ORIGINAL PAPER

PREGNANCY IN WOMEN WITH AUTOIMMUNE DISEASES – FETAL OUTCOMES

Andreea Grațiana Boiangiu[1,2], Anca Bobircă[1,3], Andra Bălănescu[1,4], Simona Popescu[1,5], Sorina Nechita[6], Mona Zvanca[1,2], Radu Vlădăreanu[1,2], Simona Vlădăreanu[1,5]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Obstetrics and Gynecology Department, "Elias" University Hospital, Bucharest, Romania
[3]Internal Medicine and Rheumatology Department, "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania
[4]Internal Medicine and Rheumatology Department "Sf. Maria" Hospital, Bucharest, Romania
[5]Neonatology Department, "Elias" University Hospital, Bucharest, Romania
[6] Department of General Surgery, University Emergency Hospital of Bucharest, Bucharest, Romania

Corresponding author: Andreea Boiangiu
Email: andreeaboiangiu@gmail.com

ABSTRACT

Pregnancy is known to induce dramatic neuroendocrine and immune changes to the female body, adjusting the elements and the functions of the cellular and humoral system and therefore, creating an immunosuppressive state in order to support nidation, placenta fixation and fetal development. These adjustments are necessary in order to promote maternal tolerance to the fetus and, unfortunately, they are known to set off a rheumatic disease and create pregnancy complications along the way. The present study was designed in order to observe clinical and paraclinical changes in pregnant women with and without an underlying autoimmune rheumatic or gastrointestinal disease and to evaluate the fetal growth and development along with appraising the risk of complications. The study included a group of 70 patients and a control group of 995 cases. The study showed that there are no statistically significant differences regarding the clinical and paraclinical maternal and fetal parameters evaluated in the groups examined. The risk of complications during pregnancy, such as preeclampsia and intra-uterine growth restriction, is higher in women with underlying autoimmune diseases, but the difference is not significant. An important result of the study is the proven higher risk of developing chromosomal abnormalities (trisomy 13, 18 and 21) in pregnancies associated with autoimmune conditions.

KEYWORDS: *pregnancy, autoimmune disease, complications, immunosuppression, inflammation*

INTRODUCTION

Pregnancy is known to induce dramatic neuroendocrine and immune changes to the female body, adjusting the elements and the functions of the cellular and humoral system and therefore, creating an immunosuppressive state in order to support nidation, placenta fixation and fetal development [1], [2]. These adjustments are necessary in order to promote maternal tolerance to the fetus and, unfortunately, they are known to set off a rheumatic disease and create pregnancy complications along the way [1]. Furthermore, the systemic chronic inflammation can cause more harm to a pregnant body than suppressive medication used to control the activity of a

rheumatic disease [3]–[5]. The most frequent complications that can occur during pregnancy are activity flares, relapses, thromboembolic events, preeclampsia, intra-uterine growth restriction, preterm delivery and fetal loss [6]–[10].

During pregnancy, women should be in remission or should have a low activity disease, as long as modern-day medicine can recommend administration of immunosuppressive drugs, while offering comprehensive information regarding risks and management and can assist women with counselling [11]. Prenatal and during pregnancy guidance is constructed to offer good maternal and fetal outcome [11]–[14].

The present study was designed in order to observe clinical and paraclinical changes in pregnant women with and without an underlying autoimmune rheumatic or gastrointestinal disease and to evaluate the fetal growth and development along with appraising the risk of complications.

MATERIALS AND METHOD

The study was unicentric, retrospective (2013-2019), non-experimental, descriptive and correlational.

Based on the proposed purpose and the specific objectives established, the eligibility criteria for the study group were identified: rheumatological or gastrointestinal disease diagnosed before pregnancy, regular monitoring of pregnancy and autoimmune disease, as well as the presence in the observation sheets of all necessary anamnestic, clinical and paraclinical information.

Based on the evaluation of cases in terms of eligibility criteria, the study group was established, which included 70 patients.

In order to fulfill the proposed purpose, a control group was also developed which included a number of 995 cases followed during pregnancy, cases that did not present previously, or during pregnancy diagnosis or symptoms specific to autoimmune pathologies.

RESULTS

A central element of the analysis of the present study is the underlying inflammatory bowel disease or rheumatic disease previously diagnosed by pregnancy. The autoimmune diseases identified in the study were: Crohn's disease (7 cases), lupus (11 cases), rheumatoid arthritis (27 cases), Sjogren's syndrome (8 cases), rectocolitis (9 cases), antiphospholipid syndrome (3 cases) and ankylosing spondylitis (1 case). A number of 3 patients associated 2 diseases: rheumatoid arthritis and Sjogren's syndrome (2 cases), respectively antiphospholipid syndrome and lupus (1 case).

The comparative analysis of the two groups from considering the patients' age, highlights similar values of the averages - 31.02 years in the control group, respectively 31.95 years in the study group, without a difference of the averages with a statistical significance. Also, the range of values is similar to a 1-year difference of the minimum and the same maximum. Although the distribution of cases shows a slight deviation to the left of the curve in the case of the study group, it has no statistical significance, and can be said that the two groups have similar age characteristics.

In both the study group and the control group, the natural conception predominated that a percentage of 97.14%, respectively 94.87%, in vitro fertilization being identified in 51 patients, representing 5.12% in the control group, respectively in 2 patients, representing 2.85% in the study group.

The mean blood pressure, assessed in the first trimester of pregnancy, showed comparable values in the two groups analyzed, with an average of 86.13 mmHg and 87.24 mmHg, respectively, and a standard deviation of 7.05 mmHg and 7.27 mmHg, respectively, the difference being without statistical significance (Table 1). Also, the distribution of cases in relation to this parameter proves a similarity between the two.

The bHCG value measured in the first trimester of pregnancy, expressed in MoM equivalent, showed an average of 1.27, with a standard deviation of 0.87, in the control group, respectively an average of 1.31, with a deviation of 0.90 in the study group, these data indicating a comparable dispersion for the two groups, there were no statistically significant differences (Table 1).

Pregnancy-associated plasma protein (PAPP-A) dose in the first trimester of pregnancy, expressed in MoM equivalent, shows

similar statistical values for the two groups, without being able to identify the significant difference: mean 1,166 for the control group, with a standard deviation of 0.630, respectively 1.117, with a standard derivation of 0.515 for the study group (Table 1).

	Mean Blood Pressure		ß-hCG MoM		PAPP-A MoM	
Lot	0	1	0	1	0	1
N	995	70	995	70	995	70
Minimum	72.100	72.100	0.166	0.390	0.153	0.327
Maximum	105.300	105.300	11.704	4.483	4.734	2.579
Mean	86.132	87.247	1.276	1.316	1.166	1.117
Median	85.500	86.600	1.031	1.005	1.044	1.066
SD	7.0514	7.2736	0.8767	0.9001	0.6300	0.5146
25-75 P	80.300 to 90.100	80.500 to 90.800	0.716 to 1.578	0.702 to 1.580	0.715 to 1.469	0.754 to 1.341

Table 1 – Statistical data regarding the Mean Blood Pressure, ß-hCG MoM, PAPP-A MoM in the control and study group

The risk of developing Trisomy 13 (T13), calculated by the algorithms of Fetal Medine Foundation combining morpho-fetal ultrasound with biochemical markers in the first trimester, showed a mean of values with 0.643 higher in the study group (0.723/10,000 compared to 0.080/10,000), statistically significant difference - $p<0.001$ (Table 2). The distribution of cases highlights a percentage of 2.31% of the total number of cases with the risk of developing T13 greater than 0.5/10,000 in the control group, respectively a percentage of 17.39% in the study group. Thus, the probability of having a risk of more than 0.5/10,000 is higher than 8 times in the case of patients in the study group (OR=8.74, $p<0.0001$).

The average risk of developing Trisomy 18 (T18) was also higher in the study group with a value of 0.765/10,000, compared to the control group - 0.123/10,000. The value of the mean difference of 0.641 presented in our research a level of statistical significance $p<0.001$ (Table 2). The distribution of cases in relation to the calculated risk of developing T18 shows a probability of more than 11 times to present a risk greater than 0.5/10,000 to develop this syndrome in the case of patients in the study group - 18/65, compared to control group - 32/995 (OR=11.52, $p<0.001$).

The risk of developing Down Syndrome (T21) in the control group showed an average value of 1,351/10,000 with a standard deviation of 2.23/10,000, respectively an average of 3,319 with a standard deviation of 8,166 in the study group. The difference of the averages analyzed with the help of the T Test, presented a value of 1,698/10,000 with a statistical significance $p<0.01$ (Table 2). The assessment of the increased risk of developing Down Syndrome - over 5/10,000, shows a higher percentage in the study group -10.76%, compared to the control group 4.22% (OR=2.73, $p=0.001$).

The risk of preeclampsia (PE) calculated during the first trimester ultrasound was higher in patients in the control group - 4.79/1000 compared to the study group - 3.47/1000, but this difference was not statistically significant ($p = 0.25$) (Table 2). The distribution of cases shows a probability of approximately 4 times lower in patients within the study group to present a risk greater than 1/100 of preeclampsia, without having a statistically significance (OR=0.255, $p=0.05$).

Furthermore, regarding the risk of intrauterine growth restriction (IUGR) compared to 1000 cases, no data could be identified that suggest a higher probability in the study group containing patients with chronic rheumatic diseases - the average in the control group being 5.10/1000, compared to 6.78/100 ($p=0.38$) (Table 2). The probability of presenting a risk of more than 1/100 was higher in the study group - 16.92%, compared to the control group - 9.74%, but without presenting a satisfactory level of statistical significance (OR=1.88, $p=0.06$).

	PE RISK*		IUGR RISK*		T13 RISK**		T18 RISK**		T21 RISK**	
Lot	0	1	0	1	0	1	0	1	0	1
N	995	44	995	59	995	64	995	65	995	65
Min	0.040	0.050	0.389	0.560	0.011	0.020	0.027	0.030	0.328	0.360
Max	90.90	50.00	333.33	76.920	3.151	8.940	5.373	5.770	35.71	57.140
Mean	4.799	3.473	5.104	6.785	0.0802	0.723	0.123	0.765	1.351	3.319
Median	2.398	1.075	2.545	3.340	0.0255	0.500	0.0576	0.500	0.687	1.090
SD	7.6241	7.6605	14.5761	11.2230	0.2486	1.2367	0.2832	1.1239	2.2337	8.1664
25-75 P	1.287 to 5.291	0.485 to 4.035	1.467 to 4.849	1.663 to 9.428	0.0171 to 0.0522	0.500 to 0.500	0.0389 to 0.108	0.500 to 0.530	0.466 to 1.296	0.843 to 1.830

Table 2 – Statistical data regarding the risk of Preeclampsia, Intra-Uterine Growth Restriction, Trisomy 13, 18 and 21 in the control and study group

The ultrasound estimation of the cranial circumference during the assessment of the third trimester showed an average value in the study group with 7.06 mm higher compared to the control group (300.05 mm compared to 292.99 mm), difference statistically significant - $p<0.001$ (Table 3). The distribution of cases in relation to this parameter does not show significant differences between the two groups.

The dispersion of values of the abdominal circumference evaluated during the third trimester ultrasound showed similar values in the two groups: the average of 281.96 mm with a standard deviation of 15.97 mm in the control group, and 286.49 mm with a standard deviation of 16.46 mm in the study group (Table 3). Although the difference between averages does not show a relevant statistical significance ($p=0.02$), the distribution of cases highlights a number of discrepancies between the two groups: the control group has a relatively Gaussian distribution, while the group of cases study shows the graphic deviated to the right, however, they are not statistically significant.

Another parameter evaluated in the morpho-fetal ultrasound of the third trimester was the length of the femoral shaft, a parameter that showed an average of 61.35 mm in the control group, with a standard deviation of 2.99 mm, respectively an average of 62.95 mm in the study group, with a standard deviation of 2.67 mm. The difference of the averages between the two groups highlights a value by 1.605 mm higher in the study group ($p<0.001$) (Table 3). No significant differences were identified in the distribution of cases in relation to this parameter.

The fetal weight, estimated with the help of the third trimester ultrasound, showed in the control group values ranging from 1203 to 3151 grams, with an average value of 1948.36 g and a standard deviation of 285.004 g. In the study group, the values were between 1090 and 2611 g, with an average of 2089,257 g and a standard deviation of 312,210 g. Thus, a difference of 140.897 g ($p <0.001$) was observed between the averages of the two groups (Table 3). Due to the relatively small number of cases in the study group and their uneven distribution in relation to this parameter, no relevant comparative observations can be made on their distribution.

Reporting the data to the median specific of gestational age, there is demonstrated a median value below 50% in the case of the control group (46.1%), respectively over 50% in the study group (53.3%). The difference of the averages in the 2 groups was 7.821% with a level of statistical significance $p = 0.004$ (Table 3).

Regarding the pulsatility index of the uterine artery (PI UA), the analyzed data showed an average value of 0.689 in the control group, with a standard deviation of 0.159, respectively an average of 0.830, with a standard deviation of 0.190, the difference between the averages being 0.141 ($p <0.001$) (Table 4). The distribution of cases in relation to this parameter shows an aggregation of most cases in the range 0.6-1.

The pulsatility index of the umbilical artery (PI UmA), evaluated in the morpho-fetal ultrasound of the third trimester, did not show neither significant differences in descriptive statistical data (difference of averages with a value of 0.004, $p=0.841$) (Table 4), nor regarding the distribution of cases in relation to this parameter.

	Estimated fetal weight		Length of the Femoral Shaft		Abdominal circumference		Cranial circumference	
Lot	0	1	0	1	0	1	0	1
N	995	70	995	70	995	70	995	70
Minimum	1203.000	1090.000	52.300	56.400	230.300	249.000	257.900	275.000
Maximum	3151.000	2611.000	71.300	69.200	338.000	317.200	331.300	326.200
Mean	1948.360	2089.257	61.352	62.957	281.965	286.491	292.993	300.054
Median	1932.000	2161.000	61.300	63.200	281.600	289.000	292.500	300.250
SD	285.0041	312.2099	2.9898	2.6745	15.9769	16.4678	12.3750	9.9227
25-75 P	1738.250 to 2125.750	1910.000 to 2310.000	59.300 to 63.300	61.300 to 64.400	270.800 to 292.500	276.000 to 300.000	283.700 to 301.875	294.800 to 307.500

Table 3 – Statistical data regarding Estimated fetal weight, Length of the femoral shaft, Abdominal circumference and Cranial circumference in the control and study group

The pulsatility index of the middle cerebral artery (PI MCA) could not show significant discrepancies between the control group and the study group, the difference of the averages, having a value of 0.016 (p=0.6) (Table 4). The distribution of cases in relation to this parameter for the two groups is also similar.

	PI MCA		PI UmA		PI UA	
Lot	0	1	0	1	0	1
N	995	70	995	70	995	70
Minimum	1.090	1.340	0.590	0.700	0.335	0.500
Maximum	2.700	2.610	1.380	1.800	1.515	81.000
Mean	1.934	1.918	0.951	0.955	0.689	1.975
Median	1.940	1.915	0.950	0.925	0.660	0.815
SD	0.2421	0.2517	0.1519	0.1850	0.1588	9.5840
25-75 P	1.762 to 2.100	1.750 to 2.100	0.840 to 1.050	0.830 to 1.030	0.575 to 0.769	0.700 to 0.900

Table 4 – Statistical data regarding the Pulsatility Index of the Middle Cerebral Artery, Umbilical Artery and Uterine Artery in the control and study group

DISCUSSION

The current study has its limitations. The retrospective manner in which it was managed, depending on medical records, can imperil to missing information or inaccuracies. Furthermore, the study group evaluated had heterogeneity in their prenatal follow-up, but a rigorous monitoring into the same institution.

Social stigmatization on women at a gestational age with underlying rheumatic diseases is still occurring, even though contraception failures are not often encountered, pregnancies are being obtain at the same age as the control population and the risk of fetal abnormalities can be early detected through regular morpho-fetal ultrasound [15], [16]

Pregnancy in women with underlying rheumatic diseases should be considered a high-risk pregnancy requiring conception counselling and close monitoring by a multidisciplinary team, including a rheumatologist, an obstetrician and a neonatal doctor, in order to avoid disease complications with a significant impact on both mother and fetus [2], [14], [17]–[19].

CONCLUSIONS

The study showed that there are no statistically significant differences regarding the clinical and paraclinical maternal and fetal parameters evaluated in the groups examined. The risk of complications during pregnancy, such as preeclampsia and intra-uterine growth restriction, is higher in women with underlying autoimmune diseases, but the difference is not significant. An important result of the study is the proven higher risk of developing chromosomal abnormalities (trisomy 13, 18 and 21) in

pregnancies associated with autoimmune conditions.

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