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Acute Inflammatory Changes of the Placenta in Patients with Preterm Delivery Syndrome

Goran Kocoski[a]*, Mile Tanturovski[b], Rosa Spasova[c], Ivo Kjaev[d], Dafina Karadzova[e], Liljana Spasevska[f]

[a,b,c,d,e]*University Clinic for obstetrics and gynecology - Skopje, University of Ss. Cyril and Methodius - Skopje, Vodnjanska Bld. No.17, 1000 Skopje, Republic of Macedonia*

[f]*Institute for Pathology, University of Ss. Cyrila and Methodius – Skopje, 50 Division St., 1000 Skopje, Republic of Macedonia*

[a]*Email: goran_kocoski@yahoo.com*

Abstract

Preterm delivery is one of the most serious challenges of contemporary perinatology. Considering the multi factorial etiology of this issue, contemporary scientific approach addresses this topic as a Preterm Delivery Syndrome. If we exclude the congenital anomalies of the female reproductive system and iatrogenic causes, we can pinpoint infections, as one of the most important etiological factor for preterm delivery. The aim of the study is to determine the frequency of the histopathological changes of the placenta in patients with preterm delivery, to determine their stage and grade, according to the classification proposed by the Amniotic Fluid Infection Nosology Committee of the Perinatal Section of the Society of Pediatric Pathology (AFINCPSPP). Finally, to define the correlation between those changes and the gestational age, as well as the correlation between the degree of the histopathological changes and the time passed from the preterm premature rupture of the fetal membrane and the delivery. This cohort prospective study includes 30 patients delivered at the University clinic for Ob/Gyn in Skopje. We've selected the patients according to the previously determined inclusion and exclusion criteria: gestational age between 24^{+0}-34^{+0} weeks of gestation (w.g), premature preterm rupture of the fetal membranes (pPROM), presence of uterine contractions, cervical dilatation of ≥ 2 cm determined by vaginal examination or shortening of the cervical length by > 50% determined by vaginal ultrasound.

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* Corresponding author.

For the evaluation of the histopathological changes of the placenta, 6 samples were provided from four (4) zones of the placentas of the delivered women: chorionic plate, umbilical cord, border between amnion and chorion, and fetal membranes. Statistical analysis was performed on IBM SPSS Statistics software package, version 23.0. Probability of $p \leq 0.05$ was considered statistically significant. Differences between descriptive variables were determined using Chi square and Fisher exact tests. For determination of correlation between variables, we used Kendall tau correlation coefficient. Of all the patients included in the study, 14 (46,7%) were at gestational age of 32^{+0}-34^{+0} w.g, 7 (23,3%) were at gestational age of 28^{+0}-31^{+6} w.g, and 9 (30 %) were at gestational age of 24^{+0}-$27+^{6}$ w.g. PPROM was registered in 14 (46,7%) of the patients, out of which almost half, 42,8 % were delivered in less than 24 hours after the rupture of the membranes. In 42,8% of the patients delivered between 32^{+0}-34^{+0} w.g, histopathological analysis of the placenta did not detected presence of inflammatory response. On the other side, in patients delivered between 24^{+0}-27^{+6} w.g, histological chorioamnionitis was present in all cases. Even more, in as high as 66,7% of these cases, inflammatory changes of the placenta were categorized as Stage 3, which is highest or most advanced stage of inflammatory response. Results of our study are consistent with previously published data. They confirm the inversely proportional relationship between gestational age at the time of delivery, and the stage and grade of histopathological changes of the placenta, defined as acute chorioamnionitis. Additional evaluation of the data showed that, there is no correlation between the degree of the inflammatory response, and the time passed from the pPROM and delivery, expressed in hours.

Key words: preterm delivery; placenta; chorioamnionitis; placentitis.

1. Introduction

Preterm delivery is one of the most important and most serious issues facing contemporary perinatology. According to the World Health Organization (WHO), each year around 15 million newborn babies are delivered before 37^{th} weeks of gestation (w.g) [1]. Complications associated with preterm delivery are direct cause for almost 35% out of 3.1 million newborn deaths. On the other hand, preterm babies are exposed to increased risk for impairment in their neurological and intellectual development [2]. Globally accepted WHO definition from 1977, states that preterm delivery is every delivery prior to full 37 w.g, or 259 days starting from the first day of the last menstrual period (LMP). Depending on the gestational age, preterm delivery is divided in three categories: extremely preterm, less than 28 w.g; very preterm, starting from 28^{th} till 32^{nd} w.g, and moderate to late preterm, starting from 32^{nd} till 37^{th} w.g. The group of moderate to late preterm is divided in two sub groups: moderate, from 32^{nd} to 34^{th} w.g, and late, from 34^{th} to 37^{th} week [3]. Preterm delivery is a syndrome. There are two main groups of etiological factors responsible for the syndrome. The first group, are factors that rise from the necessity for emergency or elective termination of the pregnancy before 37^{th} week, due to indications associated with maternal or fetal condition. This group represents around 25% of all preterm deliveries. The second group represents around 20 % of all cases, and the main reasons are premature contractions or premature preterm rupture of the fetal membranes (pPROM). Premature contractions or premature labor as a spontaneous process is responsible for almost 40% of cases of preterm delivery [2,4]. One of the etiological factors that attract most attention are intrauterine infections and the inflammatory changes of the fetus and the placenta associated with these infections. Almost one quarter (26 %) of premature babied die as a result of intrauterine infections [5]. Analysis of the histopathological changes of the placenta within this clinical entity show that the

rate of acute inflammatory lesions of the placenta, fetal membranes and the umbilical cord varies in the range of 22-59%. The prevalence of these changes is inversely proportional to gestational age [6]. Data published in studies and systematic reviews, analyzing the connection between clinically manifested chorioamnionitis and histopathological changes of the placenta, show that placental lesions develop much more earlier than the clinical expression of the condition. In only 13% of patients with histologically proven chorioamnionitis, clinical signs develop [7]. On the other hand, only in 12.2 % of these patients, microbial agents can be detected in the amniotic fluid, using amniotic culture, (depending on the gestational age, the rate of isolation of microorganisms from the amniotic fluid varies from 0-48%). These data lead to a conclusion that the intrauterine infection, which is responsible for the inflammatory lesions of the placenta and the umbilical cord, may be responsible for the initiation of the process of preterm labor and preterm delivery itself [8]. Additional studies were carried out at the beginning of the 21st century, after the introduction of a novel system for classification of the histopathological changes of the placenta and umbilical cord by R.W Redline later on modified by the Amniotic Fluid Infection Nosology Committee of the Perinatal Society of the Society of Pediatric Pathology (AFINCPSPP) [9,10]. Results of these studies have shown that the presence of placental lesions classified as acute chorioamnionitis, are far more prevalent in patients delivered between 21st and 24th week of gestation, and there was a descending trend of these changes in grous with higher gestational age. In 94.4% of the cases, there were inflammatory changes of the placenta and the umbilical cord on histopathological findings, contrary to 39.6% of cases delivered between 25th and 28th w.g, 35.4% in the group delivered between 29th and 32nd w.g and only 10,7% in the group that delivered between 33rd and 36th w.g. Additional analysis within these studied showed that the degree of cervical dilatation (> 4 cm), as well as the duration of the labor and delivery are poor prognostic factors. The prevalence of acute chorioamnionitis is higher if the cervical dilatation is > 4 cm, and if the duration of the delivery is longer (30.4% in the group with cervical dilatation > 4 cm, and 11.6% in the group with cervical dilatation < 4 cm, respectively) [11, 12, 13]. The rate of prematurity in Republic of Macedonia (RM), for the past five years, is slightly increasing. Based on the LMP, in 2013, 7.42% of all deliveries on national level were prior to 37^{+0} w.g. Majority of those, were at the University clinic for obstetrics and gynecology in Skopje, as a single tertiary center in the country. Data on the dynamics of prematurity on national and institutional level, provided by the National center for reproductive health of the Republic of Macedonia, are presented in table 1 [14,15,16,17, 18].

Table 1: Rate of prematurity in Republic of Macedonia as a percentage of all deliveries on national level and at the University clinic for obstetrics and gynecology in Skopje

	Total No. of deliveries	Rate of preterm deliveries in RM (%)	Rate of preterm deliveries at the University clinic for Ob/Gyn (%)
2013	22433	7,42	17,06
2014	23202	7,69	18,11
2015	22635	7,69	18,11
2016	22485	8,09	17,67
2017	21405	8,77	21,71

The national rate of prematurity did not change dramatically throughout analyzed period, overall 1.35%. Nevertheless, despite the measures that were introduced, incorporated in the national strategies and clinical guidelines, the national rate of prematurity is, least to say, stagnant [19].

2. Material and methods

This cohort prospective study included 30 patients delivered at the University clinic for Obstetrics and Gynecology in Skopje. The histopathological analysis of the tissue samples was performed at the Institute for Pathology at the Medical faculty in Skopje. We have selected the patients according to the presence of one or more of the previously defined inclusion criteria: gestational age between 24^{+0} and 34^{+0} weeks, preterm premature rupture of the fetal membranes (pPROM), presence of the uterine contractions, dilatation of the cervix ≥ 2 cm estimated by vaginal examination or shortening of the cervix by > 50% estimated by transvaginal ultrasound. The mode of delivery was not considered as a criterion for inclusion or exclusion of the subjects in the study. According to the gestational age, subjects were divided into three groups: 24^{+0}-27^{+6} w.g, 28^{+0}-31^{+6} w.g and 32^{+0}-34^{+0} w.g.

Patients, in which preterm delivery was required due to maternal or fetal risks or conditions, were excluded from the study. Above mentioned risks or conditions included: severe preeclamsia, imminent eclampsia or HELLP Sy.; intrauterine growth restriction, bleeding placenta previa, placental abruption, fetal anomalies incompatible to life or anomalies imposing necessity for early termination of pregnancy, preexisting maternal conditions that aggravate during pregnancy and also impose necessity for preterm delivery. The study did not included patients with preterm delivery at 34-36^{+6} weeks, or so called late preterm delivery, in which the prevalence of inflammatory changes of the placenta fetal membranes and the umbilical cord was shown to be significantly lower compared to other groups (10.6%) [6].

For the purpose of histopathological analysis, six (6) samples were taken from the placentas of the delivered patients. The samples were provided from four (4) arias: umbilical cord, fetal membranes, border between amnion and chorion and chorionic plate. Samples from the fetal membranes were taken from the free surface of the amnion and packed into rolls. For the evaluation of the grade and the stage of the maternal and fetal inflammatory response we used the recommendations of the Amniotic Fluid Infection Nosology Committee of the Perinatal Section of the Society of Pediatric Pathology.

Every patient that was included in the study signed a written consent in order to participate in the study. The written consent form was previously approved by the management of the University clinic for obstetrics and gynecology in Skopje, and by the Ethical committee for research on human subjects at the University of Ss. Cyril and Methodius, Medical faculty in Skopje.

Data from the study were digitalized and entered into a data base. For the purpose of statistical analysis, IBM SPSS Statistics software package version 23.0 was used. Probability of $p \leq 0.05$ was considered statistically significant. The difference between descriptive variables was calculated using Chi square and Fisher exact tests (accordingly). Corelation between variables was determined using Kendall tau correlation coefficient.

3. Results

Out of 30 patients that reached inclusion criteria for the study, 12 (40%) were primiparous, 12 (40%) were secundiparous and 6 (20 %) were multiparous. Only one patient included in the study had a history of preterm delivery in one of her previous pregnancies. Characteristics and distribution within the group according to the inclusion criteria are presented in table 2.

Table 2: Distribution in the examined group according to inclusion criteria

Parity	
Primiparous, n (%)	12 (40%)
Secundiparous, n (%)	12 (40%)
Multiparous, n (%)	6 (20 %)
Weeks of gestation	
$24^{+0} – 27^{+6}$, n (%)	9 (30 %)
$28^{+0} – 31^{+6}$, n (%)	7 (23.3%)
$32^{+0} – 34^{+0}$, n (%)	14 (46.7%)
pPROM	
Yes, n (%)	14 (46.6%)
No, n (%)	16 (53.4%)
CL*	
< 25 mm, n (%)	18 (60%)
> 25 mm, n (%)	12 (40%)
Contractions on admission	
Yes, n (%)	20 (66.7%)
No, n (%)	10 (33.3%)
Mode of delivery	
Vaginal, n (%)	23 (67.3%)
C – section, n (%)	7 (23.3%)
* CL - Cervical length	

Majority of the patients, 14 (46.7%) were at gestational age of $32^{+0} – 34^{+0}$ w.g, 7 (23.3%) were at gestational age of $28^{+0} – 31^{+6}$ w.g, and 9 (30 %) were at gestational age of $24^{+0} – 27^{+6}$ g.w. Premature preterm rupture of membranes was detected in 14 (46.7%), out of which almost half, 42.8% delivered within less than 24 hours of the membrane rupture. Cervical shortening of < 25 mm, determined by transvaginal ultrasound was registered in 18 (60 %) of the examination group. In approximately same number of patients, 20 (66.7%) contractions were present that could be registered on admission cardiotocography. Most of the patients included in the analysis, 23 (76.7%) had a spontaneous vaginal delivery. Analysis on the presence of maternal inflammatory response, defined as a presence of histopathological changes type acute chorioamnionitis of different grade and stage, on the analyzed tissue sample of the placenta and fetal membranes, are presented in table 3. The same table

contains results on the fetal inflammatory response, defined through a presence of hystopathologycal changes type funisitis, vasculitis or umbilical vessels thrombosis, of different grade and stage, in the tissue samples from the umbilical cord. Analysis was performed for each of the inclusion criteria using Fisher's exact test. Data were considered statistically significant if $p < 0.05$.

Table 3: Influence of inclusion criteria on the presence of histopathological changes of the feto-palcental unit

Variable (inclusion criterion)			Inflammatory response				
			Maternal		p	Fetal	p
Weeks of gestation	24^{+0} - 27^{+6}	Yes	9 (30%)			4 (13.3%)	
		No	0			5 (16.6%)	
	28^{+0} - 31^{+6}	Yes	3 (10%)		0.042*	1 (3.3%)	0.237
		No	3 (10%)			5 (16.6%)	NS
	32^{+0} - 34^{+0}	Yes	6 (20 %)			2 (6.6%)	
		No	6 (20 %)			13 (43.3%)	
Cervical length	< 25 mm	Yes	13 (43.3%)			5 (16.6%)	
		No	4 (13.3%)		0.443	12 (40%)	0.427
	≥25 mm	Yes	8 (26.6%)		NS	2 (6.6%)	NS
		No	5 (16.7%)			11 (36.7%)	
pPROM	Present	Yes	8 (26.7%)			3 (10%)	
		No	6 (20 %)		0.236	11 (36.7%)	1.00
	Absent	Yes	13 (43.3%)		NS	4 (13.3%)	NS
		No	3 (10%)			12 (40%)	
Cervical dilatation	> 2 cm	Yes	11 (36.7%)			3 (10%)	
		No	3 (10%)		0.440	11 (36.7%)	1.00
	≤ 2 cm	Yes	10 (33.3%)		NS	4 (13.3%)	NS
		No	6 (20 %)			12 (40 %)	
Contractions	Present	Yes	13 (43.3%)			4 (13.3%)	
		No	7 (23.4%)		0.675	16 (53.3 %)	0.657
	Absent	Yes	8 (26.6%)		NS	3 (10 %)	NS
		No	2 (6.7%)			7 (23.4 %)	
Mode of delivery	Vaginal	Yes	19 (63.3%)			7 (23.4 %)	
		No	4 (13.3%)		0.014*	16 (53.2 %)	0.154
	C - section	Yes	2 (6.7%)			0	NS
		No	5 (16.7%)			7 (23.4 %)	

* Statistically significant for $p < 0.05$

The analysis reviled that only two of the variables (inclusion criteria), and those are gestational age and mode of delivery, have statistically significant influence on the presence of acute inflammatory changes, and this is only for the maternal inflammatory response. Prevalence of acute inflammatory changes is statistically significantly higher in patients at lower gestational age (30% in patients at gestational age of $24^{+0} – 27^{+6}$ w.g, $p<0.05$), and in the group of patients with vaginal delivery, contrary to those delivered by C – section (63.3% and 6.7% respectively, $p<0.05$). As far as the gravity, or the grade and the stage of the inflammatory changes of the placenta, fetal membranes and umbilical cord is concerned, defined according to the criteria of AFINCPSPP, cervical length (CL) and the mode of delivery are parameters with statistically significant influence. Patients with CL < 25 mm and those with vaginal delivery, more often present with higher grade and stage of the inflammatory changes of the placenta and fetal membranes ($p = 0.036$ and $p = 0.043$ respectively, for $p<0.05$).

Table 4: Distribution of the different grades of inflammatory changes of the placenta and fetal membranes in relation to the inclusion criteria and the delivery mode

Variable (inclusion criteria)		Grade of maternal inflammatory responce				X^{2*}	p
		0	**1**	**2**	**3**		
Weeks of gestation	$24^{+0} – 27^{+6}$	0	1	3	5	11.746	0.068 NS
	$28^{+0} – 31^{+6}$	3	1	0	2		
	$32^{+0} – 34^{+0}$	6	4	4	1		
CL	< 25 mm	4	2	3	8	8.539	0.036‡
	≥25 mm	5	4	4	0		
Cervical dilatation	> 2 cm	3	2	4	5	2.186	0.535 NS
	≤ 2 cm	6	4	3	3		
Contractions	Present	7	4	5	4	1.571	0.666 NS
	Absent	2	2	2	4		
pPROM	Present	6	3	3	2	3.023	0.388 NS
	Absent	3	3	4	6		
Mode of delivery	Vaginal	4	5	6	8	8.128	0.043‡
	C - section	5	1	1	0		

0 – no inflammatory response, 1 – early stadium (acute subchorionitis or chorionitis), 2 – intermediate stadium (acute chorioamnionitis), 3 – advanced stadium (necrotizing chorioamnionitis)
* Perason's X^2 coefficient
‡ Statistical significance at $p < 0.05$

The results presented above, demonstrate discrepancy between the prevalence of the inflammatory changes of the placenta and the fetal membranes (any grade and stage) and the distribution of the different grades of the inflammatory changes in the same compartments, in different gestational age groups. Namely, even though the presence of the inflammatory changes (any grade and stage) is significantly more frequent in patients at lower gestational age ($24^{+0} – 27^{+6}$ w.g), there is no statistically significant difference in the prevalence of higher grades of inflammatory changes in this group. Never the less, the correlation analysis for the different grades of the inflammatory changes of the placenta and the fetal membranes on one side, and gestational age, divided according to the inclusion criteria in three (3) subgroups ($24^{+0} – 27^{+6}$ w.g, $28^{+0} – 31^{+6}$ w.g, $32^{+0} – 34^{+0}$ w.g) on the other side, show statistically significant difference ($p<0.05$). The same statement is valid for the cervical length also, and in both cases the correlation is inversely proportional (table 5).

Table 5: Nonparametric correlation between the gestational age, cervical length and the grade of the inflammatory changes of the placenta and fetal membranes

	τ*	p
Gestationa age	- .415	.010
CL	.371	.029
* Kendall tau coefficient $p < 0.05$		

When have also analyzed the link between acute inflammatory changes of the feto-placental unit (maternal and fetal inflammatory response) of any grade and stage, and at the same time different grades of inflammatory response of the feto-placental unit on one side, and time passed from pPROM to delivery, on the other. Our data did not presented statistically significant difference in the prevalence of the inflammatory changes (any grade and stage) in correlation to the time passed from pPROM to delivery. There was also no statistically significant correlation between the time passed from pPROM to delivery and the prevalence of different grades and stages of maternal and fetal inflammatory response.

Table 6: Distribution of the inflammatory changes of the feto-placental unit depending on the time passed from pPROM to delivery and correlation analysis between the grade of inflammatory changes and time passed from pPROM to delivery

Variable		Inflammatory response					
		Maternal			Fetal		
		Present	Absent	p*	Present	Absent	p*
T passed from pPROM to delivery	< 24 h	16 (53.3 %)	5 (16.7 %)	0.513	5 (16.7 %)	16 (53.3 %)	1.00
	24-48 h	1 (3.4 %)	0		0	1 (3.4 %)	
	48-72 h	2 (6.7 %)	2 (6.7 %)	NS	1 (3.4 %)	3 (10 %)	NS
	> 72 h	2 (6.7 %)	2 (6.7 %)		1 (3.4 %)	1 (3.4 %)	
	†τ	-.127			0.046		
	p	0.434 NS			0.787 NS		

* Fisher's exact test (statistically significant at $p < 0.05$)

† Kendall tau coefficient

4. Discussion

This cohort prospective study is aimed to determine the prevalence of the acute inflammatory changes of the placenta, fetal membranes and the umbilical cord, defined as acute chorioamnionitis, funisitis, umbilical vasculitis and umbilical vessels thrombosis, in 30 patients with preterm delivery syndrome, delivered at the

University clinic for obstetrics and gynecology in Skopje. On the other hand, we have tried to determine if the prevalence of the inflammatory changes, their grade and stage, depend on the variables that were taken as an inclusion criteria for the study, and by themselves define the preterm delivery syndrome. Those were gestational age, presence of pPROM, presence of uterine contractions, degree of cervical dilatation and the degree of cervical shortening. Additional variable that we have analyzed was the mode of delivery, and its influence on the above-mentioned inflammatory changes. Basic evaluation showed that the prevalence of the inflammatory changes of the feto-placental unit, defined as acute chrioamnionitis, funisitis, umbilical vasculitis and umbilical vessels thrombosis, of any grade and stage, in our subjects was higher (70%) than in previously published studies (22-59%) [6,7,8]. Out of the total number of subjects included in the study (30), in 21 inflammatory changes of the placenta and fetal membranes, of any grade and stage, were detected. If we concentrate only on the fetal inflammatory response, defined trough the presence of acute funisitis, umbilical vasculitis or umbilical vessels thrombosis, the prevalence in our population was 23.3%. The data that were previously published, showed similar prevalence for acute funisitis, of 19.2%, but only in patients with lower grade of inflammatory changes of the placenta and fetal membranes. These data also show that the prevalence of acute funisitis, umbilical vasculitis and umbilical vessels thrombosis is much higher in patients with higher grade and stage of acute inflammatory changes of the placenta and fetal membranes, and it goes up to 55% [14,21]. This was not a case in our study group, in which we did not find statistically significant difference in the prevalence of fetal inflammatory response in any of the three gestational age groups (13.3% at gestational age of 24^{+0} - 27^{+6} w.g, 3.3% at gestational age of 28^{+0} - 31^{+6}, and 6.6% at gestational age of 32^{+0} - 34^{+0} w.g; $p = 0.237$, for $p<0.05$). One of the most common conclusions of the studies previously conducted, is that the maternal inflammatory response i.e. the prevalence of the acute histopathological changes of the placenta are inversely correlated to the gestational age, meaning that lower gestational age, more frequent is the presence of histologically verified acute chorioamnionitis [6,12,22]. Our study only confirmed this conclusion. The prevalence of acute inflammatory changes of the placenta was statistically significantly higher ($p=0.042$, $p<0.05$) in the group with lowest gestational age (24^{+0}-27^{+6} w.g) than in other two groups (28^{+0}-31^{+6} w.g and 32^{+0}- 4^{+0} w.g). Although the analysis of the distribution of the different grades of placental inflammatory response (0, 1, 2, 3; where 0 represent absence and 3 represents highest degree of inflammatory response) did not presented with statistically significant difference in correlation to gestational age, by applying nonparametric correlation analysis we have concluded that the grade of inflammatory changes of the placenta and fetal membranes is inversely correlated to the gestational age and that in patients delivered at lower gestational age there is statistically significantly higher prevalence of inflammatory changes of higher grade ($p=0.01$, $p<0.05$). Half of the patients at gestational age of 24^{+0} - 27^{+6} w.g (5/9 or 50%, had a highest degree, grade 3, of acute inflammatory changes), whereas only 30% (2/6) of the patients at gestational age of 28^{+0} - 31^{+6} w.g and only 6.6% (1/15) had the same grade of acute inflammatory changes of the placenta ($p = 0.01$, for $p < 0.05$, $\tau = - 0.415$). Of the other variables that we analyzed, mode of delivery (vaginal or C - section) was proven to have statistically significant influence on the prevalence of acute inflammatory changes of the placenta and fetal membranes, both for any grade and stage, and for higher grades and stages. Out of total number of patients (30), 27 (76.7%) had a vaginal delivery, contrary to 7 (23.3%) delivered by C – section. The prevalence of acute chorioamnionitis on the tissue samples from the placenta is significantly higher in the vaginal delivery group ($p<0.05$, $p = 0.014$). At the same time, in this group of patients, there is significantly higher presence of higher grades of inflammatory changes of the

placenta and the fetal membranes (maternal inflammatory response), ($p<0.05$, $p = 0.043$). These data can probably be explained by the inflammatory base of the uterine contractions. Studies that have been published to date, though primarily in term patients, suggest that in patients with spontaneous onset of uterine contractions and cervical dilatation > 4 cm, there is significantly higher prevalence of acute inflammatory changes of the placenta [12,23]. Cervical length (CL) < 25 mm, as an individual risk factor did not show statistically significant influence on the prevalence of the acute inflammatory changes of the feto-placental unit, neither for the maternal nor for the fetal inflammatory response ($p = 0.443$ for maternal and $p = 0.427$ for fetal inflammatory response, for $p<0.05$). On the other hand there was statistically significant difference in the distribution of the higher grades (grade 2 and 3) of acute inflammatory changes of the placenta in the group with CL < 25 mm ($p = 0.036$, for $p<0.05$)**.** As far as the time passed from pPROM to delivery is considered, and its influence on the prevalence and gravity (grade and stage) of the inflammatory changes of the feto-placental unit (acute chorioamnionitis, acute funisitis, umbilical vasculitis and umbilical vessels thrombosis), our study did not show statistically significant difference neither for the prevalence ($p<0.05$, $p=0.513$ for maternal and $p=1.00$ for fetal inflammatory response), nor for the grade of the inflammatory changes ($p<0.05$, $p=0.434$ for maternal and $p=0.787$ for fetal inflammatory response). There are very few limitations of the study. First of all, lack of control group of term patients in the study limited the possibility for evaluation of the prevalence of acute inflammatory changes of the placenta in term pregnancies, although there is evidence that acute inflammatory changes defined as acute chorioamnionitis are more prevalent in term deliveries with spontaneous onset of labor and cervical dilatation > 4 cm, contrary to term patients without spontaneous onset of labor (11.6% and 4.7% respectively) [12]. We suggest further research in this direction in order to evaluate the true influence on the spontaneous onset of labor on the prevalence, as well as the gravity, of the hystopathologicaly proven acute chorioamnionitis on the preterm delivery syndrome. On the other hand, even though the analysis of the data suggested that vaginal mode of delivery vs. cesarean delivery in preterm patients, significantly influences the prevalence and gravity of acute inflammatory changes, we feel that the results were influenced by the uneven distribution of study population (23 vaginal deliveries vs. 7 C-sections).

5. Conclusion

Preterm delivery, as one of the most important problems of contemporary perinatology, with its far-reaching health, social and economic consequences, continues to be one of the most challenging topics for the scientific and academic community. This study intended to shed light on the pathogenesis of this issue and to clarify the influence of certain factors on the appearance and prevalence of acute histopathological changes of the placenta, fetal membranes and the umbilical cord, in patients with preterm delivery syndrome. Studies that have been published to date, clearly show that there is a strong connection between this complex problem and acute inflammatory changes of the feto-placental unit. This study just confirmed the data that have been published so far i.e confirmed that there is inversely proportional correlation between gestational age and the prevalence of acute chorioamnionitis in the tissue samples of evaluated placentas. That is to say, that in patients delivered at lower gestational age, we can expect higher prevalence of acute inflammatory changes. At the same time, correlation analysis showed that inflammatory changes in the group at lower gestational age are more often of higher grade. The prevalence and the grade of acute histopathological changes, defined as acute chorioamnionitis, are not dependent only on the gestational age, but on the cervical length and the delivery

mode as well. The question on the influence of spontaneous onset of labor and its inflammatory base, on the higher prevalence of the acute inflammatory changes of the placenta and on the higher grade of acute inflammatory changes in the placentas of women delivered preterm, is still open, considering that the correlation has only been proven in term pregnancies.

Premature preterm rupture of fetal membranes and the time passed to delivery are certainly to be considered as a risk factors, even though the data from our study did not presented significant correlation neither for the prevalence of the acute inflammatory changes of the placenta, nor for their grade and stage.

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