Normoblasts in large for gestational age infants

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Abstract

Thirty one term large for gestational age (LGA) infants of non-diabetic mothers were compared with 30 appropriate for gestational age controls. Median absolute nucleated red blood cell counts, lymphocyte counts, and packed cell volumes were significantly higher in the LGA infants than the controls. It is possible that LGA babies of non-diabetic mothers are exposed to relative intrauterine hypoxia.

(Arch Dis Child Fetal Neonatal Ed 2000;83:F148-F149)

Keywords: intrauterine hypoxia; nucleated red blood cells; erythrocytes; gestational diabetes mellitus

Insulin dependent diabetes in pregnancy is a risk factor for intrauterine hypoxia.¹ A consequence of chronic fetal hypoxia is increased erythropoiesis through erythropoietin stimulation; indeed, hypoxic fetuses have increased circulating erythropoietin concentrations, increased packed cell volumes, and increased numbers of circulating normoblasts or nucleated red blood cells (NRBCs) at birth.² We recently showed that large for gestational age (LGA) infants born to gestational diabetic mothers exhibit similar haematological abnormalities to infants of insulin dependent diabetic mothers.² As at least a subset of LGA infants of non-diabetic mothers is hyperinsulinaemic, we hypothesised that, in these infants, the absolute number of NRBCs at birth will be increased.

Materials and methods

We prospectively studied two groups of term infants (38–41 weeks gestational age by last menstrual period, confirmed by early (less than 20 weeks) ultrasonographic assessment), who were born vaginally at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center between May and 31 December 1998. The first group consisted of 31 infants with non-diabetic

mothers who were born LGA (above the 90th percentile), and the second group consisted of 30 infants also with non-diabetic mothers but who were of appropriate size for gestational age (AGA; between the 10th and 90th percentile), according to the intrauterine growth curves of Lubchenco.³ Gestational diabetes was excluded in both groups by a glucose challenge at 24–28 weeks gestation. To eliminate confounding variables that could affect absolute NRBC numbers, we excluded infants born to women with pregnancy induced hypertension, placental abruption or placenta previa, chronic conditions, those who smoked or abused drugs or alcohol, and those with perinatal infection.⁴ We also excluded infants with abnormal intrapartum electronic monitoring or low Apgar scores (below 8 at one and five minutes) and those who suffered perinatal blood loss or haemolysis (blood group incompatibility with positive Coombs test) or with chromosomal anomalies.⁴

Venous blood samples for complete blood counts were collected from every infant within six hours of birth and analysed according to the laboratory routine using an STK-S counter (Coulter Counter Corporation, Hialeah, Florida, USA). Differential cell counts were performed manually, and absolute numbers of NRBCs were determined per 100 white blood cells. We have shown that the white blood cell count and the absolute NRBC count are dependent, and that expression of NRBC per 100 white blood cells may introduce a significant error.⁵ We thus expressed the number of NRBCs as an absolute number, and the white blood cell count was corrected for the presence of NRBCs.

The study was approved by our local institutional review board. As all patients are screened routinely for polycythaemia, with a complete blood count at the age of 0–12 hours, informed consent was not required.

Data are reported as mean (SD) or median and range. Statistical analysis (using Minitab Inc, State College, Pennsylvania, USA) included the Kruskal-Wallis test because of non-normal distribution of absolute NRBC and Apgar scores (normality was tested by the Ryan Joiner test for normality). $p < 0.05$ was considered significant.

Results

There were no significant differences between groups in maternal age, gravidity or parity, analgesia during labour, gestational age, sex, and one and five minute Apgar scores (table 1). As expected, the LGA group differed significantly from the AGA group with respect to weight ($p < 0.0001$). The absolute NRBC count, packed cell volume, and corrected white blood cell count were significantly higher in the

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Accepted 15 May 2000

Table 1 Characteristics of large for gestational age (LGA) and appropriately sized for gestational age (AGA) infants of non-diabetic mothers

	LGA	AGA	p Value
Birth weight (g)	4199 (169)	3253 (410)	<0.0001
Gestational age (weeks)	39.9 (0.9)	39.7 (1.1)	NS
Sex (males:females)	15:16	14:16	NS
Maternal age (years)	28.8 (3.2)	29.2 (5.9)	NS
Gravidity	1.7 (0.8)	2.3 (1.6)	NS
Parity	1.6 (0.6)	1.7 (0.9)	NS
Epidural analgesia during labour	31 (100%)	30 (100%)	NS
One minute Apgar score	9 (8–10)	9 (8–10)	NS
Five minute Apgar score	10 (9–10)	10 (9–10)	NS
Packed cell volume	62 (5)	56 (7)	<0.001
Absolute NRBC count ($\times 10^9/l$)	0.451 (0–2.19)	0.061 (0–0.59)	<0.0001
Corrected white blood cells ($\times 10^9/l$)	26.8 (0.6)	19.8 (0.7)	<0.001
Platelets ($\times 10^9/l$)	267 (55)	244 (70)	NS
Absolute lymphocyte count ($\times 10^9/l$)	6.5 (1.2)	4.6 (1.9)	<0.001

Data are expressed as mean (SD) or median (range) except for those for epidural analgesia during labour which is the number.

NS, Not significant; NRBC, nucleated red blood cell.

LGA group than the AGA control group. The difference in corrected white blood cell count was explained in part by a significant difference in lymphocyte counts (table 1). There were no significant differences in platelet counts between the two groups.

Discussion

This study shows that, as hypothesised, LGA infants of non-diabetic mothers have higher absolute NRBC counts, packed cell volume, and lymphocyte counts than AGA controls. A similar increase has been documented in infants of insulin dependent mothers and LGA infants of gestational diabetic mothers; in the latter, it is believed to reflect a compensatory increase in erythropoiesis as a result of chronic intrauterine hypoxia due to poor glycaemic control.¹ Indeed, maternal hyperglycaemia triggers fetal hyperglycaemia and hyperinsulinism,¹ with subsequent fetal hypoxaemia resulting from increased placental oxygen consumption and decreased fetal oxygen delivery.¹ Within hours, fetal hypoxia stimulates fetal erythropoietin production,⁴ which may lead to neonatal polycythaemia. The LGA infants of non-diabetic mothers had larger packed cell volumes than the control infants, which suggests that they were exposed to a relatively hypoxaemic environment for a prolonged period. Furthermore, they had elevated lymphocyte counts, another index of intrauterine hypoxia. If the theory of hyperinsulinism induced hypoxia is correct, we must ask why they were hyperinsulinaemic. Possibly, the mothers were not truly non-diabetic, and had subtle hyperglycaemia not recognised by the standard glucose challenge test. Tallarigo *et al*⁶ analysed a group of non-diabetic mothers (assessed by the normal oral glucose tolerance

test), and separated them into two groups according to the two hour values. They found an increase in macrosomia in offspring of women with higher glucose concentrations than in those with lower glucose concentrations. They concluded that mild maternal hyperglycaemia, considered to be within the normal range, may affect fetal weight.

In our study, the white blood cell count of LGA infants was higher than in the control group, confirming our previous findings.⁷ The cause of leucocytosis in these infants is only in part explained by an increase in lymphocyte count. It is possible that leucocyte demargination secondary to increased cortisol secretion is contributory.

In summary, LGA infants of non-diabetic mothers have haematological indices compatible with chronic fetal hypoxia. Particular attention should perhaps be paid to LGA fetuses in terms of testing for wellbeing during pregnancy, labour, and delivery.

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