

REVIEW

Nucleated red blood cells in the fetus and newborn

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Although nucleated red blood cells (nRBCs) are rarely found circulating in older children,¹ they are commonly seen in the blood of newborns. They are primarily produced in the fetal bone marrow in response to erythropoietin and are stored in the marrow as precursors to reticulocytes and mature erythrocytes. Many acute and chronic stimuli cause increases in the number of circulating nRBCs from either increased erythropoietic activity or a sudden release from the marrow storage pools. This paper reviews the various pathological processes associated with increased production and release of nRBCs. It emphasises the effects of acute, subacute, and chronic asphyxia on nRBC counts.

Nucleated red blood cells are sometimes called erythroblasts, normoblasts, or normocytes. For this review, the term “normoblasts” will be used to refer to the cells when they are in the bone marrow and “nRBCs” when they are in circulating blood.

Units of reporting

Clinically it is best to express nRBCs as an absolute number of cells per unit volume, either “nRBCs/mm³” or “nRBCs/l”. However, most clinical laboratories and many research publications report nRBCs relative to 100 white blood cells (WBCs). Unfortunately the extreme variability in the number of leucocytes after birth results in a wide range of values for nRBCs when they are expressed relative to the WBC count. The problem is magnified by the many pathological processes that significantly alter the total leucocyte count.² Processes that increase the leucocyte count will result in a misleadingly low value of nRBCs when reported relative to WBCs, and processes that decrease the leucocyte count will produce misleadingly high nRBC counts if reported relative to WBCs.

This review reports nRBCs as an absolute count whenever possible. However, many references report only the number/100 WBCs and these data will be presented when necessary. Data dispersion are presented as the mean (1 SD).

nRBCs and the placenta

nRBCs are present in the placental vessels through the first half of pregnancy, but are uncommon later in pregnancy and are usually

absent or present only in small numbers at term. The finding of numerous nRBCs in the term placenta is non-specific and may indicate acute or chronic fetal hypoxia, maternal diabetes, fetal anaemia, or congenital TORCH infections (toxoplasma, other viruses, rubella, cytomegalovirus, herpes).^{3–8} Fox⁶ found that acute asphyxia was the most common of these causes: 17 of 25 (68%) placentae with increased nRBCs were associated with acute asphyxia, but only 16 of 549 (3%) placentae with normal nRBC determinations were associated with acute asphyxia. However, acute asphyxia did not consistently produce the response: only 17 of the 33 (52%) acutely asphyxiated infants had increased nRBCs in the placenta.

Normal newborn values

In 1924, Lippman⁹ reported nRBCs in the blood of 41 of 42 newborns in the first day of life. These cells constituted about 500 nRBCs/mm³ or 0.1% of the newborns' circulating red blood cells. Since then, many investigators have reported similar values at and shortly after birth (table 1). It is reasonable to conclude that the mean value of nRBCs in the first few hours of life in healthy term newborns is about 500 nRBCs/mm³, and that a value above 1000 nRBCs/mm³ can be considered elevated. Expressed differently, 0–10 nRBCs/100 WBCs are typical, and values above 10–20 nRBCs/WBC are elevated, although these values are highly dependent on the total leucocyte count.

Studies have consistently shown decreasing nRBCs as the gestational age increases, except that post-term infants have higher counts than term infants.^{16–21} Small premature newborns may normally have up to 10 000 nRBCs/mm³.

In the normal neonate, nRBCs are rapidly cleared from the bloodstream after birth.^{9 10 22} By 12 hours of age, the counts fall by about 50%, and by 48 hours only 20–30 nRBCs/mm³ are found. In healthy term newborns, virtually no nRBCs are found after the third or fourth day of life, although they may persist in small numbers up to 1 week in preterm newborns.^{16 22}

Increases in nRBCs

Increased numbers of circulating nRBCs are seen in association with long standing erythropoietin induced erythropoiesis, acute stress

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Key message 1

Common causes of increased nucleated red blood cells include prematurity, increased erythropoiesis from chronic hypoxia, anaemia, and maternal diabetes, from acute stress mediated release from the marrow stores, and from postnatal hypoxia. Extreme increases may occasionally be idiopathic.

mediated release of normoblasts from the marrow, postnatal hypoxia, and in neonates with idiopathic increases. Table 2 shows the differential diagnosis of an increased nRBC count.

INCREASED ERYTHROPOIESIS*Chronic hypoxia*

Tissue hypoxia results in increased levels of erythropoietin, which in turn leads to stimulation of erythropoiesis and increased numbers of circulating nRBCs. Increased umbilical cord levels of erythropoietin have been found in pregnancies complicated by intrauterine growth restriction,^{23 24} maternal hypertension,²⁵ pre-eclampsia,^{23 26 27} maternal smoking,²⁸ Rh isoimmunisation,²⁹ and maternal diabetes.^{25 27 30 31} As expected, each of these conditions has been associated with increased nRBCs in the newborn.

Intrauterine growth restriction is a common manifestation of chronic hypoxia. Studies have found nRBC counts in growth restricted preterm and term infants to be about twice the values in non-growth restricted control infants.³²⁻³⁵ The counts tend to increase with worsening fetal arterial and venous Doppler flow measurements.^{34 36} Raised nRBCs have also been found in infants presumed to have experienced chronic hypoxia due to maternal pre-eclampsia with or without growth restriction.^{31 32}

Yeruchimovich *et al*³⁷ compared non-growth restricted, term infants of smoking mothers with normal controls. The infants of smoking mothers had significantly increased numbers of nRBCs, with a positive correlation between the number of cigarettes smoked a day and the nRBC count. Even passive smoking of the mother has been associated with slightly increased neonatal nRBC counts.³⁸ These

Table 2 Differential diagnosis of increased nucleated red blood cells in the fetus and newborn

I. Physiological
Labour and vaginal births
Preterm newborns
Post-term newborns
II. Increased erythropoiesis
Chronic hypoxia
Growth restriction
Maternal pre-eclampsia
Maternal smoking
Anaemia
Blood loss
Haemolysis—ABO or Rh isoimmunization, other
Maternal diabetes
Other
Leukaemia
Down's syndrome
TORCH infections
III. Acute stress release
Acute hypoxia
Subacute hypoxia
Chorioamnionitis
IV. Postnatal hypoxia
Cyanotic heart disease
Pulmonary failure
V. Idiopathic

TORCH, Toxoplasma, other viruses, rubella, cytomegalovirus, herpes.

studies support the theory that mild, but prolonged, fetal hypoxia can induce erythropoiesis and increased nRBCs.

Blood loss and haemolysis

Blood loss and haemolysis are potent stimulants of erythropoietin and increased nRBCs. Although haemolysis from any cause can result in an increase in circulating nRBCs, ABO isoimmunisation is most common.^{39 40}

Maternal diabetes

In 1944, Miller *et al*⁴¹ first reported the presence of increased nRBCs and extramedullary erythropoiesis in infants of diabetic mothers. More recently, Green and Mimoun¹¹ reported that asphyxiated infants of diabetic mothers had 1800 (2300) nRBCs/mm³, non-asphyxiated infants of diabetic mothers had 1400 (3100) nRBCs/mm³, and normal control infants had 400 (1300) nRBCs/mm³. The values from the two diabetic groups were significantly higher than that of the control group, but were not significantly different from one another. Hanlon-Lundberg *et al*¹⁵ found 14.6 (12.2) nRBCs/100 WBCs in infants of diabetic mothers, compared with 8.3 (10.1)

Table 1 Normal nucleated red blood cell (nRBC) count

Reference (first author)	Sample size	nRBCs	Age	Gestation/birth weight
Naeye ¹⁰	84	919 (1425) nRBCs/mm ³ 560 (771) nRBCs/mm ³	1 hour 6 hours	Term, AGA
Green ¹¹	102	400 (1300) nRBCs/mm ³	12–24 hours	37–41 weeks, AGA
Sinha ¹²	84	2.3 (0.7) nRBCs/100 WBCs	Birth (cord blood)	2501 and 3500 g
Shivhare ¹³	33	4.1 (2.4) nRBCs/100 WBCs	Birth (cord blood)	Term and near-term
Phelan ¹⁴	83	3.4 (3.0) nRBCs/100 WBCs	Birth (cord blood)	≥37 weeks, >2700 g
Hanlon-Lundberg ¹⁵	1,112	8.5 (10.3) nRBCs/100 WBCs	Birth (cord blood)	37–41 weeks*
Green ¹⁶	26	2900 (3600) nRBCs/mm ³	Day 1	23–26 weeks
	37	1200 (1800) nRBCs/mm ³	Day 1	27–29 weeks
	86	1000 (900) nRBCs/mm ³	Day 1	30–32 weeks
Buonocore ¹⁷	47	8521 (1620) nRBCs/mm ³	Birth (cord blood)	24–27 weeks
	185	4548 (473) nRBCs/mm ³	Birth (cord blood)	28–36 weeks
	105	1689 (290) nRBCs/mm ³	Birth (cord blood)	37–41 weeks
Axt ¹⁸	304	3.7 (median) nRBCs/100 WBCs 6.5 (median) nRBCs/100 WBCs	Birth (cord blood) Birth (cord blood)	261–289 days 290+ days

Results are mean (1 SD).

*Excludes eight infants with extreme idiopathic increases (>100 nRBCs/100 WBCs) and includes infants with maternal diabetes, growth retardation, birth asphyxia, and other causes known to increase the circulating nRBCs. AGA, appropriate size for gestational age; WBC, white blood cell.

Table 3 Relation of nucleated red blood cell (nRBC) count to severity of acute asphyxia⁴⁸

	nRBCs/mm ³
pH	
7.40–7.49	630 (870)
7.30–7.39	840 (1630)
7.20–7.29	1240 (2090)
7.10–7.19	2330 (5130)
7.00–7.09	3040 (2060)
<7.00	7780 (13 810)
Apgar score	
Apgar 1: 7–10	1060 (2240)
Apgar 1: 4–6	2040 (3780)
Apgar 1: 0–3	3030 (5730)
Apgar 5: 7–10	1140 (2250)
Apgar 5: 4–6	4140 (7830)
Apgar 5: 0–3	8300 (14 720)

Results are mean (1 SD).

nRBCs/100 WBCs in control infants whose mothers were not diabetic. Infants of diabetic mothers who are large for gestational age have higher nRBC counts than those who are of appropriate size for gestational age.⁴² The increased erythropoiesis is probably due to both an increase in erythropoietin levels and a direct haemopoietic effect of hyperinsulinaemia.^{31 40}

Other chronic causes

Other less common causes of long standing erythropoiesis are leukaemia,⁴³ Down's syndrome,²² and TORCH infections. Congenital toxoplasmosis, syphilis, rubella, cytomegalovirus, and parvovirus have all been associated with increased nRBCs. Infants with congenital syphilis may have up to 500 nRBCs/100 WBCs, probably resulting from the presence of active haemolysis and extramedullary haemopoiesis.⁴⁴

Key message 2

When increased nRBC counts are seen with acute and subacute asphyxia, the magnitude of the increase is a function of the severity and duration of the asphyxia. However, there is a large overlap between the nRBC values found after acute, subacute, and chronic asphyxia; asphyxia of any duration does not always cause an increased nRBC count, and extreme increases may be found without asphyxia.

ACUTE STRESS

Acute and subacute asphyxia

It is a common misconception that only long standing conditions cause raised circulating nRBCs at birth;⁴⁵ acute and subacute stress can also cause such increases. Interestingly, even the relative hypoxia of normal labour without asphyxia has been associated with increased cord erythropoietin levels⁴⁶ and nRBCs⁴⁷ compared with samples from infants born by elective caesarean section without labour.

In 1970, Merenstein *et al*⁴⁸ reported increased nRBCs in the blood of three infants within six hours of birth after acute intrapartum asphyxia. Numerous subsequent studies have confirmed the finding of increased nRBCs in cord blood^{47 49} and neonatal blood^{10 14 50 51} following acute asphyxia.

Thilaganathan *et al*⁵⁷ found significant differences in cord nRBCs of infants born by emergency caesarean section (median = 1100 nRBCs/mm³) compared with infants born by elective caesarean section (median = 300 nRBC/mm³). However, there was significant

overlap between the groups: in some infants born by emergency caesarean section no nRBCs were detected, and some infants born by elective caesarean section had large numbers of nRBCs.

Naeye and Localio¹⁰ compared 16 term and preterm infants who developed cerebral palsy following acute asphyxia with seven newborns having long standing developmental disorders unrelated to a perinatal event, and also with 84 normal controls. Few normal controls had nRBC values exceeding 2000 nRBCs/mm³. All of the infants with cerebral palsy caused by developmental events unrelated to birth had less than 2000 nRBCs/mm³. nRBCs increased to 2000/mm³ or more in 15 of the 16 infants injured from acute ischaemia and hypoxaemia.

The magnitude of the increase in nRBCs following acute asphyxia is a function of both the severity and duration of the asphyxia. Hanlon-Lundberg and Kirby⁴⁹ evaluated the relation between the severity of asphyxia and increased nRBCs by comparing cord nRBCs with cord pH and Apgar scores (table 3). The nRBC counts increased with progressive increases in cord acidosis and with progressive decreases in the Apgar scores. However, not all infants with low Apgar scores had increased nRBCs; in some infants with very low Apgar scores, almost no nRBCs were detected, and other infants with normal Apgar scores had as many as 2250 nRBCs/mm³. Similarly, some infants with a pH < 7.00 had as few as 260 nRBCs/mm³, while others had normal cord pH values but considerably increased nRBCs. Other investigators have also found increased nRBCs associated with a fall in cord pH.^{45 47}

Korst *et al*⁵⁰ and Phelan *et al*⁵¹ evaluated the relation between the duration of asphyxia and increases in nRBCs (table 4). Infants with a persistent non-reactive fetal heart rate pattern from admission to delivery were presumed to have suffered a more long standing, subacute, asphyxial episode. Samples from these infants were compared with values from infants who had suffered acute intrapartum asphyxia, often from a catastrophic event such as a cord prolapse or a ruptured uterus. Both groups had significantly increased nRBC counts compared with historical controls. Although infants with the subacute asphyxia had higher nRBC counts, there was much overlap between the groups: some infants with subacute injury had no nRBCs and other infants in the acute group had as many as 11 476 nRBCs/mm³. The infants with preadmission injury had longer nRBC clearance times than the acute injury group, but again there was a large overlap between the two groups. The data appear to show that the clearance rate for the groups was similar, the preadmission group merely beginning with higher values and therefore requiring longer clearance times. These studies did not indicate the severity of the asphyxia of the two groups. It remains possible that the group with subacute injury was more severely asphyxiated than the group with acute injury, in which case the difference in nRBCs may, in part, reflect the increased severity of asphyxia rather than

Table 4 Relation of nucleated red blood cell (nRBC) count to duration of asphyxia^{14 50 51}

	nRBCs/100 WBCs	nRBCs/mm ³	Clearance time (hours)
Preadmission (subacute) injury	49 (107)	3100 (median) 0–100 000 (range)	119 (123)
Acute injury	13 (13)	2096 (median) 0–11 476 (range)	66 (66)

Results are mean (1 SD).
WBC, White blood cell.

solely be attributable to increased duration of asphyxia.

The precise mechanism(s) causing the rapid release of nRBCs following acute asphyxia is not known, although erythropoietin probably plays a major role in the process. Data from studies on animals⁵²⁻⁵³ and adults⁵⁴ suggest that erythropoietin increases within one to four hours of hypoxia. Elevated levels of cord blood erythropoietin have been found following acute birth asphyxia.^{24-26, 55} Increased levels of erythropoietin can be detected within one hour of acute asphyxia.

It is likely that the increase in circulating nRBCs represents erythropoietin induced release of normoblasts from their marrow stores. Various processes have been identified that may contribute to this release. High titres of erythropoietin have been shown to accelerate mitotic divisions of the normoblasts,⁵⁶⁻⁵⁷ increase blood flow through the marrow,⁵⁸⁻⁵⁹ and increase the porous infrastructure of the marrow, allowing escape of the relatively large and rigid normoblasts.⁶⁰⁻⁶¹ These processes can each contribute to a shorter marrow transit time and rapid release of normoblasts into the bloodstream after acute hypoxia.

The precise time required to observe an increase in circulating nRBCs in the newborn is not known. Atshuler and Hyder⁶² found that nRBCs increased to 2000/mm³ within two hours of acute blood loss in previously healthy term fetuses. Benirschke⁶³ reported a newborn with an nRBC response detectable within one hour of an acute hypoxic event. Fanaroff⁶⁴ concluded that normoblasts could enter the bloodstream within 30 minutes of a severe hypoxic injury. Naeye⁶⁵ reported finding nRBCs "in large numbers" 20 minutes after the start of neonatal hypoxia. Korst *et al*⁶⁰ and Phelan *et al*⁶¹ found increased nRBCs after acute catastrophic intrapartum events. The duration of these catastrophic events was undoubtedly less than one hour in most cases. Future studies using fetal scalp samples and cord blood at birth may be useful in determining the time necessary for the rise to be detected, although it is now reasonable to conclude that it is less than 60 minutes and perhaps as short as 20–30 minutes.

Acute chorioamnionitis

Acute chorioamnionitis has been associated with increased levels of erythropoietin and increased newborn nRBCs. Maier *et al*⁶⁶ found significantly elevated erythropoietin levels in neonates whose placentas showed signs of chorioamnionitis. Increased nRBCs have been reported in preterm infants born after pregnancies complicated by chorioamnionitis without cord acidosis or hypoxaemia.⁶⁷ Leikin *et al*⁶⁸ found an increase in nRBCs when histological chorioamnionitis was present without signs of clinical chorioamnionitis. Salafia *et al*⁶⁷ speculated that the increase in nRBCs may be a fetal response to an inflamed environment and not due to fetal hypoxia.

POSTNATAL HYPOXIA

If acute hypoxia during labour can lead to increased nRBCs within minutes or hours of birth, it would be expected that postnatal hypoxia can also lead to a rapid release of nRBCs. Indeed, infants with severe pulmonary disease and cyanotic heart disease have elevated erythropoietin levels during the first week of life.⁶⁹ Naeye and Localio¹⁰ reported on infants with severe hypoxaemia resulting from pneumonia or cyanotic congenital heart disease who had nRBC counts in excess of 2000/mm³. Infants with congenital diaphragmatic hernias may have increased nRBCs within 20 minutes of birth, presumably the result of postnatal marrow release.⁶⁵

IDIOPATHIC

About 1–2% of apparently normal newborns have idiopathic increases in nRBCs. Hanlon-Lundberg *et al*¹⁵ examined cord blood nRBCs in 1112 term newborns. Nine (0.8%) had a count greater than 100 nRBCs/100 WBCs. There was no apparent cause for the increase in eight of the nine; these eight had uneventful antepartum, intrapartum, and neonatal courses. Naeye and Localio¹⁰ reported finding two (2.4%) "outliers" among 84 normal term infants. One of these two had 12 444 nRBCs/mm³. Green and Mimouni¹¹ found that 5% of 102 normal control infants had absolute nRBC counts greater than 1700 /mm³.

Summary

nRBCs are commonly found in neonatal blood. Increased counts are often the result of prematurity, increased erythropoiesis from chronic conditions, acute stress mediated release from the marrow stores, and postnatal hypoxia. Extreme increases may occasionally be idiopathic. When increased nRBC counts are seen with acute and subacute asphyxia, the magnitude of the increase is a function of the severity and duration of the asphyxia. However, there is a large overlap between the nRBC values after acute, subacute, and chronic asphyxia; asphyxia of any duration does not always cause an increased nRBC count, and extreme increases may be found without asphyxia. Newborn nRBC counts should not be relied on as the sole determinant of the severity or duration of intrauterine asphyxia.

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