Polycythemia in the Newborn

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Abstract

Polycythemia is defined as a venous hematocrit above 65%. The relationship between viscosity and hematocrit is almost linear till 65% and exponential thereafter. Increased viscosity of blood is associated with symptoms of hypo-perfusion. The hematocrit in a newborn peaks at 2 hours of age and decreases gradually after that. The etiology of polycythemia is related either to intra-uterine hypoxia or secondary to fetal transfusion. Clinical features related to hyperviscosity may affect all organ systems and this entity should be screened for in high-risk infants. Polycythemia maybe symptomatic or asymptomatic and guidelines for management of both types are provided in the protocol.
Polycythemia in the Newborn

Polycythemia or an increased hematocrit is associated with hyperviscosity of blood. As the viscosity increases, there is an impairment of tissue oxygenation and perfusion and a tendency to form microthrombi. Significant damage may occur if these events occur in the cerebral cortex, kidneys and adrenal glands. Hence this condition requires urgent diagnosis and prompt management.

Polycythemia and Hyperviscosity

The viscosity of blood is directly proportional to the hematocrit and plasma viscosity and inversely proportional to the deformability of red blood cells. Relationship between viscosity and hematocrit is almost linear upto a hematocrit of 65% and exponential thereafter\(^1,2\). The polycythemia-hyperviscocity syndrome is usually confined to infants with hematocrit at high normal or above normal range. It is very rare with hematocrit below 60%. In non-polycythemic newborns, hyperviscosity may result from an increase in plasma proteins, especially fibrinogen, or decreased deformability of fetal erythrocytes.

Symptoms of hypoperfusion correlate better with viscosity as compared to hematocrit\(^3\). Viscosity however is difficult to measure. It is measured by Wells-Brookfield cone-plate micro-viscometer. Hyperviscosity is defined as a viscosity greater than 14.6 centipoise at a shear rate of 11.5 seconds\(^1\). Since instruments to measure viscosity are not readily available in most neonatal intensive care units, hyperviscocity is usually suspected in the presence of suggestive symptoms and an abnormally high hematocrit.
Definition of polycythemia

A diagnosis of polycythemia is made in the presence of a venous hematocrit more than 65% or a venous hemoglobin concentration in excess of 22.0 gm/dl. Hematocrit (%) is approximately three times the hemoglobin concentration in gm/dL.

Incidence

The incidence of polycythemia is 1.5-4% of all live births\textsuperscript{4,5}. The incidence is higher among small for gestational age (SGA) and large for gestational age (LGA) infants. Neonates born to mothers at high altitudes have a higher incidence of polycythemia\textsuperscript{1}. The incidence of polycythemia 15% among term SGA infants as compared to 2% in term appropriate for gestational age (AGA) infants\textsuperscript{6}. Polycythemia is unlikely to occur in neonates born at a gestational age less than 34 weeks\textsuperscript{1}.

Physiological changes in postnatal life

Significant changes take place in the hematocrit from cord blood through the first 24 hours of life. The hematocrit peaks at 2 hours of age and values upto 71% may be normal at this age\textsuperscript{7,8} It gradually declines to 68% by 6 hrs and usually stabilizes by 12 to 24 hours. The initial rise in hematocrit is related to a transudation of fluid out of the intravascular space. There is a significant correlation between cord hematocrit greater than 56% and a venous hematocrit > 70% at 2 hours of age\textsuperscript{7}.

Etiology of polycythemia
Polycythemia in newborns may be a compensatory mechanism for intra-uterine hypoxia or secondary to fetal transfusions (see Table1).

Fetal transfusions: Polycythemia secondary to fetal transfusions may occur due to twin to twin transfusion, maternal-fetal transfusion, or delayed cord clamping. Delayed cord clamping is defined as clamping more than 3 minutes after delivery of baby. This has been associated with a 30% increase in blood volume as compared to neonates with early clamping (within 30 seconds of delivery)\textsuperscript{9,10}. Possible ways of avoiding polycythemia include early cord clamping and holding the baby at the level of the introitus at the time of delivery to minimize maternal-fetal transfusion.

Intra-uterine hypoxia: The second reason for polycythemia is increased RBC production as a compensatory mechanism for intra-uterine hypoxia. Conditions associated with intra-uterine hypoxia include intrauterine growth retardation (IUGR), pregnancy induced hypertension, maternal diabetes mellitus, maternal smoking, maternal cyanotic heart disease, infants with perinatal asphyxia and post-mature deliveries. Increased number of nucleated red blood cells in IUGR babies is a marker of intra-uterine hypoxia. The incidence of polycythemia increases with increasing severity of growth retardation\textsuperscript{11}. In severely growth retarded fetuses, a hematological syndrome of polycythemia, thrombocytopenia, leukopenia and increased numbers of nucleated red blood cells has been described\textsuperscript{12}. Infants of diabetic mothers have a 22-29% incidence of polycythemia. Polycythemia in these infants correlates with macrosomia and neonatal hypoglycemia.
**Fetal causes:** Polycythemia may also occur secondary to fetal causes. Various fetal causes include trisomies 13, 18 and 21, congenital hypothyroidism, neonatal thyrotoxicosis, congenital adrenal hyperplasia and Beckwith Weidman syndrome.

*Dehydration as a cause of increased hematocrit should always be ruled out before diagnosing and intervening for polycythemia.*

**Clinical features**

Polycythemia can result in a wide range of symptoms involving several organ systems. About 50% of neonates with polycythemia develop one or more symptoms. However, most of these symptoms are non-specific and may be related to the underlying conditions rather than to polycythemia per se.

**Central nervous system:** It is the most common system to be affected. Lethargy and poor feeding are the most common symptoms of polycythemia. Easy startle, difficulty to arouse, tremors, jitteriness and rarely seizures may also occur.

**Metabolic:** Hypoglycemia is the most common metabolic problem associated with polycythemia, occurring in 12-40% neonates. Hypoglycemia may be due to the underlying disorder (e.g. IUGR or IDM) or secondary to polycythemia. Reagent strips can give falsely low values of blood sugar due to an increased red cell mass. Hence plasma glucose should be tested or a confirmatory laboratory value should be done. Hypocalcemia and hypomagnesemia can also occur in association with polycythemia.

**Cardiac and pulmonary:** Tachypnea, tachycardia, cyanosis, cardiomegaly and congestive cardiac failure (CCF) may occur in up to 50% of cases. Elevated pulmonary
vascular resistance has been demonstrated in patients with polycythemia. In severe cases (hematocrit >75%) infants appear more red than blue (rubeosis instead of cyanosis) and plethoric, with slow refilling of capillaries.

**Gastro-intestinal:** Necrotizing enterocolitis (NEC), feed intolerance and ileus may be related to hyperviscosity. It can be a result of polycythemia or secondary to its treatment by partial exchange transfusion using umbilical catheters.

**Kidneys:** Oliguria, acute renal failure decreased urinary sodium and renal vein thrombosis.

**Miscellaneous:** Poor circulation due to hyperviscosity and sludging in micro-capillaries may result in: (a) peripheral gangrene, (b) priapism, (c) testicular infarction, (d) coagulation defects, (e) thrombocytopenia, and (f) Thrombosis

**Screening for polycythemia**

Screening should be done for polycythemia in certain high-risk groups (Table 2). These include: (a) small for gestational age (SGA) infants, (b) infants of diabetic mothers (IDM), (c) large for gestational age (LGA) infants, (d) monochorionic twins especially the larger twin, (e) morphological IUGR and (f) presence of any other risk factors as mentioned above. We recommend screening in high-risk neonates at 2 hours of age. A normal value at 2 hours of age (hematocrit <65%) does not merit any further screening unless the infant is symptomatic. Hematocrit values >65% at 2 hours of age merit repeat screening at 12 and 24 hours. Polycythemia is diagnosed when a hematocrit is >65%. Any infant found to be symptomatic with clinical features suggestive of polycythemia
should be examined for polycythemia. A capillary sample can be used for screening and high values can be confirmed on venous samples.

**Capillary vs venous hematocrit**

Capillary hematocrit measurements are unreliable and highly subject to variations in blood flow. Capillary hematocrits are significantly higher than venous hematocrits. This difference is even more apparent in infants receiving large placental transfusion\(^\text{13}\). Capillary samples may be used for screening, but all high values should be confirmed by a venous sample for the diagnosis of polycythemia.

**Methods of hematocrit analysis**

The two available methods are:

*Automated hematology analyzer:* This calculates the hematocrit from a direct measurement of mean cell volume and the hemoglobin.

*Micocentrifuge:* Blood is collected in heparinized micro-capillaries (110mm length and 1-2mm internal diameter) and centrifuged at 10,000-15,000 rounds per minute (rpm) for 3-5 minutes. Plasma separates and the packed cell volume is measured to give the hematocrit. An automated analyzer gives lower values as compared to hematocrits measured by the centrifugation method\(^\text{12}\). Most of the reported data on polycythemia is on centrifuged hematocrits.

**Treatment**
Before a diagnosis of polycythemia is considered, it is mandatory to exclude dehydration. If the birth weight is known, re-weighing the baby and looking for excessive weight loss would help in the diagnosis of dehydration. If this is present, it should be corrected by increasing fluid intake. The hematocrit should be measured once again after correction of dehydration. Once a diagnosis of polycythemia is made, associated metabolic problems including hypoglycemia should be excluded. Two modes of therapy have been described for polycythemia.

(a) **Conservative management with hydration**: This mode of therapy may be tried only in asymptomatic polycythemia. An extra fluid aliquot of 20 ml/kg may be added to the daily fluid requirements. Extra fluid intake may be ensured either by the enteral route (supervised feeding) or the parenteral route (IV fluids). The rationale for this therapy is hemo-dilution and the resultant decrease in viscosity. However, liberal and extra fluid therapy may be associated with problems in preterm babies. Hence conservative management by using extra fluids should be reserved for hemodynamically stable babies with asymptomatic polycythemia.

(b) **Partial exchange transfusion (PET)**: The definitive treatment for polycythemia is a partial exchange transfusion. Indications for PET include:

- Presence of symptoms suggestive of hyperviscosity and a hematocrit >65%.
- Hematocrit >70% in an asymptomatic infant.

A partial exchange transfusion (PET) aims to decrease the hematocrit to a target packed cell volume of 55%. Following partial exchange transfusion, symptoms like jitteriness may persist for 1-2 days despite the hematocrit being lowered to physiological ranges.

The volume of blood to be exchanged is given by the formula shown in the box.
Volume to be exchanged = \frac{\text{Blood volume} \times (\text{Observed hematocrit} - \text{Desired hematocrit})}{\text{Observed hematocrit}}

*Blood volume is estimated to be 80-90 ml/kg in term babies and 90-100 ml/kg in preterm babies.

As a rough guide, the volume of blood to be exchanged is usually 20 ml/kg.

**Fluids to be used for PET**

(i) Crystalloids: normal saline, ringer lactate

(ii) Colloids: fresh frozen plasma, 5% albumin

Crystalloids are preferred because they are cheap and easily available, produce a similar reduction in hematocrit as colloids\(^{15}\), and do not have a risk of transfusion associated infections (e.g. HIV, Hepatitis B, C and CMV). Additionally, adult plasma has been shown to increase the blood viscosity when mixed with fetal erythrocytes. We use normal saline for partial exchange transfusion.

**Peripheral vs umbilical route**

A partial exchange transfusion may be carried out via the peripheral route or the central route. A peripheral route avoids umbilical vessel cannulation and is done by using a peripheral arterial and venous line. Blood is withdrawn from the arterial line and replaced simultaneously via the venous line. A central route requires cannulation of the umbilical vein. The umbilical venous catheter may be used for withdrawing blood while the same amount of saline is replaced through a peripheral vein. Alternatively the umbilical venous
catheter may be used both for withdrawal of blood and replacement with saline. Studies have shown that the peripheral route is equally efficacious and safe as compared to the central route in the treatment of polycythemia\textsuperscript{16,17}.

**Long term outcome with polycythemia**

A partial exchange transfusion reverses the physiological abnormalities associated with the polycythemia–hyperviscosity syndrome. It improves capillary perfusion, cerebral blood flow and cardiac function. However, there is very little data to suggest that PET improves long term outcome in patients with polycythemia. Bada et al\textsuperscript{6} have failed to show any beneficial effect on long term outcome with partial exchange transfusion in neonates with asymptomatic polycythemia. Similarly studies by Black et al\textsuperscript{11,18} and Goldberg et al\textsuperscript{12} also failed to demonstrate improvement in long term outcome with the use of exchange transfusions. It is possible that the underlying etiology of polycythemia is a more important determinant of ultimate outcome.

However, definitive data on long-term outcome with treatment is still unavailable in infants with hematocrit \(>70\%)\ and in infants with symptomatic polycythemia. Therefore, it may be better to do a partial exchange transfusion in this group of neonates since the procedure is safe, quick and is effective in resolving the clinical symptoms. We perform partial exchange transfusions for symptomatic patients at a hematocrit value of 65% and at 70% for asymptomatic patients.
References


### Table 1. Causes of polycythemia

#### Secondary to transfusion
- Delayed cord clamping
- Holding the baby below the level of introitus.
- Twin to twin transfusion
- Maternal fetal transfusion
- Perinatal asphyxia

#### Secondary to intrauterine hypoxia
- Intra-uterine growth retardation
- Pregnancy induced hypertension
- Maternal diabetes (insulin dependent & gestational)
- Maternal smoking
- Maternal cyanotic heart disease
- Post maturity

#### Fetal causes
- Trisomy 13,18,21
- Hypothyroidism, Thyrotoxicosis
- Congenital adrenal hyperplasia
- Beckwith Weidemann syndrome

### Table 2. Screening for polycythemia

Screening is recommended for the following:

(a) Small for gestational age (SGA) infants
(b) Infants of diabetic mothers (IDM)
(c) Large for gestational age (LGA) infants
(d) Monochorionic twins especially the larger twin
(e) Morphological features of growth retardation.
Algorithm for management of polycythemia

Capillary hematocrit >65%

Confirm with venous hematocrit

Exclude dehydration
Check weight loss

Symptomatic
PET

Asymptomatic
PCV 65-70
Consider hydration

PCV >70
PET

PET: partial exchange transfusion