CLINICAL AND BIOLOGICAL EVOLUTION OF THE NEWBORN WITH THROMBOCYTOPENIA IN THE NEONATAL INTENSIVE CARE UNIT

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Abstract

Introduction: Thrombocytopenia is one of the most common haematological disorders detected in the newborn period, especially in neonates admitted to intensive care units and usually indicates an underlying pathological process. *Objectives:* To determine the etiology, the time of onset, the clinical characteristics and the evolution of newborns with thrombocytopenia. *Material and method:* 97 newborns with platelet counts (<150,000 / µl) were selected from those admitted to the Neonatology section of the Timisoara Children's Emergency Hospital "Louis Turcanu" for a period of 3 years. The determination of the initial values of platelets was performed at the hospitalization and then daily monitoring or even twice daily in the case of newborns with severe thrombocytopenia. *Results:* Grade IV thrombocytopenia (<25000 / µl) was present in 13.4% of cases, grade III (25000-50,000 / µL) in 16.5% of cases, grade II (50,000-75,000 / µL) in 9 , 3% of cases and grade I (75,000-150000 / µL) in 60.8% of cases. Most of the newborns (55.7%) were premature and the major causes of thrombocytopenia were sepsis, in 69.1% of cases and hypoxic suffering in 66% of cases. Mortality was 12.6% (n = 14). *Conclusion:* Thrombocytopenia occurring in newborns admitted to the neonatal intensive care unit is not a negative prognostic factor but rather a marker of severity of the underlying pathology.

Abbreviations: HIE, hypoxic ischemic encephalopathy; SGA, small for gestational age; AGA, appropriate for gestational age;

Keywords: thrombocytopenia, newborns, infections, hypoxia

Introduction

Studies of fetal blood obtained by cordocentesis show that the mean fetal platelet count reaches 150 x 10^9/µL by the end of the first trimester of pregnancy and increases above 150 × 10^9 / µL by end of the second trimester. Several population studies also show that >98% of term neonates born to mothers with normal platelet counts have platelets above 150 × 10^9 / µL at birth. Therefore thrombocytopenia in a neonate of any viable gestational age can be defined as a platelet count of <150 × 10^9 / µL The incidence is 1-5% of newborns and 22-35% of newborns admitted to neonatal intensive care units[1,2,3,4].

The risk of severe thrombocytopenia is higher in preterm infants. In newborns with extremely low birth weight (<1,000 grams), the incidence of thrombocytopenia is greater than 70% and the incidence of severe thrombocytopenia (<50,000 / µL) is 40%[5]. The period of onset of thrombocytopenia can be: early (within 72 hours after birth) and late (after 72 hours of life).

Causes of early thrombocytopenia are placental insufficiency, perinatal asphyxia, autoimmune or alloimmune. Hypoxia-ischemia (HI) is a contributing factor to neonatal morbidity and mortality, often leading to chronic neurological disorders and disabilities, such as mental retardation, motor and behavioral developmental issues, cerebral palsy, seizure, and epilepsy. Newborns with mild HIE (grade I) have a favorable evolution. Approximately 80% of the patients with grade II encephalopathy recover; however, the mortality rate is 3 and 20-45% have neurological sequelae. Patients with severe HIE (grade III) have a mortality rate of 50% and survivors present severe neurological consequences [6].The incidence of HIE ranges from 1 to 8 per 1,000 live births in developed countries and is as high as 26 per 1,000 live births in underdeveloped countries [7].

Manifestations of HIE involve heart rhythm disorders, basic acid balance disorders (pH<7.0 or basic deficiency ≥12 mmol/l), low Apgar index, amniotic fluid impregnated with meconium or the need for respiratory support in the first few minutes of postnatal life [8].

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The redistribution of cerebral blood flow induced by asphyxia is the main post asphyxiation change. Brain injury results from hypoxia and ischemia. As a result of asphyxia, cardiac output is compensated by redistribution, thus increasing cerebral blood flow. If hypoxia persists, this self regulatory mechanism is no longer effective, resulting in decreased heart rate, with systemic hypotension and decreased cerebral flow leading to brain damage. At the cellular level, oxygen depletion blocks oxidative phosphorylation resulting in an anaerobic metabolism, which is energy inefficient, resulting in: i) Rapid depletion of phosphate reserves, including adenosine triphosphate, ii) accumulation of lactic acid and iii) inability to maintain cellular functions.

Severe maternal autoimmune thrombocytopenic disease, before or during pregnancy, was associated with an increased risk of severe fetal thrombocytopenia [9].

Late onset of thrombocytopenia is most commonly caused by infections / septicemia and necrotizing enterocolitis. Sometimes the causes of thrombocytopenia are prenatal viral infections (Cytomegalovirus, Toxoplasmosis, Rubella, HIV), perinatal bacterial infections (Group B streptococcus, Escherichia coli and Haemophilus Influenzae), or aneuploidy (especially trisomy 18, 13 and 21) [1,10].

Thrombocytopenia is usually seen with Gram positive septicemia as compared to Gram negative septicemia and low platelet is usually seen even before the pathogens are cultured from the blood. Therefore, thrombocytopenia may be considered as an important and early tool in diagnosis of septicemia in neonates [11].

Also among the factors that cause thrombocytopenia were incriminated in the literature also H2 antagonists - a case of severe thrombocytopenia induced by Ranitidine [4] and also by Vancomycin [12] has been described.

Previous detailed studies have attempted to define the mechanisms by which these conditions cause thrombocytopenia, but, until recently, the mechanism underlying many neonatal thrombocytopenias remained unknown [13].

The rather complex process of platelet production and release can be schematically represented as being made up of four main stages:

1) the production of thrombopoietic cytokines, mostly thrombopoietin, which is produced in the liver and is the main regulator of platelet production in humans [14]. Platelets are involved in hemostasis, influence the coagulation cascade and are the main source of many biologically active substances [15].

2) proliferation of megakaryocyte progenitors;

3) maturation of megakaryocytes in large polypoid cells capable of producing platelets;

4) release of platelets into circulation. Megakaryocytes in newborns are smaller and less mature than adult megakaryocytes, and smaller megakaryocytes are known to produce fewer platelets than larger and more mature megakaryocytes. This developmental feature may limit the ability of newborns to increase platelet production in response to platelet consumption. In addition, preterm infants appear to have relatively low levels of thrombopoietin during thrombocytopenia, which may limit their ability to rapidly regulate platelet production during increased platelet consumption [16]. Thrombopoietin is elevated during hypoxia. The number of platelets is negatively correlated with thrombopoietin levels on days 1, 3 and 7 of life in hypoxic infants [17].

Current evidence suggests that most platelet destruction in the newborn is immunologically mediated. It is shown that 15% to 20% of all neonatal thrombocytopenia present at birth results from transplacental passage of allo and / or autoantibodies [10]. Alloimmunization is the most common cause of severe thrombocytopenia [18].

Prematures babys born from the mother with preeclampsia who develops early bacterial sepsis and the baby with intrauterine growth restriction who develops necrotizing enterocolitis can both become thrombocytopenic (after pre-eclampsia or intrauterine growth restriction), combined with thrombocyte intake (during sepsis or necrotizing enterocolitis) [13].

It was found a strong correlation between delivery by cesarean section and thrombocytopenia. Disseminated intravascular coagulation occurs during sepsis and is found in 10% - 15% of thrombocytopenia cases admitted in neonatal intensive care [19].

In some studies it was concluded that birth weight and head circumference in infants with thrombocytopenia were significantly lower than in infants without thrombocytopenia. There was also a smaller number of hematopoietic progenitor cells in the blood from the umbilical cord of the SGA compared to the AGA [20].

Material and method:

This is a retrospective, cross-sectional cohort study carried out in the Neonatology Section of the Emergency Hospital for Children "Louis Turcanu" Timisoara. The study was conducted for a period of 3 years, from 01.01.2016 to 31.12.2018. The study included 97 newborns with a birth weight between 450 grams and 4900 grams.

Inclusion criteria:

1) Newborn suffering from birth asphyxia and subsequently developing hypoxic ischaemic encephalopathy or newborns with neonatal infection.

2) Newborn who fulfill the case definition criteria

3) Birth weight 450 grams and 4900 grams

4) Neonates surviving more than 24 hrs.

Exclusion Criteria:

1) incomplete data about the patient, information unavailable in the computer system of the hospital unit

2) major congenital anomalies, birth trauma

3) newborn borns to mothers having major diseases like malaria, severe anaemia, pre eclamsia/eclamsia, thyroid disorder, idiopathic purpura, placental disorder like vascular thrombosis, abruptio placenta

4) H/o maternal intake of any drugs causing bone marrow suppression/ thrombocytopenia

5) Newborn with congenital leukaemia, those having exchange transfusion.

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The demographic, gestational and perinatal data for the newborns included in the study were reviewed, including the presence of antenatal risk factors for both thrombocytopenia and sepsis of any kind (especially when associated with maternal diabetes, maternal use of steroid, maternal fetal infections, chorioamniotitis etc.).

All thrombocytopenic newborns were identified by computerized search of medical records in the online medical unit database.

Hemotological investigation. Hematological investigations were performed with a Sysmex XS800i analyzer using imped-ance spectroscopy, flow cytometry, Hydro Dynamic Focusing (DC Detection method) and the reagents were provided by Sysmex Corp. (Kobe, Japan). The cell blood count (CBC) was collected from peripheral venous blood, 1 ml of blood, and the sample was taken in a test tube with EDTA (sodium calcium edetate). The unit of measurement for thrombocytopenia was µl.

Data analyzes were performed using the statistical package (SPSS), version 23.0. Comparisons between group means were analyzed using the ANOVA test. Pearson's chi-squared test was used for each separate variable. If Pearson's chi-squared test could not be used the Fisher test was used. A p value of less than 0.05 was considered to be significant.

Results and discussion:

Thrombocytopenia is a common problem in the newborn period and is a significant cause of morbidity and mortality in children with different pathologies, both for term and premature births. Newborns are particularly vulnerable to infections due to a deficient immune defense.

Neonatal thrombocytopenia is usually mild to moderate; with spontaneous resolution and without requiring any specific therapy. The major risk of severe thrombocytopenia is intracranial hemorrhage leading to death or neurological disability [21,22], but no direct relationship between the severity of thrombocytopenia and the severity of intracranial hemorrhage has been observed [22]. The frequency of intracranial hemorrhage was estimated in 1% -3% of cases [23]. The relationship between platelet count and hemorrhage was unclear.

The frequency of bacterial infections in intensive care units was 10% - 32.3%, with an average occurrence of thrombocytopenia around the 17th day. Another study reports that thrombocytopenia was observed in 38% of all sepsis episodes. This was however not significantly different in infections by gram-negative and fungal versus gram-positive organisms [24,25].

The frequency of neonatal hypoxia reported in the literature was 23.9% term hypoxic neonates and 33.3% at preterm hypoxic neonates [26]. Reduced platelet count is a frequent finding in HIE. During the early period (0-2) days it is related to severity of HIE [found only in HIE Gr III], but in the later period (3-14 days) it may be found in all categories [27].

Studies report that the most common etiological diagnosis in all the admitted cases was sepsis (67%) followed by prematurity (52%) and perinatal asphyxia (21%). More than one diagnosis was present in the cases admitted with thrombocytopenia. Disseminated intravascular coagulation, necrotizing enterocolitis, and meconium aspiration syndrome were also some of the important causes identified [28].

During the 3 years in which the study was performed, 1247 newborns were hospitalized in the Neonatology Department of the "Louis Turcanu" Children's Emergency Hospital in Timisoara, of which 97 (7.7%) were included in the study with the diagnosis of neonatal thrombocytopenia. Of these, 57 (58.8%) were male and 40 (41.2%) were female. As a medium of origin, 55.7% came from urban areas and 44.3% from rural areas. Of these, 54 (55.7%) were premature and 43 (44.3%) full-term newborns. The average gestational age was 35.51 weeks and an average weight of 2401.55 grams at birth.

The mean onset of thrombocytopenia was 8.76 days.

Regarding the duration of thrombocytopenia, we have an average of 4.97 days (figure 1).

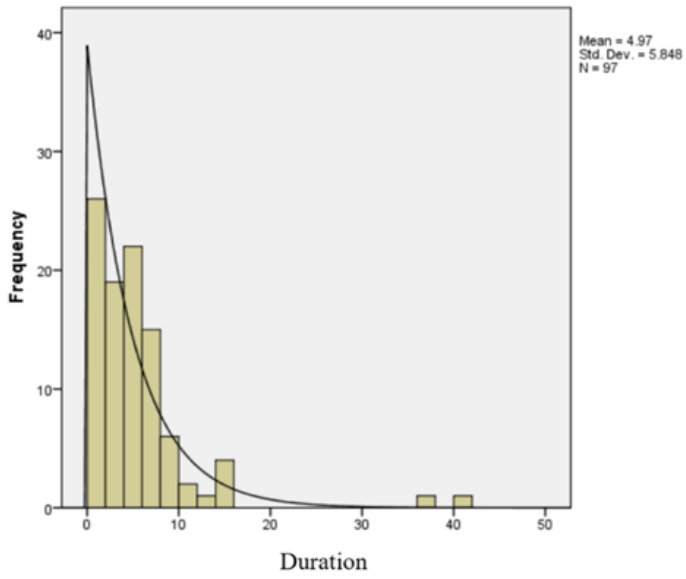

Fig.1 Mean duration of thrombocytopenia.

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Patients were divided into two study groups, namely, a group with a duration of thrombocytopenia less than 3 days and a group with an evolution over 3 days. Thus, 46.4% (n = 45) had an evolution duration of less than 3 days with subsequent remission and 53.6% (n = 52) had an evolution duration of thrombocytopenia over 3 days. It can be deduced that in our study group the vast majority of patients developed mild thrombocytopenia compared to the other study groups where moderate and severe thrombocytopenia predominated both in the first 72 hours and at more than 72 hours (table 1).

The mean value of platelets was 93.510 / µl. Depending on the value of platelets, patients were classified in severity, so 59 newborns (60.8%) were classified in the first grade of severity (75000 – 150000 /µL), 9 newborns (9.3%) in grade II (50000 – 75000 /µL), 16 newborns (16.5%) in grade III (25000 – 50000 /µL) and 13 newborns (13.4%) in grade IV (<25000 /µL) (figure 2).

Table 1. Duration of thrombocytopenia.

Study on neonatal thrombocytopenia in NICUs	**<72 hours**		**>72 hours**	
	Moderate	**Severe**	**Moderate**	**Severe**
Castle et al[24]	66.11%	47.01%	39.24%	52.23%
Rajeev mehta[24]	13%	20%	36.2%	51%
Patil et al[24]	73.11%	44.68%	26.88%	55.31%
Our study	**12.9%**	**11.2%**	**22,8%**	**14.2%**

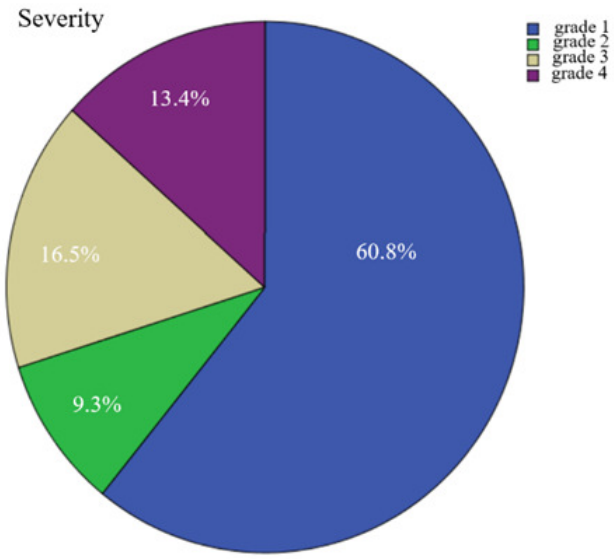

Fig.2 Severity of thrombocytopenia.

Knowing that thrombocytopenia occurs more frequently in the first 3 days in patients with hypoxia and after 3 days in patients with infections or ulceronecrotic enterocolitis, it was observed that the onset of thrombocytopenia in the first 3 days of life was found in 62 newborns (63.9 %), and after 3 days of life in 35 newborns (36.1%).

Hypoxia was found in 66% of thrombocytopenic patients, of whom 51.5% were premature newborns, predominantly male (57.5%) (Table 2).

Infections were detected in 69.1% of newborns, and hemorrhagic pathology or hemorrhagic syndromes were observed in 37.1% of newborns (table 3).

Tabel 2. Prevalence of hypoxemia.

Studies on neonatal thrombocytopenia in NICUs	Prevalence of hypoxemia
Nadkarniet al[21]	23.9% term hypoxic neonates 33.3% preterm hypoxic neonates
Our study	**48.5% term hypoxic neonates** **51.5% preterm hypoxic neonates**

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Tabel 3. Prevalence of infections.

Studies on neonatal thrombocytopenia in NICUs	Prevalence of infections
Castle et al[24]	10%
Hale Oren et al[24]	5.4%
Patil et al[24]	28.17%
Our study	**69.1%**

37.1% (n = 36) of male patients and 23.7% (n = 23) of female patients were classified in the first grade of severity of thrombocytopenia.

Regarding the severity of thrombocytopenia, we can say that 41.2% (n = 40) of the patients in grade I had a limited evolution in less than 3 days, and 19.5% (n = 19) of those in grade I had an evolution more than 3 days of thrombocytopenia, while the evolution of all patients in grade IV severity (13.4%) was over 3 days (figure 3).

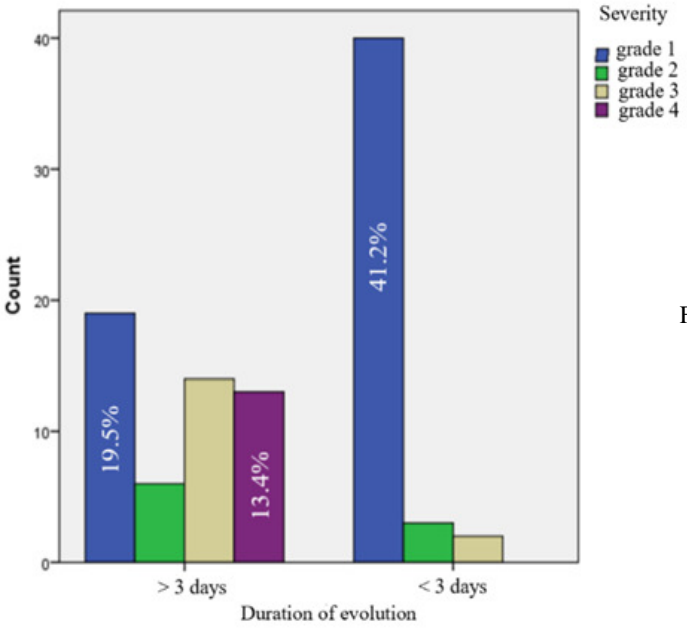

Fig.3 Severity depending on the duration of evolution.

Knowing that 53.6% (n = 52) of patients with thrombocytopenia had a duration of evolution over 3 days, 30.9% (n = 30) were male and 22.6% (n = 22) female. In both the group with evolution less than 3 days and in the group with evolution over 3 days, male patients were predominant.

Prematurity was found in 55.7% (n = 54) of cases, predominating male - 51.8% compared to 48.1% females. We observe that in case of the study group with evolution over 3 days of thrombocytopenia, 34% (n = 33) were born prematurely, while in the case of the group with evolution under 3 days, 24.7% (n = 24) were newborn at term. Knowing that in the first 3 days thrombocytopenia is more common due to hypoxia, we can say that in newborns at term thrombocytopenia the date of hypoxia was more common in the first 3 days (figure 4). Regarding the severity of thrombocytopenia, the vast majority of premature infants 48.4% (n = 31) were classified in the first grade of severity (figure 5).

Hypoxia was found in 66% (n = 64) of thrombocytopenic patients, 54.6% (n = 35) were male and 45.4% (n = 29) female. Analyzing the incidence of hypoxia depending on the duration of thrombocytopenia, we observe that in patients with less than 3 days of evolution, 45.3% (n = 29) were hypoxic, while in the case of the group with more than 3 days of thrombocytopenia, 54.6% (n = 35) were hypoxic (figure 6). The vast majority of 40.2% hypoxic patients (n = 39) were classified in the first grade of severity (figure 7).

In figure 8 are supported the previously reported, that 68.7% (n = 44) of premature babies were hypoxic.

As values with statistical significance ($p < 0.05$), it was observed that in the case of female newborns, thrombocytopenia started on average at 4.43 days; while in male newborns at 11.8 days (table 4).

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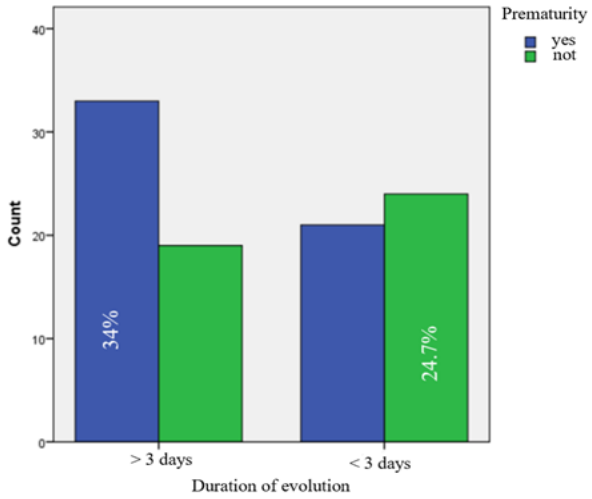

Fig.4 Duration of evolution in premature newborns.

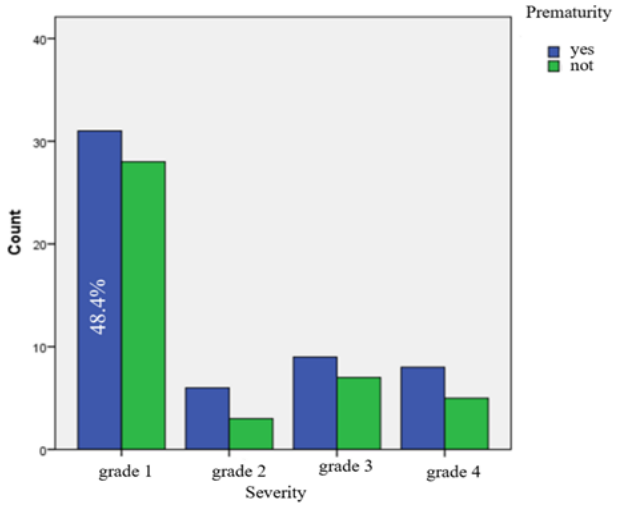

Fig.5 Severity of thrombocytopenia in premature infants.

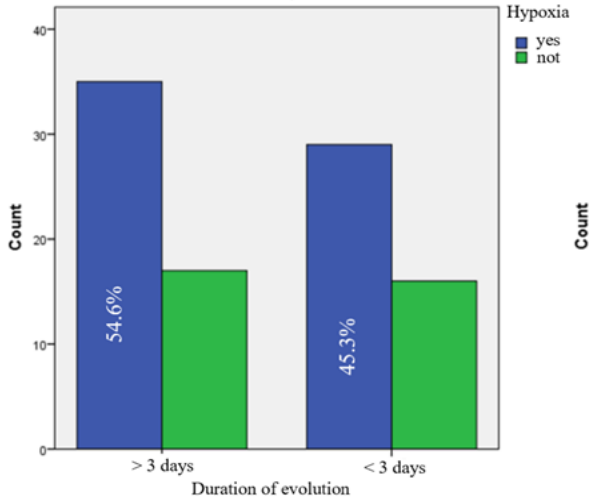

Fig.6 Duration of thrombocytopenia in hypoxic newborns.

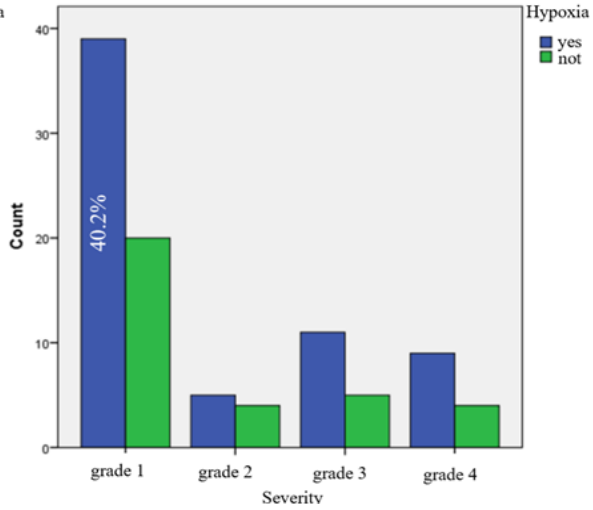

Fig.7 Severity of thrombocytopenia in hypoxic newborns.

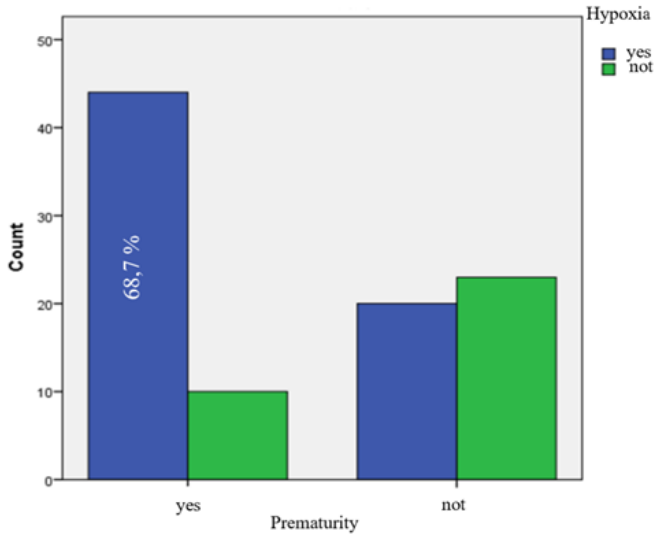

Fig.8 Prematurity in hypoxic newborns.

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Table 4. The onset of thrombocytopenia by gender.

Gender		Gestation	Weight	Onset (p<0,05),	Duration	Platelet count/ x10^9/µl
F	N	40	40	40	40	40
	Mean	35.90	2280.25	4.43	4.60	93.85
	Std. Deviation	3.774	750.782	6.193	5.697	43.857
	Std. Error of Mean	.597	118.709	.979	.901	6.934
M	N	57	57	57	57	57
	Mean	35.23	2486.67	11.81	5.23	93.26
	Std. Deviation	4.448	934.135	19.251	5.988	44.033
	Std. Error of Mean	.589	123.729	2.550	.793	5.832

In grade I thrombocytopenic patients (n = 59), the mean weight was 2404.41 grams, the onset of thrombocytopenia was on average on day 8.37, the mean duration of thrombocytopenia was 3 days and the mean platelet count was 117,000 /µL. Grade II thrombocytopenic patients (n = 9) had an average weight of 2308.89 grams, the onset of the pathology was on day 17.44, the mean duration of thrombocytopenia was 4.78 days and the mean platelet count was 102,670/µL. Grade III newborns (n = 16) had an average weight of 2285 grams, the pathology began on average day 7.19, an average duration of thrombocytopenia of 8.38 days and an average value of platelets of 60,690/µL. Grade IV (n = 13) had an average weight of 2596.15 grams, the onset was on day 6.46, an average duration of 9.8 days and an average platelet count of 17,770/µL.

Values with statistical significance (p <0.05) were observed when comparing duration with severity, where it is observed that the lower is the severity, the lower is the duration of thrombocytopenia, so it can be seen that the first grade of severity corresponds to a duration of 3 days of evolution, compared to grade IV where a duration of 9.85 days is observed (table 5).

Table 5. The severity of thrombocytopenia depending on the duration.

Severity		Gestation	Weight	Onset	Duration (p<0.05)	Platelet count/ x10^9/µl
grade 1	N	59	59	59	59	59
	Mean	35.29	2404.41	8.37	3.00	117.69
	Std. Deviation	4.263	911.836	15.113	2.512	23.496
	Std. Error of Mean	.555	118.711	1.968	.327	3.059
grade 2	N	9	9	9	9	9
	Mean	36.11	2308.89	17.44	4.78	102.67
	Std. Deviation	4.755	920.346	28.880	2.906	27.281
	Std. Error of Mean	1.585	306.782	9.627	.969	9.094
grade 3	N	16	16	16	16	16
	Mean	35.50	2285.00	7.19	8.38	60.69
	Std. Deviation	4.099	774.700	11.940	9.150	31.455
	Std. Error of Mean	1.025	193.675	2.985	2.287	7.864
grade 4	N	13	13	13	13	13
	Mean	36.08	2596.15	6.46	9.85	17.77
	Std. Deviation	3.840	767.078	7.501	8.513	17.589
	Std. Error of Mean	1.065	212.749	2.080	2.361	4.878

Depending on the duration of thrombocytopenia, patients were divided into two groups; lasting less than 3 days and lasting more than 3 days.

Thus with the statistically significant value (p <0.05) it was observed that in the case of patients in whom thrombocytopenia lasted up to 3 days (n = 45) the average onset was on day 12.36; the mean duration of thrombocytopenia was 1.6 days and the average platelet count was 115,640/µL. In neonates in whom thrombocytopenia lasted more than 3 days (n = 52), it was observed that on average the onset was in day 5.65, the mean duration of thrombocytopenia was 7.88 days and the mean value of platelet count was 74,350/µL (table 6).

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Table 6. Duration of thrombocytopenia.

Duration		Gestation	Weight	Onset (p<0.05)	Duration (p<0.05)	Platelet count/ x10^9/µl (p<0.05)
>3 days	N	52	52	52	52	52
	Mean	35.65	2335.77	5.65	7.88	74.35
	Std. Deviation	4.134	810.213	8.232	6.720	45.251
	Std. Error of Mean	.573	112.356	1.142	.932	6.275
<3 days	N	45	45	45	45	45
	Mean	35.33	2477.56	12.36	1.60	115.64
	Std. Deviation	4.264	927.940	20.775	.780	29.399
	Std. Error of Mean	.636	138.329	3.097	.116	4.382

In the case of hypoxic patients (n = 64) compared to those who did not suffer from hypoxia, with statistically significant value (p <0.05), it was observed that the average birth weight was 2197.66 grams, the average gestational age was 34.42 weeks and onset of thrombocytopenia on day 5.33. In the case of newborns without hypoxic distress, it was observed that the average birth weight was 2796.97 grams, the average gestational age was 37.6 weeks and the onset of thrombocytopenia on day 15.42 (Table 7).

Table 7. Evaluation of hypoxic newborns.

Hypoxia		Gestation (p<0.05)	Weight (p<0.05)	Onset (p<0.05)	Duration	Platelet count/ x10^9/µl
yes	N	64	64	64	64	64
	Mean	34.42	2197.66	5.33	5.09	91.89
	Std. Deviation	4.305	897.327	12.947	5.628	44.687
	Std. Error of Mean	.538	112.166	1.618	.703	5.586
not	N	33	33	33	33	33
	Mean	37.61	2796.97	15.42	4.73	96.64
	Std. Deviation	2.989	644.765	18.329	6.336	42.319
	Std. Error of Mean	.520	112.239	3.191	1.103	7.367

It was also observed that in the case of hypoxic patients the mean duration of thrombocytopenia was 5.09 days with a mean platelet count of 91,890/µL, and in neonates without hypoxic distress, the mean duration of thrombocytopenia was 4.7 days with a mean platelet count of 96,640/µL.

In patients with infection (n = 67), the mean time to onset of thrombocytopenia was 10.99 days, while in patients without infection (n = 30) the mean time to onset of thrombocytopenia was 3.80 days, with a mean duration smilara and an average platelet value approximately equal (Table 8).

Table 8. Evaluation of thrombocytopenic infections in newborns.

Infections		Gestation	Weight	Onset	Duration	Platelet count/ x10^9/µl
yes	N	67	67	67	67	67
	Mean	35.55	2433.13	10.99	4.75	90.85
	Std. Deviation	4.415	914.965	17.990	5.417	44.618
	Std. Error of Mean	.539	111.781	2.198	.662	5.451
not	N	30	30	30	30	30
	Mean	35.40	2331.00	3.80	5.47	99.43
	Std. Deviation	3.654	751.598	6.155	6.786	41.807
	Std. Error of Mean	.667	137.222	1.124	1.239	7.633

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Conclusion

The most common cause of early-onset thrombocytopenia is fetal hypoxia; most often it is self-limited and rarely severe.

After 72 hours, the most common cause of thrombocytopenia among newborns admitted to the intensive care unit is infectious pathology.

In our study, the hypoxic infants with whom thrombocytopenia was associated were predominant in males.

In the case of hypoxic patients, thrombocytopenia started earlier, had a longer duration and a higher grade of severity compared to newborns without hypoxic suffering.

It was observed that the more severe are the form of thrombocytopenia, the longer is the regeneration period. As the severity of thrombocytopenia was lower, the duration of thrombocytopenia was shorter and appeared later. The onset of thrombocytopenia among the patients in study was 8.7 days and with an average duration of 4.97 days.

Thrombocytopenia occurring in neonates admitted to the neonatal intensive care unit is not a negative prognostic factor but rather a marker of severity of the underlying pathology.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AIM and MB conceived and designed the study; AIM and AMM collected the data. AMM and CMJ analyzed the data; AIM and CMJ edited the figures and AIM, AMM and CMJ drafted the manuscript. MB revised the manuscript critically for important intellectual content. All authors contributed to the data interpretation and approved the submitted version.

Ethics approval and consent to participate

Approval of the local ethics committee (Ethics Committee for Scientific Research of the Emergency Hospital for Children 'Louis Turcanu) was obtained prior to starting the study. Parental or caregiver consent was obtained where applicable. This publication and the database does not contain personal data, does not compromise anonymity or confidentiality or breach local data protection laws.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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