Polycythemia of the newborn

MARIA HAJDUCZENIA1, OSKAR JAREMA1, MARTA SZYMANKIEWICZ2

Abstract
Polycythemia is defined as a venous hematocrite above 65%. The relationship between viscosity and hematocrite is almost linear till 65% and exponential thereafter. The etiology of polycythemia is related either to intrauterine hypoxia or secondary to fetal transfusion. Most polycythemic infants are asymptomatic. Increased viscosity of blood may be associated with symptoms of hypoperfusion. Clinical features related to polycythemia may affect all organ systems. Screening for polycythemia should be performed in certain high-risk groups. Partial exchange transfusion (PET) is accepted yet still controversial treatment of polycythemia. There is no clinically important difference between crystalloids and colloids in reducing hematocrite. Since crystalloids are more readily available and cheaper and do not confer any risk of infection or anaphylaxis, crystalloids are the optimal therapeutic fluid. PET is effective in reducing hematocrite and in relieving symptoms related to polycythemia. However, there is no reliable evidence of clinically important benefit from PET, especially of a long term neurological benefit.

Key words: polycythemia, hyperviscosity, partial exchange transfusion, newborn

Definition and epidemiology
Polycythemia is described as a condition in which an increased red cell mass leads to increased viscosity of the blood [1]. Clinically it is most commonly defined as venous blood hematocrite higher than 65% [1-6] or hemoglobin concentration higher than 22.0 g/dl [2, 5].

The incidence of polycythemia varies within the range of 1.5 and 4% of all live births [3-7] and differs depending on gestational age, as well as birth weight and length [6]. The incidence is higher among both small for gestational age (SGA – approximately 15%) and large for gestational age (LGA – approximately 6-8%) infants, as compared to 2% of appropriate for gestational age (AGA) term newborns. Polycythemia is less likely to occur in patients born at gestational age less than 34 weeks [3-6]. Birth at centers located at higher altitudes is also associated with greater incidence of polycythemia [3, 5].

Physiological changes of hematocrite value
Newborn hematocrite undergoes physiological changes after birth. It peaks in second hour after birth, when its normal value may reach 71%. The increase in hematocrite is directly proportional to the amount of blood that newborn received from the placenta. Moreover, these changes stay in causal relationship with the transudation of fluid out of the intravascular space. After 6 hours hematocrite falls to approximately 68% and reaches its full stability in 12-24 hour of life. Up until first week of life it reaches the values comparable to the primary values measured in the umbilical cord [2, 5].

It is highly worth mentioning that the definition of abnormal hematocrite at the time of birth tends to vary in terms of gestational age. Still there are very few publications concerning desirable hematocrite values for newborns with extremely low birth weight (ELBW) [9].

Venous vs. capillary hematocrite
RBC concentration values in the newborn blood differ depending on the type of the vessel, from which the sample was drawn. For hematocrite measurements both venous and capillary blood are used. However, it should be emphasised that capillary hematocrite measurements are less reliable and highly susceptible to variations in blood flow. Moreover, they tend to be significantly higher than venous hematocrites. It is caused by RBC’s ruleaux formation and their migration through vessel walls. As an outcome the capillary hematocrite values can be 5 to 25% higher than venous ones, which in turn are greater than those from umbilical vein [3]. Warming of the heels before taking a capillary blood sample is compulsory and results in better correlation between values elicited from capillary and venous blood. Capillary samples are used for polycythemia screening. However, in case of increased hematocrite values the diagnostic test has to be confirmed using venous sample.

1 Perinatology Student Scientific Working Group, Poznań University of Medical Sciences, Poland
2 Department of Neonatology, Poznań University of Medical Sciences, Poland
Venous hematocrit significantly correlates with hematocrit of arterial blood [4, 5].

**Polycythemia and hyperviscosity syndrome**

Polycythemia stays in close relationship with hyperviscosity [10]. In literature polycythemia tends to be called a marker of hyperviscosity syndrome [11]. Viscosity, as defined by Poiseuille, is the ratio of shear stress to shear rate. The shear stress represents the pressure gradient along the blood vessel, while the shear rate represents the velocity between two fluid planes, divided by the distance between them [3]. Therefore, blood viscosity is basic physical feature of the blood, reflecting its resistance against the flow and defining flow conditions in the whole vascular system [12]. The viscosity of blood does not remain constant [3]. It is directly proportional to the hematocrit. This correlation is almost linear up to a hematocrit of 65% and exponential thereafter [2, 3, 5, 6]. Hyperviscosity is diagnosed when blood viscosity value is greater than 2 standard deviations from the mean for given population [1, 3, 5]. This phenomenon almost exclusively coexists with high hematocrit values, overreaching 60%. However, it should be emphasized that hyperviscosity may also result from an increase in plasma proteins (especially fibrinogen), decreased deformability of fetal erythrocytes [1, 3, 5, 6], decreased erythrocyte aggregation and interaction of cell components with vessel walls [6]. At a given hematocrit, whole blood viscosity decreases with decreasing maturity of the neonate due to reduced plasma viscosity. Mixing neonatal RBC with adult plasma and adult RBC with neonatal plasma changes blood viscosity at given hematocrit to values respectively for adult and neonatal suspensions (i.e., neonatal RBC in adult plasma behave like adult blood). Moreover, fetal transfusion of adult blood increases fetal blood viscosity in a manner that is dependent on both the rise in hematocrit and in plasma protein concentration. Thus, the effects of plasma proteins on haemorheological properties have to be considered when plasma is transfused together with RBC [13].

The increased blood viscosity may result in tendency to microclot formation as well as in symptoms of hypoperfusion and hypoxia. Particularly hazardous are consequences of brain cortical lesion, damage to the liver and adrenal glands. Symptoms of hypoperfusion correlate better with blood viscosity as compared to hematocrit. However, viscosity is difficult to measure. Wells-Brookfield cone-plate micro-viscosimeter is used for the purpose of viscosity measurement. Since such instruments are not readily available in most neonatal intensive care units, hyperviscosity suspicion usually bases on the presence of suggestive symptoms and an abnormally high hematocrit [3, 5].

**Etiology of polycythemia**

Polycythemia of the newborns may be the consequence of compensatory mechanism for intrauterine hypoxia, as well as may occur secondary to fetal transfusions or have fetal origin.

Polycythemia secondary to fetal transfusions may occur due to delayed cord clamping after birth, acute fetal distress, twin-to-twin transfusion syndrome, maternal-fetal transfusion, perinatal asphyxia, holding the baby below the level of introitus [3, 5]. Acute fetal distress results in a shift of blood volume from the placenta to the fetus, leading to an increased blood volume and red-cell mass [3]. Delayed umbilical cord clamping is defined as performed later than 3 minutes after delivery of baby [5]. Statistically significant difference in the incidence of polycythemia has been observed even within at-risk patients group that underwent early umbilical cord clamping (i.e., in less than 3 minutes after delivery). In one subgroup of mentioned neonates umbilical cords were clamped within first 10 seconds of life and in the second subgroup between 11 and 120 second of life. The polycythemia rate in the first group of infants turned out to be significantly lower [14]. Therefore, early cord clamping and holding the baby at the level of the introitus at the time of delivery could serve as methods of polycythemia prevention, by minimizing maternal-fetal transfusion [5]. There are however publications that proved no significant differences in hematocrit values between patients after early (up to 30 seconds) and delayed (after 3 minutes) umbilical cord clamping [15].

Intrauterine hypoxia induces compensatory increase in eryththropoietin and therefore in RBC production [3, 6]. This phenomenon is observed in conditions like maternal hypertension (12 fold increased risk) [16], maternal diabetes (type I diabetes mellitus (DM) and gestational diabetes) [17], maternal cyanotic heart disease, intrauterine growth retardation, post-mature deliveries, perinatal asphyxia, maternal smoking [3, 5] (the dose-response significant relationship was observed [18]). The incidence of polycythemia in infants of diabetic mothers (type I DM or gestational diabetes) accounts for 22-29%. Polycythemia in these newborns correlates with macrosomia and neonatal hypoglycaemia [3, 5]. In the group of LGA infants, born from the pregnancies complicated by gestational diabetes, elevated absolute nucleated RBC counts (which is considered to be one of the intrauterine
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hypothesized markers) as well as increased hematocrite levels were observed within first 12 hours of life. In this group of patients hematocrite at birth correlated with maternal glycohemoglobin A1 (HbA1c) level at delivery, which is an index of glycemic control during the last trimester of pregnancy. The mentioned abnormalities have not been observed in AGA infants of diabetic women. This fact supports the theory, that it is actually impaired glycemic control during pregnancy that is responsible for elevated absolute nucleated RBC counts and increased hematocrite in newborns [17].

Among possible fetal conditions related to the increased risk of polycythemia there are genetic syndromes, including trisomies, especially 18, but also 13 [19] and 21 [20], as well as Beckwith-Wiedemann syndrome. Another fetal causes include congenital hypothyroidism, neonatal thyrotoxicosis, congenital adrenal hyperplasia [3, 5]. It is important to emphasize that the most common cause for increased hematocrite is dehydration, which usually results from feeding problems, improper (too high) environmental temperature, neonatal fever, diarrhea, vomiting. Dehydration should always be ruled out before diagnosing and treatment of polycythemia [3, 5]. The summary of possible polycythemia causes is presented in the Table 1.

### Table 1. Causes of polycythemia [5]

<table>
<thead>
<tr>
<th>Secondary to intrauterine transfusion</th>
<th>Delayed cord clamping</th>
<th>Acute fetal distress</th>
<th>Feto-fetal transfusion</th>
<th>Maternal-fetal transfusion</th>
<th>Holding the baby below the level of introitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary to intrauterine hypoxia</td>
<td>Intrauterine growth retardation</td>
<td>Gestational hypertension,</td>
<td>Maternal diabetes</td>
<td>Maternal smoking</td>
<td>Maternal cyanotic heart disease</td>
</tr>
<tr>
<td>Fetal causes</td>
<td>Trisomy 13, 18, 21</td>
<td>Beckwith-Wiedemann syndrome</td>
<td>Hypothyroidism/Thyrotoxicosis</td>
<td>Congenital adrenal hyperplasia</td>
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### Symptoms of polycythemia

Mild polycythemia is most commonly asymptomatic, particularly if becomes apparent only on routine neonatal screening. Symptoms, when present, can affect all the systems and organs. They are usually attributable to hyperviscosity and poor tissue perfusion or to associated metabolic abnormalities such as hypoglycaemia and hypocalcaemia [1, 4, 8].

Newborns with severe polycythemia may be characterized by flushed face (plethora), which is the feature of the greatest diagnostic significance, because all the other clinical symptoms are highly unspecific and similar to various pathological conditions [6]. Elevated hematocrite value leads to impaired oxygen transport due to flow disturbances resulting from hyperviscosity [8]. The most common problems in symptomatic patients with severe polycythemia are central nervous system disorders. As early neurologic symptoms may occur hypotonia and lethargy, irritability and jitteriness, seizures, generalized tremor (including fibrillation). Moreover, cyanosis (due to peripheral stasis), hypothermia, poor sucking and feeding can be observed [5, 8, 21]. Serious complications include cardiopulmonary distress (with or without congestive heart failure) with tachycardia and tachypnea [8]. Chest X-ray may reveal cardiomegaly and pulmonary congestion. In echocardiographic examination increased pulmonary vascular resistance as well as decreased cardiac output may be observed. In relation to impaired flow of the hyperviscous blood through mesenteric vessels increased risk of necrotizing enterocolitis was described [3, 5, 6]. Another documented pathology correlated with polycythemia is a decrease in hepatic blood flow, which leads to delay in bile acids elimination and reduced trypsin and lipase activity. This could explain the alimentary disorders the polycythemic patients suffer from [6]. Polycythemia may also result in renal function disturbances, such as decrease in renal blood flow or in glomerular filtration, leading to oliguria, hematuria, proteinuria and fluid retention with impaired elimination of sodium and potassium [5, 6]. However, only infants with normovolemic polycythemia would be expected to have a reduction in renal function. Newborns with an increased blood volume should have normal renal function [3]. Incidents of renal vein thrombosis, peripheral gangrene and priapism were described [5, 22]. Among metabolic disturbances, the most common one is hypoglycaemia (12-40%). Jaundice (due to increased hemolysis) or hypocalcaemia can also appear [3, 5, 23]. Another described abnormality was increased level of calcitonin gene related peptide (CGRP), which may be implicated in the circulatory adaptation to extrauterine life. In polycythemic neonates CGRP is probably increased to compensate for blood hyperviscosity. In some cases high CGRP concentrations may induce hypocalcaemia [24]. Hematologic disturbanc-
ces which can coexist with polycythemia include mild thrombocytopenia, low antithrombin III levels and occasionally thrombosis, e.g. umbilical venous catheter-related thrombosis in preterm infants or cerebral venous sinus thrombosis [3, 5, 22, 25]. Explanations for the low platelet count include their impaired production secondary to tissue hypoxia, predominance of erythropoietic cells in the bone marrow, slow spleen blood flow and decreased plasma fraction with normal platelet concentration [3].

Most of the mentioned complications are usually transient in character and mild, even in cases of advanced polycythemia [25]. The principle clinical concern is that polycythemia may be associated with adverse long term neurological sequelae (psychomotor deficits, lower IQ scores) [1, 5, 25]. It is worth to emphasise that most of the mentioned polycythemia symptoms are non-specific and may be related to the underlying conditions rather than due to polycythemia per se [1, 3, 5].

Screening

Polycythemia screening involves patients from certain high-risk groups (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Indications for polycythemia screening [5]</th>
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<tbody>
<tr>
<td>a) Small for gestational age (SGA) neonates</td>
</tr>
<tr>
<td>b) Large for gestational age (LGA) neonates</td>
</tr>
<tr>
<td>c) Infants of diabetic mothers (IDM)</td>
</tr>
<tr>
<td>d) Newborns with morphological features of growth restriction</td>
</tr>
<tr>
<td>e) Monochorionic twins especially the recipient twin</td>
</tr>
</tbody>
</table>

Screening test includes hematocrite measurement in second hour of life. If its value is less than 65% and patient does not present any of clinical symptoms, further hematocrite measurement is not required. However, if hematocrite value exceeds 65%, it is recommended to repeat the test in 12 and 24 hour of life, using venous blood samples. In clinical practice, hematocrite measurements in such cases are performed more frequently. Every patient presenting symptoms suggestive of polycythemia requires hematocrite control [5].

Therapeutic management

Before a diagnosis of polycythemia is established, it is mandatory to exclude dehydration, which is the most common cause of increased hematocrite values. A very helpful management in the establishment of correct diagnosis can be repeated weighing of the newborn and looking for excessive weight loss, which suggests dehydration. If present, it should be corrected by increasing fluid intake, e.g. by supervised feeding. After proper rehydration subsequent measurement of patient hematocrite should follow.

In case of established diagnosis of polycythemia it is essential to rule out coexisting metabolic disturbances, especially the most common one – hypoglycaemia [3, 5].

Two models of polycythemia therapy have been described: conservative management with rehydration and partial exchange transfusion (PET). Conservative management is indicated in cases of asymptomatic polycythemia with hematocrite values 70-75%. It consists of accessory oral or intravenous fluid administration (approximately 20 ml/kg/24h). The idea of this therapy is hemodilution and the resultant decrease in blood viscosity. Liberal and excessive fluid therapy, especially in preterm babies, may be however the cause of further complications, like volume overload, hyponatremia, patent ductus arteriosus or sepsis. That is why this specific type of treatment should be reserved only for hemodynamically stable infants with asymptomatic polycythemia [5].

PET is accepted yet still controversial method of polycythemia treatment [26]. This therapy is indicated for newborns with symptoms suggestive of polycythemia (with the exception of plethora [28]) or hyperviscosity as well as for asymptomatic infants with hematocrite greater that 75% [5, 6]. Neonates of mothers who smoked during pregnancy when compared to the babies of non-smokers require PET significantly more often [27]. PET performance rate was described to be significantly higher also in infants with coexisting thrombocytopenia. Moreover, statistically significant rise in platelets counts after PET was observed, which may imply that thrombocytopenia is a possible marker of hyperviscosity [28].

The summary of polycythemia management algorithm is presented in Figure 1.

The aim of PET is to reduce packed cell volume and thereby blood viscosity while at the same time maintaining intravascular volume [25]. A target hematocrite value for this kind of therapy is approximately 55%.

The volume of blood that has to be exchanged is calculated using the following formula [5, 6]:

$$\text{blood volume} \times \frac{(\text{measured hematocrite} - \text{desired hematocrite})}{\text{measured hematocrite}}$$
Blood volume of the newborn depends on its birth weight. This correlation is presented in the Table 3.

<table>
<thead>
<tr>
<th>Birth weight [g]</th>
<th>Blood volume [ml/kg]</th>
</tr>
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<tbody>
<tr>
<td>&lt; 2000</td>
<td>100</td>
</tr>
<tr>
<td>2000-2500</td>
<td>95</td>
</tr>
<tr>
<td>2500-3000</td>
<td>85</td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>80</td>
</tr>
<tr>
<td>Infants of diabetic mothers</td>
<td>80-85</td>
</tr>
</tbody>
</table>

There are two possible routes of carrying out PET: peripheral and central. The first one is performed by the placement of peripheral venous and arterial lines. The blood is drawn from the arterial line (single draw volume of approximately 5-10 ml [6]) and its volume is simultaneously replenished with fluids through the venous line. A central route requires cannulation of the umbilical vein. This catheter is used for blood drawing, while replenishment of the blood volume is performed by simultaneous fluid administration via peripheral vein. Alternatively, the umbilical venous catheter is used both for blood drawing and for replenishing its volume with fluids [5]. In clinical practice PET is most commonly performed using the last of the mentioned methods.

The fluids that can be used to carry out PET are both crystalloid (saline, Ringer lactate) and colloid (fresh frozen plasma, 5% albumins) solutions. Clinical trials showed no statistically significant difference in the efficacy of hematocrite reduction between these two types of fluids [5, 23]. Plasma transfusion, however, carries the potential risk of transfusion associated infections (e.g. HIV, HBV, HCV, CMV) and anaphylactic reactions [1, 5]. What is more, adult plasma is characterized by greater viscosity when compared to neonatal one (plasma viscosity increases with gestational age of the fetus). For this reason, mixing adult plasma with fetal erythrocytes may result in the increase of blood viscosity [13]. As compared to fresh frozen plasma the use of albumins showed lower complication rate [30]. However, since normal saline does not carry the potential risk of transfusion associated infections and is readily available and cheap, normal saline is considered to be the optimal fluid for PET in polycythaemic neonates [1, 5].

At the time of PET being carried out it is compulsory to monitor vital signs, circulatory and respiratory parameters, temperature. Hematocrite control has to be performed before the beginning of procedure [6] and shortly before the removal of the venous line.

The possible PET complications include: sepsis, abnormal final hematocrite, coagulopaties, thrombocytopenia, electrolyte abnormalities, hemodynamic instability, hypothermia and gastrointestinal disturbances [6].
Various researches suggest a temporal and causative relation between NEC and umbilical PET [5, 25, 29]. However, in many clinical trials this complication has not been noted [25]. In polycythaemic patients who underwent PET, an increase of resting energy expenditure (REE) proportional to the decrease in hematocrite was observed. Moreover, symptomatic polycythaemic infants have a greater rise in REE following PET than asymptomatic ones. As a possible reason for this phenomenon one suggests increase of cardiac output and blood flow velocity in carotid and visceral arteries [21].

PET succesfully reduces hematocrite and blood viscosity [29], as well as physiological disturbances and other symptoms related to polycythaemia and hyperviscosity syndrome [1]. It improves capillary perfusion, cerebral perfusion and heart function increasing the cardiac output and blood flow velocity. However, symptoms of polycythaemia in majority of cases are still transient in character [21]. That is why more important seems to be the question, whether PET improves long-term neurological outcome. By far, there is no evidence of long term benefit from PET in polycythaemic infants [25, 26].

Although the outcome of polycythaemic in newborns is poorer than non-polycythaemic ones, this is probably related to the underlying cause of polycythaemia, and is not improved by PET. Poor outcome was described to be associated with intrauterine fetal hypoxia, hypoglycaemia and maternal pre-eclampsia. There are no randomized trials of PET in only symptomatic patients, which is probably due to a tendency to treat all symptomatic patients with PET, most likely because of published recommendations. It remains possible, that infants with severe neurological symptoms could benefit from PET, as the literature does not appear to have enough power to eliminate such a benefit [21].

Despite the lack of final and certain data concerning the long-term benefits in patients treated with PET, it seems that both in newborns with symptomatic polycythaemia and asymptomatic infants with hematocrite >75%, introducing therapy (PET or fluid intake) can be of greater benefit than maintenance management [5, 25]. Efficacy and reasonability of using PET in the treatment of polycythaemia have to be analysed in further trials.

References


