

## REVIEW

## Nucleated red blood cells in the fetus and newborn

M C Hermansen

Although nucleated red blood cells (nRBCs) are rarely found circulating in older children,<sup>1</sup> 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/mm<sup>3</sup>” 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.<sup>2</sup> 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).<sup>3–8</sup> Fox<sup>6</sup> 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, Lippman<sup>9</sup> reported nRBCs in the blood of 41 of 42 newborns in the first day of life. These cells constituted about 500 nRBCs/mm<sup>3</sup> 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/mm<sup>3</sup>, and that a value above 1000 nRBCs/mm<sup>3</sup> 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.<sup>16–21</sup> Small premature newborns may normally have up to 10 000 nRBCs/mm<sup>3</sup>.

In the normal neonate, nRBCs are rapidly cleared from the bloodstream after birth.<sup>9 10 22</sup> By 12 hours of age, the counts fall by about 50%, and by 48 hours only 20–30 nRBCs/mm<sup>3</sup> 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.<sup>16 22</sup>

### Increases in nRBCs

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

Department of  
Pediatrics, Dartmouth  
Medical School,  
Southern New  
Hampshire Medical  
Center, Nashua, NH  
03062, USA  
M C Hermansen

Correspondence to:  
Dr Hermansen, Dartmouth  
Medical School, Southern  
New Hampshire Medical  
Center, 8 Prospect Street,  
Nashua, NH 03061-2014,  
USA  
Marcus.Hermansen@  
SNHMC.org

**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,<sup>23 24</sup> maternal hypertension,<sup>25</sup> pre-eclampsia,<sup>23 26 27</sup> maternal smoking,<sup>28</sup> Rh isoimmunisation,<sup>29</sup> and maternal diabetes.<sup>25 27 30 31</sup> 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.<sup>32-35</sup> The counts tend to increase with worsening fetal arterial and venous Doppler flow measurements.<sup>34 36</sup> Raised nRBCs have also been found in infants presumed to have experienced chronic hypoxia due to maternal pre-eclampsia with or without growth restriction.<sup>31 32</sup>

Yeruchimovich *et al*<sup>37</sup> 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.<sup>38</sup> 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.<sup>39 40</sup>

*Maternal diabetes*

In 1944, Miller *et al*<sup>41</sup> first reported the presence of increased nRBCs and extramedullary erythropoiesis in infants of diabetic mothers. More recently, Green and Mimoun<sup>11</sup> reported that asphyxiated infants of diabetic mothers had 1800 (2300) nRBCs/mm<sup>3</sup>, non-asphyxiated infants of diabetic mothers had 1400 (3100) nRBCs/mm<sup>3</sup>, and normal control infants had 400 (1300) nRBCs/mm<sup>3</sup>. 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*<sup>15</sup> 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 <sup>10</sup>	84	919 (1425) nRBCs/mm <sup>3</sup> 560 (771) nRBCs/mm <sup>3</sup>	1 hour 6 hours	Term, AGA
Green <sup>11</sup>	102	400 (1300) nRBCs/mm <sup>3</sup>	12–24 hours	37–41 weeks, AGA
Sinha <sup>12</sup>	84	2.3 (0.7) nRBCs/100 WBCs	Birth (cord blood)	2501 and 3500 g
Shivhare <sup>13</sup>	33	4.1 (2.4) nRBCs/100 WBCs	Birth (cord blood)	Term and near-term
Phelan <sup>14</sup>	83	3.4 (3.0) nRBCs/100 WBCs	Birth (cord blood)	≥37 weeks, >2700 g
Hanlon-Lundberg <sup>15</sup>	1,112	8.5 (10.3) nRBCs/100 WBCs	Birth (cord blood)	37–41 weeks*
Green <sup>16</sup>	26	2900 (3600) nRBCs/mm <sup>3</sup>	Day 1	23–26 weeks
	37	1200 (1800) nRBCs/mm <sup>3</sup>	Day 1	27–29 weeks
	86	1000 (900) nRBCs/mm <sup>3</sup>	Day 1	30–32 weeks
Buonocore <sup>17</sup>	47	8521 (1620) nRBCs/mm <sup>3</sup>	Birth (cord blood)	24–27 weeks
	185	4548 (473) nRBCs/mm <sup>3</sup>	Birth (cord blood)	28–36 weeks
	105	1689 (290) nRBCs/mm <sup>3</sup>	Birth (cord blood)	37–41 weeks
Axt <sup>18</sup>	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 asphyxia<sup>48</sup>

	nRBCs/mm <sup>3</sup>
<b>pH</b>	
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)
<b>Apgar score</b>	
Apgar 1: 7–10	1060 (2240)
Apgar 1: 4–6	2040 (3780)
Apgar 1: 0–3	3030 (5730)
<b>Apgar 5: 7–10</b>	
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.<sup>42</sup> The increased erythropoiesis is probably due to both an increase in erythropoietin levels and a direct haemopoietic effect of hyperinsulinaemia.<sup>31 40</sup>

#### Other chronic causes

Other less common causes of long standing erythropoiesis are leukaemia,<sup>43</sup> Down's syndrome,<sup>22</sup> 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.<sup>44</sup>

#### 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;<sup>45</sup> 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 levels<sup>46</sup> and nRBCs<sup>47</sup> compared with samples from infants born by elective caesarean section without labour.

In 1970, Merenstein *et al*<sup>48</sup> 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<sup>47 49</sup> and neonatal blood<sup>10 14 50 51</sup> following acute asphyxia.

Thilaganathan *et al*<sup>57</sup> found significant differences in cord nRBCs of infants born by emergency caesarean section (median = 1100 nRBCs/mm<sup>3</sup>) compared with infants born by elective caesarean section (median = 300 nRBC/mm<sup>3</sup>). 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 Localio<sup>10</sup> 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/mm<sup>3</sup>. All of the infants with cerebral palsy caused by developmental events unrelated to birth had less than 2000 nRBCs/mm<sup>3</sup>. nRBCs increased to 2000/mm<sup>3</sup> 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 Kirby<sup>49</sup> 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/mm<sup>3</sup>. Similarly, some infants with a pH < 7.00 had as few as 260 nRBCs/mm<sup>3</sup>, 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.<sup>45 47</sup>

Korst *et al*<sup>50</sup> and Phelan *et al*<sup>51</sup> 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/mm<sup>3</sup>. 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<sup>14 50 51</sup>

	nRBCs/100 WBCs	nRBCs/mm <sup>3</sup>	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 animals<sup>52-53</sup> and adults<sup>54</sup> suggest that erythropoietin increases within one to four hours of hypoxia. Elevated levels of cord blood erythropoietin have been found following acute birth asphyxia.<sup>24-26, 55</sup> 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,<sup>56-57</sup> increase blood flow through the marrow,<sup>58-59</sup> and increase the porous infrastructure of the marrow, allowing escape of the relatively large and rigid normoblasts.<sup>60-61</sup> 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 Hyder<sup>62</sup> found that nRBCs increased to 2000/mm<sup>3</sup> within two hours of acute blood loss in previously healthy term fetuses. Benirschke<sup>63</sup> reported a newborn with an nRBC response detectable within one hour of an acute hypoxic event. Fanaroff<sup>64</sup> concluded that normoblasts could enter the bloodstream within 30 minutes of a severe hypoxic injury. Naeye<sup>65</sup> reported finding nRBCs "in large numbers" 20 minutes after the start of neonatal hypoxia. Korst *et al*<sup>60</sup> and Phelan *et al*<sup>61</sup> 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*<sup>66</sup> 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.<sup>67</sup> Leikin *et al*<sup>68</sup> found an increase in nRBCs when histological chorioamnionitis was present without signs of clinical chorioamnionitis. Salafia *et al*<sup>67</sup> 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.<sup>69</sup> Naeye and Localio<sup>10</sup> reported on infants with severe hypoxaemia resulting from pneumonia or cyanotic congenital heart disease who had nRBC counts in excess of 2000/mm<sup>3</sup>. Infants with congenital diaphragmatic hernias may have increased nRBCs within 20 minutes of birth, presumably the result of postnatal marrow release.<sup>65</sup>

#### IDIOPATHIC

About 1–2% of apparently normal newborns have idiopathic increases in nRBCs. Hanlon-Lundberg *et al*<sup>15</sup> 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 Localio<sup>10</sup> reported finding two (2.4%) "outliers" among 84 normal term infants. One of these two had 12 444 nRBCs/mm<sup>3</sup>. Green and Mimouni<sup>11</sup> found that 5% of 102 normal control infants had absolute nRBC counts greater than 1700 /mm<sup>3</sup>.

#### 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.

- 1 Sills RH, Hadley RAR. The significance of nucleated red blood cells in the peripheral blood of children. *Am J Pediatr Hematol Oncol* 1983;5:173–7.
- 2 Manroe BL, Weinberg AG, Rosenfeld CR, *et al*. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. *J Pediatr* 1979;95:89–98.
- 3 Ryerson CS, Sanes S. The age of pregnancy. Histologic diagnosis from percentage of erythroblasts in chorionic capillaries. *Arch Pathol* 1934;17:648–51.
- 4 Javert CT. The occurrence and significance of nucleated erythrocytes in the fetal vessels of the placenta. *Am J Obstet Gynecol* 1939;37:184–94.
- 5 Anderson GW. Studies on the nucleated red blood cell count in the chorionic capillaries and the cord blood of various ages of pregnancy. *Am J Obstet Gynecol* 1941;42:1–14.
- 6 Fox H. The incidence and significance of nucleated erythrocytes in the fetal vessels of the mature human placenta. *J Obstet Gynaecol Br Commonw* 1967;74:40–43.
- 7 Altshuler G. Some placental considerations related to neurodevelopmental and other disorders. *J Child Neurol* 1993;8:78–94.
- 8 Young SA, Crocker DW. Occult congenital syphilis in macerated stillborn fetuses. *Arch Pathol Lab Med* 1994;118:44–7.

- 9 Lippman HS. Morphologic and quantitative study of blood corpuscles in the newborn period. *American Journal of Diseases in Children* 1924;27:473-515.
- 10 Naeye RL, Localio AR. Determining the time before birth when ischemia and hypoxemia initiated cerebral palsy. *Obstet Gynecol* 1995;86:713-19.
- 11 Green DW, Mimouni G. Nucleated erythrocytes in healthy infants and in infants of diabetic mothers. *J Pediatr* 1990;166:129-31.
- 12 Sinha HB, Mukherjee AK, Bala D. Cord blood haemoglobin (including fetal haemoglobin) and nucleated red cells in normal and toxemic pregnancies. *Indian J Pediatr* 1972;9:540-3.
- 13 Shivhare K, Chawla K, Khan MA, et al. Effect of maternal toxemia on total haemoglobin, foetal haemoglobin and nucleated red blood cells in cord blood. *Indian J Pediatr* 1976;43:349-56.
- 14 Phelan JP, Ahn MO, Korst LM, et al. Nucleated red blood cells: a marker for fetal asphyxia? *Am J Obstet Gynecol* 1995;173:1380-4.
- 15 Hanlon-Lundberg KM, Kirby RS, Gandhi S, et al. Nucleated red blood cells in cord blood of singleton term neonates. *Am J Obstet Gynecol* 1997;176:1149-56.
- 16 Green DW, Hendon B, Mimouni FB. Nucleated erythrocytes and intraventricular hemorrhage in preterm neonates. *Pediatrics* 1995;96:475-8.
- 17 Buonocore G, Perrone S, Gioia D, et al. Nucleated red blood cell count at birth as an index of perinatal brain damage. *Am J Obstet Gynecol* 1999;181:1500-5.
- 18 Axt R, Ertan K, Hendrik J, et al. Nucleated red blood cells in cord blood of singleton term and post-term neonates. *J Perinat Med* 1999;27:376-18.
- 19 Simpson JL, Elias S. Isolating fetal cells from maternal blood. *JAMA* 1993;270:2357-61.
- 20 De Waele M, Foulon W, Renmans W, et al. Hematologic values and lymphocyte subsets in fetal blood. *Am J Clin Pathol* 1988;89:742-6.
- 21 Forestier F, Daffos F, Catherine N, et al. Developmental hematopoiesis in normal human fetal blood. *Blood* 1991;77:2360-3.
- 22 Oski FA, Naiman JL. Normal blood values in the newborn period. In: *Hematologic problems in the newborn*. 2nd ed. Philadelphia: WB Saunders, 1972:1-30.
- 23 Ruth V, Fyhrquist F, Clemons G, et al. Cord plasma vasopressin, erythropoietin, and hypoxanthine as indices of asphyxia at birth. *Pediatr Res* 1988;24:490-4.
- 24 Maier RF, Bohme K, Dudenhausen JW, et al. Cord blood erythropoietin in relation to different markers of fetal hypoxia. *Obstet Gynecol* 1993;81:575-80.
- 25 Teramo KA, Widness JA, Clemons GK, et al. Amniotic fluid erythropoietin correlates with umbilical plasma erythropoietin in normal and abnormal pregnancy. *Obstet Gynecol* 1987;69:710-16.
- 26 Ruth V, Widness JA, Clemons G, et al. Postnatal changes in serum immunoreactive erythropoietin in relation to hypoxia before and after birth. *J Pediatr* 1990;116:950-4.
- 27 Mamopoulos M, Bill H, Tsantali C, et al. Erythropoietin umbilical serum levels during labor in women with pre-eclampsia, diabetes, and preterm labor. *Am J Perinatol* 1994;11:427-9.
- 28 Varvarigou A, Beratis NG, Makri M, et al. Increased levels and positive correlation between erythropoietin and hemoglobin concentrations in newborn children of mothers who are smokers. *J Pediatr* 1994;124:480-2.
- 29 Vuutilainen PE, Widness JA, Clemons GK, et al. Amniotic fluid erythropoietin predicts fetal distress in Rh-immunized pregnancies. *Am J Obstet Gynecol* 1989;160:429-34.
- 30 Widness JA, Susa JB, Garcia JF, et al. Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic rhesus fetuses. *J Clin Invest* 1981;67:637-42.
- 31 Salvesen DR, Brudenell JM, Sniijders RJM, et al. Fetal plasma erythropoietin in pregnancies complicated by maternal diabetes mellitus. *Am J Obstet Gynecol* 1993;168:88-94.
- 32 Leikin E, Verma U, Klein S, et al. Relationship between neonatal nucleated red blood cell counts and hypoxic-ischemic injury. *Obstet Gynecol* 1996;87:439-43.
- 33 Soothill PW, Nicolaides KH, Campbell S. Prenatal asphyxia, hyperlactacemia, hypoglycemia, and erythroblastosis in growth retarded fetuses. *BMJ* 1987;294:1051-3.
- 34 Bernstein PS, Minior VK, Divon MY. Neonatal nucleated red blood cell counts in small-for-gestational-age fetuses with abnormal umbilical artery Doppler studies. *Am J Obstet Gynecol* 1997;177:1079-84.
- 35 Philip GS, Tito AM. Nucleated red blood cell counts in small for gestational age infants with very low birthweight. *American Journal of Diseases in Children* 1989;143:164-9.
- 36 Baschat AA, Gembruch U, Reiss I, et al. Neonatal nucleated red blood cell counts in growth-restricted fetuses: Relationship to arterial and venous Doppler studies. *Am J Obstet Gynecol* 1999;181:190-5.
- 37 Yeruchimovich M, Dollberg S, Green DW, et al. Nucleated red blood cells in infants of smoking mothers. *Obstet Gynecol* 1999;93:403-6.
- 38 Dollberg S, Fainaru O, Mimouni FB, et al. Effect of passive smoking in pregnancy on neonatal nucleated red blood cells. *Pediatrics* 2000;106:592.
- 39 McCormack MK, Geller GR, Zak S, et al. Complex alpha-thalassaemia-like syndrome: a cause of neonatal normoblastemia. *J Pediatr* 1976;89:446-61.
- 40 Perrine SP, Green MF, Lee PDK, et al. Insulin stimulates cord blood erythroid progenitor growth: Evidence for an aetiological role in neonatal polycythemia. *Br J Haematol* 1986;64:503-11.
- 41 Miller HC, Johnson RD, Durlacher SH. A comparison of newborn infants with erythroblastosis fetalis with those born to diabetic mothers. *J Pediatr* 1944;24:603-15.
- 42 Yeruchimovich M, Mimouni FB, Green DW, et al. Nucleated red blood cells in healthy infants of women with gestational diabetes. *Obstet Gynecol* 2000;95:84-6.
- 43 Mori T, Kaneko H, Kumagai M, et al. Congenital leukaemia with a mixed phenotype of megakaryoblasts and erythroblasts: a case report and characterization of the blasts. *Br J Haematol* 1997;96:740-2.
- 44 Ingall D, Sanchez PJ. Syphilis. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. 5th ed. Philadelphia: WB Saunders, 2001:654.
- 45 Blackwell SC, Refuerzo JS, Wolfe HM, et al. The relationship between nucleated red blood cell counts and early-onset neonatal seizures. *Am J Obstet Gynecol* 2000;182:1452-7.
- 46 Widness JA, Clemons GK, Garcia JF, et al. Increased immunoreactive erythropoietin in cord serum after labor. *Am J Obstet Gynecol* 1984;148:194-7.
- 47 Thilaganathan B, Athanasios S, Ozmen S, et al. Umbilical cord blood erythroblast count as an index of intrauterine hypoxia. *Arch Dis Child Fetal Neonatal Ed* 1994;70:F192-4.
- 48 Merenstein GB, Blackmon LR, Kushner J. Nucleated red-cells in the newborn. *Lancet* 1970;i:1293-4.
- 49 Hanlon-Lundberg KM, Kirby RS. Nucleated red blood cells as a marker of acidemia in term neonates. *Am J Obstet Gynecol* 1999;181:196-201.
- 50 Korst LM, Phelan JP, Ahn MO, et al. Nucleated red blood cells: An update on the marker for fetal asphyxia. *Am J Obstet Gynecol* 1996;175:843-6.
- 51 Phelan JP, Korst LM, Ahn MO, et al. Neonatal nucleated red blood cell and lymphocyte counts in fetal brain injury. *Obstet Gynecol* 1998;91:485-9.
- 52 Widness JA, Teramo KA, Clemons GK, et al. Temporal response of immunoreactive erythropoietin to acute hypoxemia in fetal sheep. *Pediatr Res* 1986;20:15-19.
- 53 McMullin MF, Lappin TRJ, Elder GE, et al. Erythropoietic response to hypobaric hypoxia in rabbits. *Biomed Biochem Acta* 1988;47:523-7.
- 54 Eckardt KU, Boutellier U, Kurtz A, et al. Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. *J Appl Physiol* 1989;66:1785-8.
- 55 Eckardt KU, Hartmann W, Vetter U, et al. Serum immunoreactive erythropoietin of children in health and disease. *Eur J Pediatr* 1990;149:459-64.
- 56 Finch CA, Deubelbeiss K, Cook JD, et al. Ferrokinetics in man. *Medicine (Baltimore)* 1970;49:17-53.
- 57 Erslev AJ, Beutler E. Action of erythropoietin. In: Beutler E, Lichtman MA, Coller BS, et al, eds. *Williams hematology*. 5th ed. New York: McGraw-Hill 1995:435-6.
- 58 Iversen PO. Blood flow to the haematopoietic bone marrow. *Acta Physiol Scand* 1997;159:269-76.
- 59 Iversen PO, Nicolaysen G, Benestab HB. Blood flow to bone marrow during development of anemia or polycythemia in the rat. *Blood* 1992;79:549-601.
- 60 Chamberlain JK, Leblond PF, Weed RI. Reduction of adventitial cell cover. An early direct effect of erythropoietin on bone marrow ultrastructure. *Blood Cells* 1975;1:655.
- 61 Rothstein G. Release of cells from bone marrow. In: Lee GR, Bithell TC, Foerster J, et al, eds. *Wintrobe's clinical hematology*. 9th ed. Philadelphia: Lea and Febiger, 1993:62.
- 62 Atshuler G, Hyder SR. Nucleated erythrocytes. In: Pitkin RM, Scott JR, eds. *Clinical obstetrics and gynecology*. Philadelphia: Lippincott-Raven, 1996:553-6.
- 63 Benirschke K. Placenta pathology questions to the perinatologist. *J Perinatol* 1994;14:371-5.
- 64 Fanaroff AA. In: Fanaroff AA, Maisels MJ, Stevenson DK, eds. *Year Book of Neonatal and Perinatal Medicine* 1997. St. Louis: Mosby, 1997:331.
- 65 Naeye RL. How to time when hypoxic-ischemic fetal brain damage took place. In: Maulik D, ed. *Asphyxia and fetal brain damage*. New York: Wiley-Liss 1998:153-8.
- 66 Maier RF, Gunther A, Vogel M, et al. Umbilical venous erythropoietin and umbilical arterial pH in relation to morphologic placental abnormalities. *Obstet Gynecol* 1994;84:81-7.
- 67 Salafia CM, Ghidini A, Pezzullo JC, et al. Early neonatal nucleated erythrocyte counts in preterm deliveries: clinical and pathologic correlations. *Journal of the Society for Gynecologic Investigation* 1997;4:138-43.
- 68 Leiken E, Garry D, Visintainer P, et al. Correlation of neonatal nucleated red blood cell counts in preterm infants with histologic chorioamnionitis. *Am J Obstet Gynecol* 1997;177:27-30.
- 69 Miller DR. Neonatal and postnatal erythropoiesis. In: Miller DR, Baehner RL, eds. *Blood diseases of infancy and childhood*. 7th ed. St Louis: CV Mosby, 1995:153.



## Nucleated red blood cells in the fetus and newborn

M C Hermansen

*Arch Dis Child Fetal Neonatal Ed* 2001 84: F211-F215  
doi: 10.1136/fn.84.3.F211

---

Updated information and services can be found at:  
<http://fn.bmj.com/content/84/3/F211.full.html>

---

### References

*These include:*

This article cites 59 articles, 9 of which can be accessed free at:  
<http://fn.bmj.com/content/84/3/F211.full.html#ref-list-1>

Article cited in:  
<http://fn.bmj.com/content/84/3/F211.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Notes

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>