Down Syndrome) in the control group had a mean value of 1,351/10.000 with a standard deviation of 2,23/10.000 and a mean value of 3,319 with a standard deviation of 8,166 for the study group. The difference between the means, analyzed using the T-Test, had a value of 1,698/10.000 with a statistical significance of p<0.01*(Figure 17).*

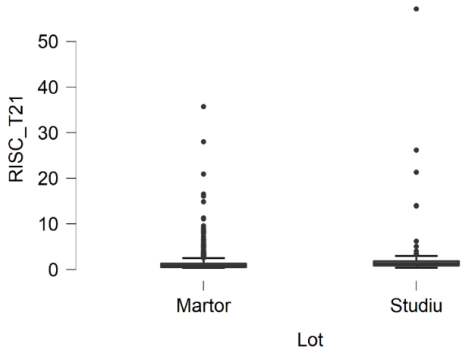

Figure 17. Descriptive statistics regarding to the risk of Trisomy 21 in the two groups

The risk of preeclampsia was higher for the patients in the control group - 4,79/1000 compared to the ones in the study group, 3,47/1000; however, this difference had no statistical significance (p=0,25)*(Figure 18).*

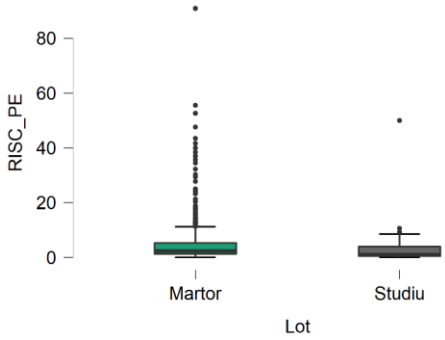

Figure 18. Descriptive statistic regarding to the risk of preeclampsia in the two groups

Regarding the risk of intrauterine growth restriction scaled to 1000 cases, no data suggesting a higher probability for the study group containing patients with rheumatic/inflammatory autoimmune intestinal diseases could be identified – the mean for the control group was 5,10/1000, compared to 6,78/1000 (p=0,38)*(Figure 19).*

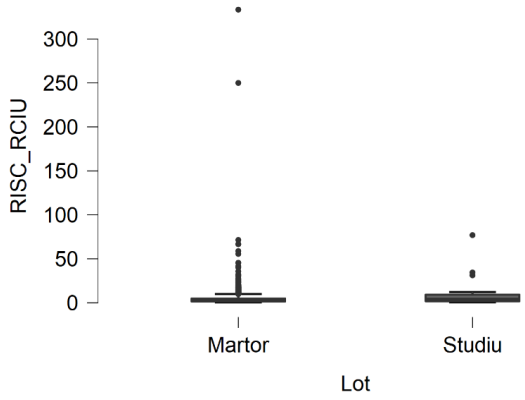

Figure 19. Descriptive statistic regarding to the risk of growth restriction (/1000) in the two groups

Regarding the biometric evaluation of the third trimester, no notable differences were identified between the two study groups. Fetal weight, estimated by ultrasound in the third trimester, showed values between 1203-3151 g in the control group, with a mean value of 1948,36 g and a standard distribution of 285,004 g. The study group's values ranged between 1090 and 2611 g, with a mean of 2089,257 g and a standard deviation of 312.210 g. The difference between the means of the two groups was 140,897 g (p<0.001) (*Figure 20*). Due to the relatively low number of cases in the study group and their irregular distribution, no relevant comparative observations can be formulated regarding their distribution.

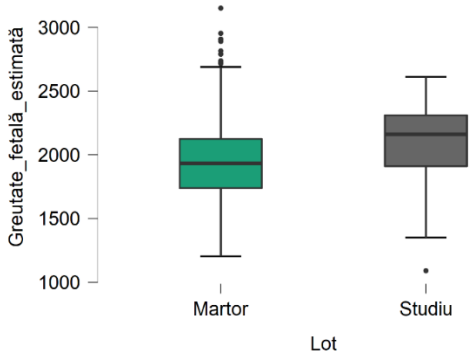

Figure 19. Descriptive statistics regarding fetal weight (g) in the two groups

Regarding comparing the velocimetric indexes of the uterine, umbilical and middle cerebral arteries, no statistical differences were identified regarding the distribution of cases between the two studied groups.

Table 14 summarizes the results of the comparative study of the two study groups in terms of maternal-fetal and neonatal prognosis. The main statistically validated differences were found for oligohydramnios (OR=2.57) and hypertensive pathologies in pregnancy (OR=3.09); the rest of the results show a slightly increased tendency in the study group for the occurrence of maternal-fetal complications and neonatal but without statistical power. This fact is mainly because most of the patients in the study group got pregnant planned and in a moment of lull, as it has been proven by other published specialized studies [2,3,9,20–23] that getting pregnant in - an opportune moment significantly reduces the risk of maternal-fetal and neonatal complications until they overlap with the risks of the general population.

Table 14. Comparative evaluation of maternal-fetal and neonatal outcome

Criteria	Patients with autoimmune disease n (%)	Patients without autoimmune disease n (%)	P value
No.	70 (100%)	995 (100%)	
Age – Median (Min-Max)	32 (19-43)	31 (20-43)	
Smoking YES NO	 9 (12.85%) 61 (87.15%)	 149 (14.97%) 846 (85.03%)	0.63
IMC (average +/- DS)	23.09 +/- 3.97	23.50 +/- 4.40	0.40
accumulated Kg	12.46 +/- 4.74	13.04 +/- 4.89	0.33
Live births	69 (98.57%)	994 (99.89%)	0.06
Premature births	9 (12.85%)	100 (10.05%)	0.45
Intruterine growth restriction	15 (21.42%)	180 (18.09%)	0.48
Oligohydramnios	*6 (8.57%)*	*35 (3.51%)*	*0.04; OR:2.57*
Gestational diabetes	4 (5.71%)	61 (6.13%)	0.88
Pregnancy- induced hypertension	*16 (22.85%)*	*87 (8.74%)*	*<0.001; OR:3.09*
Cesarean birth	50 (71.42%)	634 (63.71%)	0.19
Fetal distress*)	5 (7.14%)	86 (8.64%)	0.66
IVF	2(2.85%)	51 (5.12%)	0.43
Deep vein thrombosis	1 (1.42%)	13(1.30%)	0.93
Wound infections	1 (1.42%)	37 (3.71%)	0.33
Admission to neonatal intensive	12 (17.14%)	119 (11.95%)	0.20

care			
Birth weight - SGA	15 (21.42%)	182 (18.30%)	0.51
APGAR <7	2 (2.85%)	34 (3.31%)	0.80
Neonatal mechanical ventilation	2 (2.85%)	27 (2.71%)	0.94
Neonatal antibiotic therapy	21 (30%)	285 (28.64%)	0.80
Average duration of hospitalization of the newborn	4.68 +/- 2.77	4.5 +/- 2.13	0.07

DISCUSSIONS

An essential element in obtaining a good prognosis in pregnancy is the careful planning of the moment of conception after the stabilization of the disease at least six months before and the adaptation of the therapy [24,25]. The rate of improvement of the disease activity score in pregnancy in our study group (25%) is below the values of other specialized studies based on larger groups of patients. Thus, Hannah Jethwa and her collaborators carried out a systematic review and meta-analysis in which they included a number of 10 studies whose main objective was to measure the rheumatoid arthritis activity score during pregnancy and postpartum and concluded that the disease improved in 60% of patients during pregnancy [26]. Other authors, such as Atta [14], reported the amelioration rate at 40.4% and a significantly higher amelioration rate than the amelioration rate obtained in the present study (25%). Regarding the risk of relapse in postpartum (48%), this is similar to those presented in other studies; the meta-analysis presented by Jethwa reported an average of 47% of relapses in lousy [26]. Dolhain[27], in his study, on the other hand, presented a percentage of only 12.2% for relapses after delivery in the first six months. Van der Brandt [28] identifies a percentage of 29% of reactivations of the disease before delivery, a percentage that he correlates with stopping the biological medication (anti-TNFα) in the first trimester of pregnancy. Pregnancy in patients with rheumatoid arthritis remains a challenge for obstetricians and rheumatologists, requiring the collaboration of a multidisciplinary team to improve maternal, fetal, and neonatal prognosis [29,30]. Keeling [31] identified rheumatoid arthritis as an additional risk factor for preterm birth (13.5%), pregnancy-induced hypertension (10.5%), and intrauterine growth restriction (15.6%), all these percentages being statistically significantly higher compared to the rates obtained in the general population. In a pilot study carried out in the Netherlands, the PARA study, researchers demonstrated that disease activity, which they evaluated using the DAS28CRP activity score, correlates with maternal-fetal prognosis, and at the same time, these findings have supplemented by the PreCARA study in 2020, when it was concluded that a stable, well-controlled disease overlaps the maternal-fetal risks with those of the general population [32,33]

J Buyon[34] in the prospective study PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) included 385 pregnant patients and evaluated lupus-induced pregnancy complications identifying complications in 19% of cases: fetal death in 4% of cases, neonatal deaths in 1%, premature birth in 9%, newborns with low birth weight in 10% of cases, lupus relapses in the II and III trimesters in

2.5% and 3% of cases, respectively. Smyth [35], in his meta-analysis presented in 2010, reported an incidence of relapses in pregnancy of 26%, data similar to those obtained in the PROMISSE study, which estimated exacerbations in pregnancy at 24%. In general, the exacerbations of lupus that occur during pregnancy are not severe; they usually manifest as skin rash or musculoskeletal, hematological manifestations with incidences between 10-40% [36]. The most important predictor of disease flares is disease activity six months before conception and usually correlates with stopping immunosuppressive medication [37]. There is evidence that exacerbations are reduced by continued hydroxychloroquine treatment throughout pregnancy – the Hopkins cohort [34,38,39]. A 2018 Norwegian study shows lupus as a risk factor for preterm birth and low birth weight and active disease as a potentiating factor for preeclampsia [40]. Clowse et al. published a recent meta-analysis (2022) in which they followed 668 pregnancies in patients with systemic lupus erythematosus, of whom 63% continued hydroxychloroquine throughout the pregnancy and concluded that hydroxychloroquine use correlates with the stability of the disease during pregnancy and with the improvement of maternal-fetal prognosis [41]. The incidence of preeclampsia in patients with lupus is about five times higher, and the risk factors are lupus nephritis, low serum complement, and thrombocytopenia [42].

In a recent study published in 2019, the authors report a higher incidence of preeclampsia, premature rupture of membranes, and cesarean deliveries [43]. Upala and his colleagues published a meta-analysis of 7 studies and concluded no association between Sjögren's syndrome and pregnancy losses and preterm births [44]. Related to fetal complications, the most well-known are the occurrence of congenital heart block and neonatal lupus. None of the patients in the doctoral study had such complications in their newborns.

Studies on the evolution of spondyloarthropathies in pregnancy rarely show an increase in activity during pregnancy, but when this happens, the maximum occurs in the second trimester of pregnancy [45]. There is also a tendency toward an increased incidence in these patients of preeclampsia, growth restriction, and cesarean delivery; the findings of the doctoral study overlap the conclusions of the meta-analysis published in 2020 by SineadMaguire[45].

In 2021 Kim and his collaborators published a systematic review and meta-analysis that included 28 studies related to inflammatory bowel disease and pregnancy complications. They concluded that active disease increases the risk of complications: 3.8 times for low weight at birth and 2.42 times for preterm birth [46]. Similar data comes from Kammerlander's 2017 study of the effects of inflammatory bowel disease activity in pregnancy: active disease in pregnancy increases the risk of low birth weight by 2.05 times and preterm birth by 2.64 times; and when the disease has increased

activity, the risk of premature birth increases up to 3.6 times [47]. Achieving pregnancy when inflammatory bowel disease is not stable leads to a higher risk of worsening the disease during pregnancy and postpartum [25].

In the doctoral study, we obtained the following statistical correlations similar to the data in the literature: an activity score >1 in preconception increases the risk of recurrence of the disease by approximately three times, and getting pregnant in a moment of calm, stability and control of the disease with a score <1 acts as a protective factor for potential disease relapses during pregnancy. The risk of pregnancy complications (pregnancy-induced hypertension, intrauterine fetal growth restriction, spontaneous abortion, gestational diabetes, premature birth) is six times higher in patients who conceived without the disease being in remission (activity score >1). Patients with a disease activity score >2 in the third trimester had a 4.5 times higher risk of preterm delivery. Statistical significance was also identified between the disease activity score and the Apgar score, admission to neonatal intensive care, the average length of hospital stay of the newborn, and the need for postnatal antibiotic therapy.

Introducing new therapeutic molecules to address autoimmune diseases has led to better disease control and, therefore, a decrease in the rate of complications during pregnancy [15,48–51]. In the presented study group, biological therapy was the therapeutic method for 50% of patients during the preconception period. Later, the therapy was adjusted according to standard recommendations, most biologicals being stopped at the end of the second trimester [51,52]. The appearance of Certolizumab pegol as a very safe molecule during pregnancy and breastfeeding, as it does not cross the placental barrier and the amount excreted in breast milk is minimal, may bring significant benefits [53–55]. Given that most relapses of autoimmune diseases in pregnancy correlate with stopping biological medication at the end of the second trimester, using Certolizumab pegol can bring promising results [53]. Although the study group is small, we can associate our results with those of other international studies regarding the risk of maternal and neonatal infectious complications. Thus, we did not identify a significantly higher risk of wound infections in the mother. However, we did provide increased care for potential infectious risks in the newborn, and the data were similar to those presented by Nicole W Tsao and colleagues in a larger cohort of patients who followed biological therapy during pregnancy [50].

Sousa et al. included in their study, which was carried out prospectively between March 2006 and February 2011, a group of 47 patients with SLE and a control group of 45493 patients with singleton pregnancies which were evaluated using combined screening for first-trimester fetal abnormalities between 11 and 13 weeks and six days of pregnancy at the Harris Birthright Maternal-

Fetal Medical Centre at King College Hospital in London, United Kingdom and identified a MoM value for free beta-HCG greater in the case group (1.402, IQR 0.872-2.290 vs. 0.994, IQR 0.676-1.508) and concluded that the free beta-HCG value must be adjusted based on the presence of SLE in order to avoid false positive results and limit the necessary invasive diagnostic tests [56].

Another recently published study by Martinez-Sanchez [57], a prospective observational study from January 2011 until April 2017, followed 55 pregnant patients with positive anti-Ro and anti-La antibodies. These patients were compared with a cohort of 12971 patients without autoimmune diseases; the first-trimester screening analysis is also based on the Fetal Medine Foundation protocol. Comparing their cohort with the patients in our thesis study, we found a difference regarding the median age, this being lower for patients included in our study, 32 vs. 35,4, but similar regarding the BMI 23,09 vs. 22,25 and race – caucasian. The authors identified a lower PAPP-A level associated with pregnant patients with autoimmune disease (22 with SLE, 19 with Sjogren syndrome, 13 healthy carriers of anti-Ro or anti-La antibodies), this result being correlated on the one hand with a greater risk for false positive results and on the other hand with an induced risk for placentation abnormalities [57].

Therefore, literature data regarding the association of a greater risk for aneuploidies in patients with autoimmune diseases is not entirely solved, the studies being limited. Published data from recent studies on this subject identifies possible risks of false positive results due to the risk of interaction between specific antibodies and free beta-HCG or PAPP-A, and measurements for the first-trimester screening must be adjusted for this type of patient [56].

Comparing terms of maternal complications which can occur during pregnancy for a patient with an autoimmune disease, we identified a greater risk for the development of pregnancy-induced hypertensive diseases (pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP syndrome) with a greater significant statistical value in the case study compared to the control group: 22,85% vs. 8,74%, OR=3,09, p<0,001, an approximate 2.5 greater risks to develop oligohydramnios: 8,57% vs. 3,51%, OR=2,57, p=0,04. Furthermore, we identified greater risk for: preterm birth 12,85% vs 10,05%, p=0,45, intrauterine fetal growth restriction 21,42% vs 18,09%, p=0,48, Caesarean delivery 71,42% vs 63,71%, p=0,19, as well as lower risks for development of acute fetal distress with the necessity for emergency birth 7,14% vs 8,64% , p=0,66 and gestational diabetes 5,71% vs 6,13%, p=0,88, but all these findings didn't have statistical significance in the studied groups. Most cases associating pregnancy and hypertension were developed after 28 weeks of pregnancy (11 out of 16), and 11 cases out of 16 with pregnancy-induced hypertension developed preeclampsia. Andrew Williams et al. [23] published 2019 a similar study about the obstetric and

neonatal prognosis for patients with autoimmune diseases in which were included patients with systemic erythematosus lupus, polyarthritis, Chron's disease, type I diabetes, and multiple sclerosis, which were compared with a control group of 204384 patients without autoimmune diseases. They compared groups of diseases and obtained similar results to those presented in this thesis. Therefore, they identified patients with a cumulative risk for preterm birth for patients with lupus, polyarthritis, and Chron's disease of

25% vs. 11,10% for patients without autoimmune disease, the risk for preeclampsia of 10,09% vs. 4,64%, and risk for Caesarean delivery of 38,07% vs. 27,85%; in this matter, identifying the presence of autoimmune disease as a risk factor for maternal prognosis. We must specify that the results obtained in the Williams study [23] were adjusted based on maternal age, race, BMI, smoking during pregnancy, alcohol consumption during pregnancy, and the presence of other chronic diseases. The results had a statistical significance of $p<0,05$. We observe a greater incidence of preterm births in their study group compared with our study group, as well as a greater incidence in our study group compared to theirs for pregnancy-associated hypertension diseases and Caesarean delivery; however, a high threshold is maintained for these incidences for patients with autoimmune diseases in both study groups.

By comparing the neonatal prognosis, Williams [23] obtained the following data: admission to the neonatal intensive care unit was 22,41 vs. 11.54%, $p<0,05$, being practically double the risk for admission to the neonatal intensive care unit for babies born from mothers with autoimmune diseases; respiratory distress syndrome was found in 6,99% vs. 3,11%, $p<0,05$, it was identified several children small for gestational age of 15,77% vs. 10,93%, $p<0,05$, and perinatal mortality of 0,85% vs. 0,59%, $p<0.05$; all this data suggests the fact that presence of maternal autoimmune diseases correlates statistically with a more severe neonatal prognosis. In our study group were identified the following: admission to the neonatal intensive care unit 17,14% vs 11,95%, respiratory distress syndrome: 5,79% vs 3,4%, children small for gestational age 21,42% vs 18,30%. Therefore, we note similarities to the data obtained in larger studies on better-represented populations. We can conclude that maternal autoimmune disease is an additional risk factor for neonatal prognosis. However, the patients in our study group, a small study group, could not obtain significant statistical results. We consider that this thesis brings valuable information regarding the management and risks for this category of pregnant women.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

Autoimmune diseases primarily affect women of fertile age; therefore, pregnancy and the impact of the disease on the product of conception is a subject of great importance.

- The interaction between pregnancy and autoimmune disease is two-sided; both pregnancies influence the prognosis of the underlying disease, and the autoimmune disease affects fertility, pregnancy, and newborns.
- Monitoring the activity of autoimmune disease at least six months before conception and obtaining remission or disease stability at a low activity are positive prognosis factors in terms of pregnancy evolution, disease recurrence during pregnancy, and neonatal impact; moreover, a high activity score of the underlying disease before conception or during pregnancy rises the risk of maternal, fetal and neonatal complications.
- The disease activity score before preconception>1 was related with an increased risk of reccurence during pregnancy by threefold (OR=12,778, CI95% =1,395-117,074; RR= 2,967, CI95% = 2,829 – 3,105), with an increased risk of onset of pregnancy related complications by six-time (OR=12,778, CI95% =1,395-117,074; RR= 2,967, CI95% = 2,829 – 3,105), with an increased risk of obtaining an Apgar score lower than 8 by tenfold (OR=15,250, CI95%=1,680-138,408, RR=10.526, CI95% = 10,447 – 10,605), with an increased risk of admission to the neonatal intensive care unit by fivefold.
- A disease activity score before conception >2 was associated with a risk of 17,24 greater for emergency birth. In contrast, an activity score>2 during the third trimester was associated with a risk of 4,5 more excellent for this complication.
- A disease activity score >1 during the third trimester was associated with a hospitalization period of the newborn greater than five days. (RR = 3,012 CI95% = 2,863 – 3,161).
- We identified the primary protective factor for disease evolution during pregnancy and complications during pregnancy as a disease activity score of less than 1 (remission or low activity).
- Obtaining a pregnancy during a moment of stability and disease remission and controlling the disease during pregnancy ensures a maternal-fetal and neonatal prognosis similar to the general population.
- Medication used before conception and during pregnancy can be directly correlated with pregnancy evolution and the appearance of potential complications – on the one hand as a result of disease stability and on the other hand as a result of the effects of immunosuppressors determined on the mother and transmitted to the fetus; there are required additional studies to confirm the impact which these treatments can have.

- The primary purpose remains, on the one hand, the therapy adjustment for autoimmune disease during preconception in order to obtain disease control using this medication without teratogenic potential and, on the other hand creating therapeutic protocols during pregnancy that can rightly control the disease and be associated with minimal maternal-fetal and neonatal complications.
- In Western countries from Western Europe and Northern America, there are particular establishments for guiding and treating women of fertile age who desire pregnancy, pregnant women with autoimmune disease, and newborns who come from diseased mothers. Unfortunately, there are no guidance facilities or specific therapy protocols during pregnancy in Romania. However, willingness and cross-disciplinary collaboration can be the premises for building such facilities and teams for patients' benefit.
- Is wanted this dissertation thesis to be a road opener for creating regional and national registries for monitoring pregnant women with autoimmune diseases and newborns and further long-term monitoring of children born from these mothers, in this way lining up with international standards in this field.