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Intra-Uterine Starvation and Fetal Leucocyte Count

Norman Davies, Rosalinde Snijders, Kypros H. Nicolaides

Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, Medical School King's College Hospital, London, UK

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Abstract. In 104 severely growth-retarded fetuses, the mean white blood cell count (WBC), as well as neutrophil, lymphocyte and monocyte counts were reduced. Furthermore, the severity of the leucopenia was significantly related to the degree of fetal 'smallness' and anaemia. These findings suggest that leucopenia observed in growth-retarded neonates may be a consequence of intra-uterine starvation due to deficiency of haematinics.

Introduction

In postnatal life protein-calorie malnutrition is associated with leucopenia and increased susceptibility to infection [1, 2]. Indeed, in severe cases there is thymolymphatic atrophy or 'nutritional' thymectomy [3]. In prenatal life, placental insufficiency is associated with hypoglycaemia and deficiency in essential amino acids [4, 5].

The aim of the present study was to investigate the extent to which intra-uterine starvation affects fetal leucocyte count.

Patients and Methods

The white blood cell (WBC) and differential counts were determined in 104 small-for-gestational age (SGA), chromosomally and anatomically normal fetuses referred to our unit for further assessment during 1987–1990. In all cases ultrasound examination had demonstrated that the fetal abdominal circumference was below the 5th centile for gestation and Doppler ultrasound investigation of the uterine and umbilical arteries was suggestive of placental insufficiency. Twenty mothers had pregnancy-induced hypertension and 10 of these were receiving β-blockers. In 32 cases there was oligohydramnios and in an additional 38 cases the amniotic fluid volume was subjectively assessed by ultrasonography to be reduced. Subsequently, 26 fetuses died in utero, and there were 11 neonatal deaths. Fifty-nine infants survived. In all cases the birth weight was below the 5th centile for gestation (fig. 1) [6].

Continuous wave Doppler studies (Dopptek Ltd., Chichester, UK) of the uterine and umbilical arteries were performed immediately before cordocentesis. An early diastolic notch in the waveform from at least one of the uterine arteries, and/or absent end-diastolic frequencies in the waveform from the umbilical artery, was regarded as evidence suggestive of placental insufficiency [7, 8] and was observed in all cases.

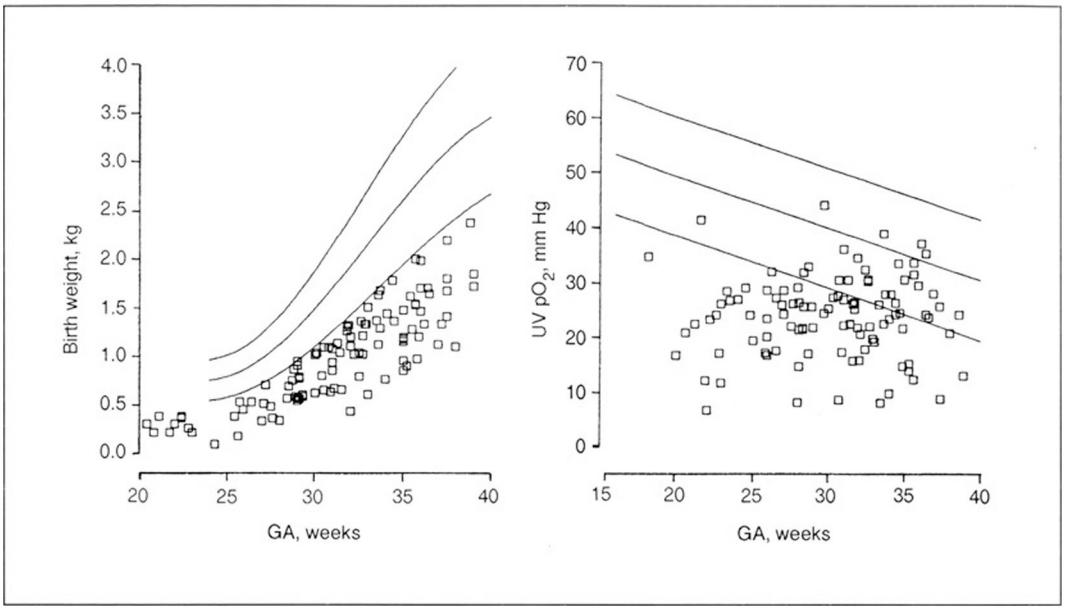


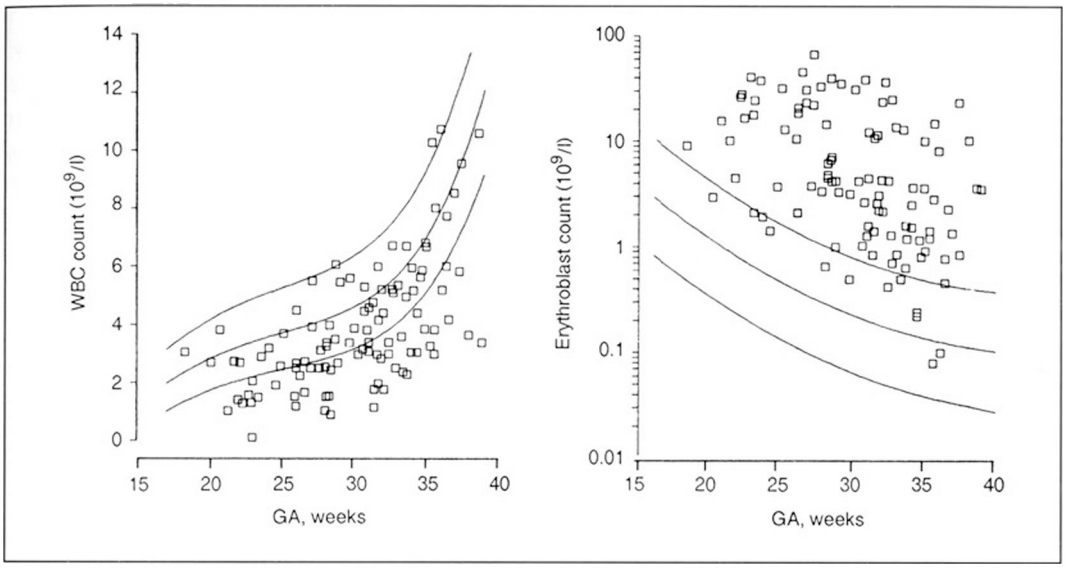
Fig. 1. The umbilical venous pO_2 at cordocentesis and birth weight of 104 SGA fetuses plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation.

Gestation at cordocentesis was 18–39 (mean = 30) weeks and this was determined from the menstrual history or an ultrasound scan performed in early pregnancy. Umbilical cord blood samples were obtained by cordocentesis, which was performed without maternal sedation or fetal paralysis [9]. Fetal blood gases were measured in samples (250 µl) collected into heparinised syringes (Radiometer ABL 330, Copenhagen, Denmark). Fetal blood (180 µl) was also collected into 20 µl of isotonic edetic acid solution (0.5 mmol/l in 0.15 mmol/l of sodium chloride) and the full blood count was determined on a Coulter Stacker counter (Coulter Electronics plc, Luton, UK). Blood films were stained with Jenners Giemsa on an automatic processing machine and the erythroblast count per 100 white cells determined. The corrected WBC count was calculated (WBC count = uncorrected WBC count × 100/erythroblast count + 100). To determine the differential WBC count, 100 WBCs were examined and classified.

During the same period an additional 55 SGA fetuses were investigated by cordocentesis in our unit. The reasons for exclusion from this study were: fetal anatomical or chromosomal abnormalities (n = 25), failure to meet Doppler criteria (n = 18), differential WBC or erythroblast counts not performed (n = 9), maternal disease such as systemic lupus erythematosus treated by steroids (n = 3).

Statistical Analaysis

In normal pregnancy the fetal blood gases, haemoglobin concentration, platelet count, WBC and differential counts change with gestation [9–12]. The values obtained from the SGA pregnancies were expressed as the number of standard deviations by which the individual values differed from the appropriate normal mean for gestation (delta values, SDs). Two-tailed Student's t test was applied to determine if the mean values in the SGA fetuses were significantly different from the appropriate normal mean for gestation. Regression analysis was used to determine the significance of any associations between delta WBC count and delta values for the other parameters. Multiple regression was applied to examine which of the parameters found to be related to leucopenia contributed significantly in explaining the degree of leucopenia.



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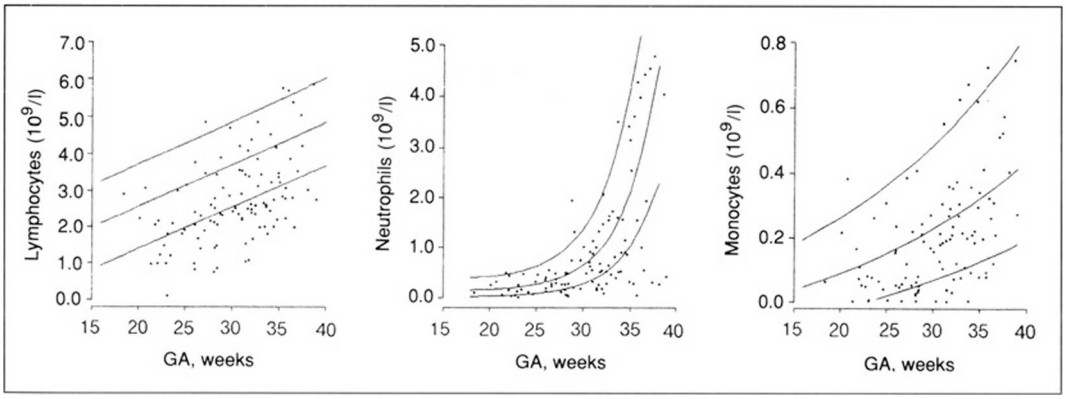

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Fig. 2. The corrected WBC and nucleated red blood cell counts in 104 SGA fetuses plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation.

Fig. 3. The lymphocyte, neutrophil and monocyte counts in 104 SGA fetuses plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation.

Results

In the 104 SGA fetuses the mean abdominal circumference, birth weight, pO_2, pH and oxygen content were significantly lower than the appropriate normal mean for gestation (fig. 1). The mean WBC, lymphocyte, neutrophil, monocyte and platelet counts were significantly reduced, but the mean erythroblast count was significantly increased (fig. 2, 3; table 1). Although the mean haemoglobin concentration was also increased, many of the leucopenic fetuses were anaemic (fig. 4).

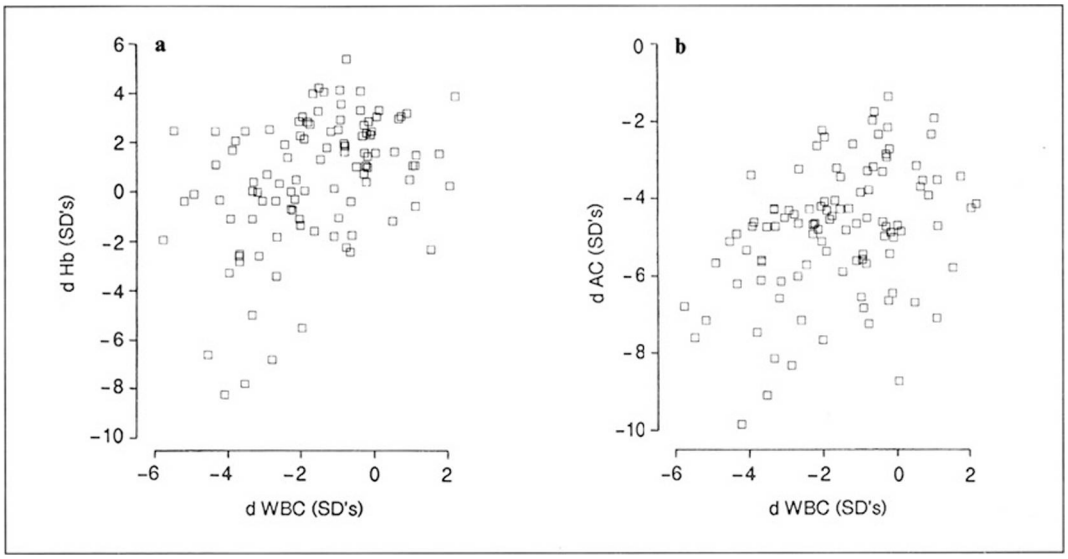

Fig. 4. Relation of delta white blood cell count with delta haemoglobin concentration (**a**) and delta abdominal circumference (**b**) in 104 SGA fetuses. Delta values are the number of standard deviations by which the individual values differed from the appropriate normal mean for gestation. The most leucopenic fetuses (< 2 SDs) were also anaemic.

Table 1. Comparison of data from the 104 SGA fetuses to the appropriate normal mean for gestation

	MD	SEM	t
WBC count	−1.60	0.17	−8.3**
Lymphocyte count	−1.50	0.14	−9.5**
Neutrophil count	−0.89	0.19	−4.6**
Monocyte count	−0.30	0.13	−2.3*
Abdominal circumference	−4.83	0.17	−29.3**
Birth weight	−3.06	0.09	−34.3**
Fetal blood pO_2	−2.51	0.14	−17.7**
Fetal blood pH	−2.90	0.26	−11.0**
Fetal blood oxygen content	−2.57	0.32	−8.0**
Haemoglobin concentration	0.58	0.26	2.2*
Platelet count	−1.68	0.13	−12.8**
Erythroblast count	3.70	0.18	21.0**

(MD = Mean difference in SDs; SEM = standard error of the mean; t from Student's t test).

* $p < 0.05$; ** $p < 0.0001$.

Table 2. Relationship between delta for WBC count and delta values for the other parameters measured

	Correlation coefficient	Residual SD
Lymphocyte count	0.81	0.86**
Neutrophil count	0.69	1.40**
Monocyte count	0.60	1.01**
Abdominal circumference	0.38	1.56**
Birth weight	0.39	0.84**
Fetal blood pO_2	0.19	1.42
Fetal blood pH	0.02	2.69
Fetal blood oxygen content	0.34	3.09*
Haemoglobin concentration	0.38	2.50**
Platelet count	0.34	1.26*
Erythroblast count	−0.05	1.81

* $p < 0.05$; ** $p < 0.0001$.

There were significant associations between delta WBC and delta lymphoyte, delta neutrophil and delta monocyte counts, delta abdominal circumference, delta birth weight, delta haemoglobin concentration, delta oxygen content and delta platelet count (table 2). Multiple regression demonstrated that delta abdominal circumference and delta haemoglobin contributed independently in explaining variance in delta WBC (delta WBC = 0.366 × delta abdominal circumference + 0.254 × delta haemoglobin, F to remove 156.3 and 21.69, respectively). In contrast, delta platelet count and delta oxygen content did not contribute significantly after accounting for delta abdominal circumference and delta haemoglobin concentration (F to remove 1.61 and 2.58, respectively).

Discussion

This study has demonstrated that severe growth retardation, presumed to be due to placental insufficiency, is associated with neutropenia, lymphopenia and monocytopenia. Furthermore, the severity of the leucopenia is significantly related to the degree of fetal 'smallness' and anaemia. These findings suggest that the previously reported leucopenia in growth-retarded neonates might be a consequence of deficiency in haematinics due to intra-uterine starvation. Indeed, in growth-retarded neonates iron stores are reduced [13].

In addition to an impaired supply of nutrients causing reduced production of white cells, there may be impaired development of leucopoietic sites due to decreased peripheral perfusion, which is well described in hypoxaemic growth retardation [14, 15]. Supportive evidence for this hypothesis is provided by a post-mortem study, which demonstrated that in the SGA group, the thymus was smaller and the mass of haemopoietic tissue in the liver was reduced compared to appropriately grown infants [16]. In growth-retarded fetuses that survive, impaired cell-mediated immunity may persist until at least the age of 5 years [17, 18].

An alternative mechanism for leucopenia associated with growth retardation is 'channelling' haemopoietic stem cells [19]. Stem cell differentiation in favour of erythropoiesis may occur in an attempt to fulfil the primary requirement of tissue oxygenation. Such 'channelling' could leave the fetus relatively deficient in leucocytes and platelet precursors. In neonates of pregnancies complicated by maternal hypertension and/or fetal growth retardation, the numbers of circulating granulocyte-macrophage progenitors [20]. However, in the present study leucopenia was associated with anaemia while in most fetuses with increased haemoglobin concentration, the WBC count was normal.

Intra-uterine starvation and associated leucopenia may in part account for increased susceptibility to infection on the neonatal life [21]. Additionally, chronic intra-uterine starvation may interfere with normal development of leucopoietic sites and therefore, predispose to long-term immunological deficiencies [17, 18].

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K.H. Nicolaides, MD
Harris Birthright Research Centre
for Fetal Medicine
Department of Obstetrics and Gynaecology
Medical School King's College Hospital
Denmark Hill
London SE 8RX (UK)