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A decade of neonatal polycythaemia – has anything changed in this field?

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ABSTRACT

Introduction: This study aims to determine the prevalence, clinical features, and methods of treating polycythaemia (PC) and hyperviscosity (HVS) syndrome in newborns over a 10-year period (2012–2022). Furthermore, it aims to determine whether there have been changes in the incidence of PC in the region encompassed by the study.

Material and methods: This retrospective study sample included all the newborns with a diagnosis upon admittance and discharge of PC and HVS syndrome.

Results: Incidence of PC and HVS syndrome was 0.8% (153/18.407) of the total number of babies born and 2.8% (153/5.483) of the treated newborn. Polycythaemia was more common in newborn males, in newborn weighing more than 2500 grams, with normal vitality scores, born at full term, and with other pathological conditions. The most common pathological condition in the newborn with PC was jaundice, and the most common symptoms were plethoric and dry skin, rash, and hypotonia. Furthermore, mothers with and without pathological conditions, who gave birth naturally, were equally represented.

Conclusions: This 10-year study concludes that the prevalence of PC was constant over the years. Furthermore, mothers with and without pathological conditions, who gave birth naturally, were equally represented. The newborns were more frequently male, full-term babies, with good vitality scores and birth weights. Also, all the above leads to the conclusion that the newborns had passive PC that was not caused by a medical indication at birth, which led to the spectrum of various symptoms and pathological conditions that accompany PC. On the basis of the above results, it can be concluded that PC is most often passive in our region, which is why PC must be taken into consideration in the daily care of newborns despite the controversial opinions on the above-mentioned pathology.

KEY WORDS:

infants, haematocrit, neonatal polycythaemia, hyperviscosity, plethoric skin.

INTRODUCTION

Neonatal polycythaemia (PC) and hyperviscosity (HVS) are well-known pathological conditions in practice, but many differing, controversial opinions exist regarding the diagnosis and treatment of the same conditions [1]. Neonatal PC and HSV are defined as haematocrit $\geq 65\%$ and viscosity values > 2 standard deviations greater than the normal range [2]. Although the true incidence of this

condition is not known, it has been suggested that the PC rate in healthy, full-term newborn babies is 0.4–5% [3]. Venous haematocrit levels are used as a surrogate marker for viscosity because diagnosis is primarily based on haematocrit values and on symptoms that can vary from subtle to acute, but not on viscosity values. Neonatal PC can develop in post-term newborn or in those who are small for their gestational age, in newborn babies of mothers with hypertension or diabetes, in twin-to-twin trans-

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fusion syndromes [4], and in newborn with chromosomal abnormalities [5]. Usually there are multifactorial reasons for PC; thus, it can be identified as active (increased foetal erythropoiesis) or passive (red-blood cell transfusion) PC. Passive PC can be linked to delayed cord clamping [6]. When umbilical cord clamping is delayed for more than 3 minutes after birth, the volume of blood increases by 30%, which can lead to the development of PC and hyperbilirubinaemia [3]. In this respect, a high prevalence of PC and hyperbilirubinaemia was observed in cohorts of healthy newborns during the first phase of the COVID-19 pandemic. A study published in 2022 [7] found that placental malperfusion, even in asymptomatic women infected with SARS-CoV-2, led to increased foetal erythropoiesis and thereby to PC. Polycythaemia has a wide range of complications, affecting multiple organ systems, and 50% of the newborns with PC developed one or more symptoms. Moreover, most of these symptoms were non-specific and could be ascribed to other primary health conditions [8]. Haematocrit values are not routinely measured in the neonatal population, probably due to the controversies surrounding the treatment of an asymptomatic child. The bottom line is that PC increases blood viscosity, which complicates microcirculation of the blood and leads to neurological, gastrointestinal, cardio-pulmonary, renal, thrombotic, and metabolic manifestations in the untreated newborn [1–3]. The treatment of asymptomatic neonatal PC is contentious; however, this is due to the lack of proof indicating that strong treatment improves long-term results [3]. Partial exchange transfusion (PET) has been traditionally used as a method to lower haematocrit levels and treat HVS [1]. However, it is unclear whether this is an effective approach to preventing long-term neurological consequences [9].

Neonatologists need to combine their extensive knowledge of the possible causes of PC, particularly of passive PC caused by delayed cord clamping for various reasons, which then causes practical problems in daily work. Furthermore, knowledge of the pathophysiology, clinical features, and symptoms can contribute to early diagnosis and successful treatment of newborns with PC and HSV, thereby reducing possible long-term consequences.

MATERIAL AND METHODS

This study aims to determine the prevalence, clinical features, and methods of treating PC and HSV in newborns over a 10-year period (2012–2022). Furthermore, it aims to determine whether there have been changes in the incidence of PC in the region encompassed by the study.

EXAMINEES AND METHODS

This retrospective 10-year study was conducted at the Department of Neonatology of the Clinic for Children's Diseases at the University Clinical Hospi-

tal (UCH) in the period 1 January 2012 – 31 December 2022. The study used data collated from protocols, patient histories, and discharge letters of newborns treated at the Department of Neonatology of the Clinic for Children's Diseases UCH. The study sample included all the newborns whose diagnoses upon admittance and discharge were PC and HVS syndrome. The data were obtained from medical documentation, patient histories, and discharge letters of the newborns treated at the departments of the Clinic for Children's Diseases UCH, and through access to the transfer lists of mothers and children. The parameters analysed for the mother were age, parity, type of pregnancy, mode of delivery, spontaneous abortion, medication, and pathological conditions during pregnancy (diabetes, hypertension, hyperthyreosis, infection before labour, and other pathological conditions). The parameters analysed for the newborn were: gender, birth weight, gestational age, age at which PC manifested, time of birth, season of birth, vitality score, method of treatment, length of treatment, HVS syndrome clinical picture, and other pathological conditions in the newborn (jaundice, asphyxia, hypotrophy, perinatal infection, brain hypoxia, thrombocytopaenia, hypoglycaemia, chromosome abnormality). Symptoms of the newborns included jaundice, hypotonia, bradycardia, rash, high-pitched crying, lethargy, apnoea, cyanosis, heart murmur, and blocked nose. The following definitions were used: hypoglycaemia – capillary or serum glucose value < 2.5 mmol/l; thrombocytopaenia – platelet count $< 150 \times 10^3/\text{mm}^3$; erythrocyte reference interval $3.9\text{--}5.5 \times 10^9/\text{l}$, haemoglobin $136\text{--}199$ g/l; and haematocrit $0.391\text{--}0.580$ l/l. The newborns were diagnosed with PC and HVS syndrome if erythrocyte values exceeded $6 \times 10^9/\text{l}$, haemoglobin concentration exceeded 220 g/l, and haematocrit values exceeded 0.650 l/l. For the purposes of biochemical laboratory analysis, a 2 ml venous blood sample was drawn into a test tube with no anticoagulant, and a 2 ml sample for the blood count was drawn into a test tube with anticoagulant. The University Clinical Hospital laboratory employs immuno-turbidimetric testing on latex particles to determine concentration in venous blood serum and measures it using an Olympus AU 680 analyser.

STATISTICAL ANALYSIS

Categorical data are expressed as numbers and percentages. The χ^2 test was used to test the significance of differences for specific characteristics. Statistical analysis was calculated in IBM SPSS Statistics, version 25 (Armonk, NY: IBM Corp.). The statistical significance limit was $p = 0.05$.

RESULTS

A total of 18,407 newborns were born at UCH during the period of the study 1 January 2012 – 31 December 2022. Of these, 5483 newborns were treated at the De-

partment of Neonatology, of whom 153 were diagnosed with PC and HSV. Based on these data, the percentage of incidence of PC and HVS syndrome was 0.8% of the total number of babies born and 2.8% of the treated newborns. During the study period, the highest number of newborns treated for PC was recorded in 2020 and 2021 during the COVID-19 pandemic. Asymptomatic pregnant women were not tested during pregnancy, unless they were in labour. Of the total 40 PC cases during the pandemic, 6 of the mothers had a COVID-19 infection during labour, and 9 of them had had the infection while pregnant.

Distribution of the characteristics of the mothers of newborn with PC during the study period 2012–2022 are shown in Table 1.

Polycythaemia was equally represented in single parity and multiple parity mothers. No difference was found regarding the incidence of PC in relation to medication consumption during pregnancy or to the presence of pathological conditions during pregnancy. The pathological conditions during the pregnancies were as follows: hypertension (32/153), diabetes (12/153), hypothyreosis (8/153), infection (20/153), and other pathological conditions (10/153). Of the mothers of the newborn who were diagnosed with PC, the results indicate that they most often had not had abortions, gave birth naturally, and had single pregnancies, as presented in Table 1.

Distribution of the characteristics of the newborn with PC during the study period from 2012 to 2022 are shown in Table 2.

Polycythaemia was more common in newborn males, in newborns weighing more than 2500 grams, with normal vitality scores, born at full term, and with other pathological conditions. The treatment administered to most of the newborns lasted less than 7 days. Polycythaemia was more common in newborns who were born between 8 p.m. and 8 a.m., i.e. during the night shift. The incidence of PC did not differ much according to season, although there were a few more cases during autumn. A detailed overview of the characteristics is presented in Table 2.

Pathological conditions, symptoms, and mode of treatment of the newborns with PC in the study period 2012–2022 are shown in Table 3.

The most common pathological condition in the newborn with PC was jaundice, and the most common symptoms were plethoric and dry skin, rash, and hypotonia. All the newborns with PC were given infusions during treatment. Only a few newborn babies were treated with PET in the 10-year period. The pathological conditions, PC symptoms, and mode of treatment are presented in Table 3.

DISCUSSION

Neonatal PC and HVS syndrome can be caused by numerous conditions that develop intrauterine, during pregnancy or during labour. This 10-year study indicates a 0.8% prevalence of PC among newborn babies, which concurs with the findings of other global studies [3, 10]. Polycy-

TABLE 1. Distribution of the characteristics of the mothers of newborn with polycythemia during the study period

Parameters	<i>n</i>	Percentage	χ^2	<i>p</i> -value
Parity			0.163	0.686
Primipara	74	48.4		
Multiparus	79	51.6		
Type of birth			45.026	< 0.001
Natural	118	77.1		
Caesarean section	35	22.9		
Type of pregnancy			112.163	< 0.001
Singleton pregnancy	142	92.8		
Multiple pregnancy	11	7.2		
Abortion			64.059	< 0.001
No	126	82.4		
Yes	27	17.6		
Medications during pregnancy			3.458	0.063
No	88	57.5		
Yes	65	42.5		
Pathology in pregnancy			0.320	0.571
No	80	52.3		
Yes	73	47.7		

TABLE 2. Distribution of the characteristics of the newborn with polycythemia during the study period

Parameters	<i>n</i>	Percentage	χ^2	<i>p</i> -value
The gender			12.085	0.001
Male	98	64.1		
Female	55	35.9		
Weight [g]			80.529	< 0.001
≥ 2500	132	86.3		
< 2500	21	13.7		
Vital score			98.882	< 0.001
10/10	138	90.2		
< 10/10	15	9.8		
Gestational age (weeks)			64.059	< 0.001
37+	126	82.4		
–37	27	17.6		
Pathological conditions			47.222	< 0.001
No	34	22.2		
Yes	119	77.8		
Length of treatment (days)			49.471	<0.001
< 7	120	78.4		
≥ 7	33	21.6		
Hour of birth			41.216	< 0.001
08–14	57	37.3		
14–20	16	10.5		
20–08	80	52.3		
Season			6.346	0.096
Winter	30	19.6		
Spring	35	22.9		
Summer	37	24.2		
Autumn	51	33.3		
Meal tolerance time			5.497	0.019
In the first 12 hours after birth	62	40.5		
12 hours after birth	91	59.5		

thaemia was more prevalent during the COVID-19 pandemic. Polycythaemia was most common during the mid-year period (2020–2021). This finding concurs with the conclusion of an Italian study that found a high prevalence of PC and hyperbilirubinaemia in cohorts of healthy babies born during the first phase of the COVID-19 pandemic. It is a reasonable assumption that even an asymptomatic SARS-CoV-2 infection during pregnancy could result in vascular placental malperfusion triggering PC [7]. Possible reasons for this are the delayed ligation of the umbilical cord, which has been a trend in recent years among women in labour. In support of this is the fact that no child needed resuscitation during the examined period, which would have been the reason for the delayed ligation of the umbilical cord. Although other studies found PC to

be more prevalent in the newborn of mothers with hypertension and diabetes who gave birth via C-section [11], this result was not confirmed by our study. Polycythaemia was more common in the newborns of mothers who gave birth naturally, and it was equally prevalent in healthy mothers and mothers with pathological conditions. This confirms the supposition that hypoxic changes during natural childbirth can be linked to the incidence of PC, although none of our newborns had asphyxia as an additional pathological condition [8]. Although most of the newborn with PC were born at full term, the number of post-term babies with PC was 14.4%, which suggests that it is not uncommon in post-term babies, a finding confirmed by a cohort study [12]. Neurological symptomatology manifested in a third of the newborns, which is similar to the findings

of a study from 2008 [11], whereas other studies found that 60% of children with PC developed neurological symptoms [13]. The most common pathological conditions connected with PC were jaundice, infection, and changes in the brain. Hypoglycaemia was not observed, and there were 2 cases of newborns who were small for their gestational age. Other studies have also found that hypoglycaemia was not common in PC [14], and that jaundice was found to be the most common pathological condition [7, 11]. Our study indicated that PC was more common during natural childbirth, during night shifts and in early morning shifts, after emergency C-sections, and where cord clamping could be delayed due to potential reanimation procedures. A subjective observation is that a possible reason for PC in our study is passive PC caused by the above factors. Contrary to our findings, a 2017 study found that delayed cord clamping did not trigger passive PC [5], compared to early umbilical cord clamping which reduced the prevalence of PC [3]. In addition, our study indicates that every newborn with PC developed a symptom that could not be ascribed to other pathological conditions, such as heart murmurs and blocked noses (approximately 10% of the cases), whilst other studies found that the symptoms were non-specific and could be attributed to other primary health conditions [8]. Our newborns were treated with standard therapies, and only a small percentage of the newborns required PET. There is no proof of clinical short-term or long-term benefits of PET in newborns with PC who were clinically well or had fewer HVS-related symptoms [15]. Due to PC's broad spectrum of specific and non-specific symptomatology, the possibility of permanent neurological complications, and the controversial opinions on the prevalence and mode of treating PC in newborn, extensive knowledge and long-term experience are needed to predict the possible development of PC in newborns with a predisposition for it.

The limitations of the study were the lack of data on any subsequent neurological complications of the children who had PC as newborn babies. Another limitation of the study is also the lack of data on the frequency of PC at the national level. The study was limited to only one part of the population.

CONCLUSIONS

This 10-year study concludes that the prevalence of PC was constant over the years, with the exception of the pandemic period during which the incidence of PC was more common, possibly triggered by placental malperfusion. Furthermore, mothers with and without pathological conditions, who gave birth naturally, were equally represented. The newborns were more frequently male, full-term babies, with good vitality scores and birth weights. Also, all the above lead to the conclusion that the newborns had passive PC that was not caused by a medical indication at birth, which led to the spec-

TABLE 3. Pathological conditions, symptoms and mode of treatment of the newborn with polycythemia in the study period

Parameters	n	Percentage
Other pathological conditions		
Jaundice	85	55.6
Infection	32	20.9
Hypoxic changes in the brain	27	17.6
Premature baby	22	14.4
Thrombocytopenia	17	11.1
Small for date (IUGR)	7	4.6
Cromosomal diseases	2	1.3
Symptoms		
Dry skin and rash	62	40.5
Plethoric skin	60	39.2
Hypotonia	45	29.4
A murmur over the heart	17	11.1
Stuffy nose	15	9.8
Sobbing	11	7.2
Bradycardia	10	6.5
A shrill cry	10	6.5
Treatment method		
Infusion	153	100.0
Phototherapy	79	51.6
Antibiotics	37	24.2
Fresh frozen plasma	29	19.0

trum of various symptoms and pathological conditions that accompany PC. Based on the above results, it can be concluded that PC is most often passive in our population, which is why PC must be taken into consideration in the daily care of newborns despite the controversial opinions on the above-mentioned pathology.

DISCLOSURES

1. This retrospective study was conducted in accordance with the ethical principles of the University Clinical Hospital. Ethical approval was obtained from the Ethics Committee of the Clinical Hospital Centre.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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