CLINICAL RESEARCH

Prenatal asphyxia, hyperlacticaemia, hypoglycaemia, and erythroblastosis in growth retarded fetuses

P W SOOTHILL, K H NICOLAIDES, S CAMPBELL

Abstract

The umbilical venous oxygen and carbon dioxide tensions, pH, lactate and glucose concentrations, nucleated red cell (erythroblast) count, and haemoglobin concentration were measured in 38 cases of intrauterine growth retardation in which fetal blood sampling was performed by cordocentesis. The oxygen tension was below the normal mean for gestational age in 33 cases; in 14 it was below the lower limit of the 95% confidence interval for normal pregnancies. The severity of fetal hypoxia correlated significantly with fetal hypercapnia, acidosis, hyperlacticaemia, hypoglycaemia, and erythroblastosis.

These findings indicate that "birth asphyxia" is not necessarily due to the process of birth.

Introduction

Growth retarded fetuses are at increased risk of intrauterine death, premature delivery, fetal distress in labour, and asphyxia at birth, all of which lead to increased perinatal mortality and long term morbidity.[1] Neonatal findings include asphyxia,[2] hypoglycaemia,[2] hyperlacticaemia,[3] and polycythaemia,[4] but non-invasive methods of fetal assessment, such as antenatal cardiotocography, suggest that some growth retarded fetuses have hypoxia and acidosis before labour.[5] Furthermore, after apparently atraumatic delivery neonates that are small for dates may have severe hypoxia. These observations suggest that chronic intrauterine hypoxia occurs and that the cause of growth retardation in some fetuses may be inadequate placental transfer. Lack of access to fetuses has prevented confirmation of these ideas, but the technique of fetal blood sampling by cordocentesis for karyotyping severely growth retarded fetuses[6 7] has permitted access to the fetal circulation and hence measurement of the indicators of hypoxia prenatally.

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Patients and methods

Umbilical venous blood was sampled by cordocentesis[6] for karyotyping at 21-36 weeks' gestation in 38 consecutive pregnancies in which intrauterine growth retardation was diagnosed in our unit. The extra 500 μl fetal blood required for this study did not increase fetal risk because it was at most 1% of the fetoplacental blood volume.[8] Fetuses with other structural abnormalities were excluded, and only those in which pure umbilical venous blood was obtained were included. The study was approved by the hospital ethical committee.

All the mothers were healthy; they were aged 16-40, and their parity ranged from one to six. All yielded negative results on screening for toxoplasmosis, rubella, cytomegalovirus, hepatitis, syphilis, and auto-antibodies. Two patients had hypertension induced by pregnancy.

The gestational age of the fetuses was determined from the last menstrual period and confirmed by ultrasonographic measurement of the fetal biparietal diameter at 16-18 weeks. Intrauterine growth retardation was diagnosed when the abdominal circumference, determined by ultrasound, was below the fifth centile for gestational age.[9] The outcome of the pregnancies and the long term follow up of these babies are the subject of another study.

Fetal blood (500 μl) was collected into heparinised syringes; 200 μl was placed into a sodium fluoride tube (Vacutainer, Rutherford, New Jersey, USA) for estimation of glucose and lactate concentrations and 180 μl into 20 μl of isotonic edetic acid solution for haematological studies. Blood gas tensions and acid-base values were determined with a Corning 178 blood gas analyser (Halstead, England). Blood glucose and plasma lactate concentrations were measured in 28 samples by, respectively, glucose oxidase (YSI model 23 AM, Yellow Spring Instrument Co, Ohio, USA) and lactate dehydrogenase techniques (kit 149993, Boehringer, Mannheim, West Germany). Full blood counts were determined with a Coulter S-Plus counter (Coulter Electronics Ltd, Luton, England). Blood films were stained with Jenner's Giemsa by an automatic processing machine and nucleated red cell counts per 100 white cells determined in 31 patients. Kleihauer testing showed that all samples contained only fetal red cells.

The umbilical venous oxygen tension, carbon dioxide tension, pH, and lactate concentration were compared with the established normal ranges, which were obtained from 150 fetuses at 16-38 weeks' gestation[10]; umbilical venous blood oxygen tension, carbon dioxide tension, and plasma lactate concentration change with gestational age. For this study the numbers of nucleated red cells per 100 white cells were counted in 117 control fetal blood samples obtained at 16-38 weeks' gestation, and umbilical venous blood glucose concentration was measured in 51 samples at 18-36 weeks. These fetuses were undergoing prenatal diagnosis and were subsequently shown not to be affected by the condition under investigation.

To test whether the oxygen tension of the fetuses with intrauterine growth retardation was significantly different from that of normal fetuses analysis of covariance was used after the effect of gestational age had been taken into

account. The degree of hypoxia in each growth retarded fetus was then expressed as the difference between the normal mean oxygen tension for gestational age and the observed umbilical venous oxygen tension. Similarly, the normal mean carbon dioxide tension and lactate concentration were subtracted from the observed values and the results called hypercapnia and hyperlacticaemia respectively. The severity of growth retardation was expressed as the number of standard deviations by which the abdominal circumference differed from the normal mean.[9]

Results

In the control samples the umbilical venous blood glucose concentration (mean 3·8 (SD 0·75) mmol/l; n=51) did not correlate significantly with gestational age (r=0·006, n=51). The mean nucleated red cell count fell from 72/100 white cells at 16 weeks' gestation to 25/100 at 23 weeks and remained at a similar value thereafter (mean 25 (25)/100 white cells).

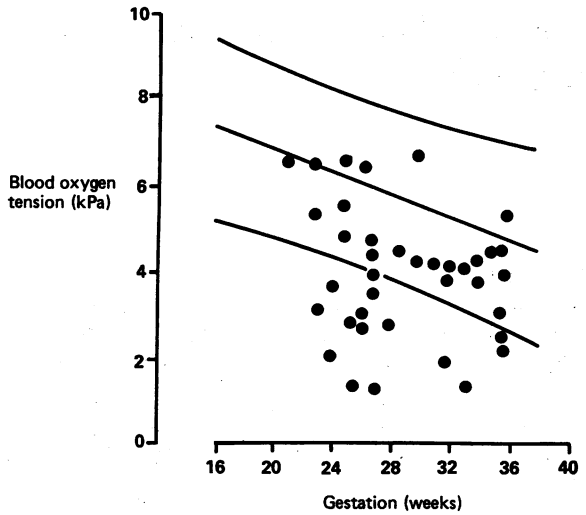

FIG 1—Umbilical venous blood oxygen tension in 38 growth retarded fetuses plotted against mean and 95% confidence interval in normal fetuses.

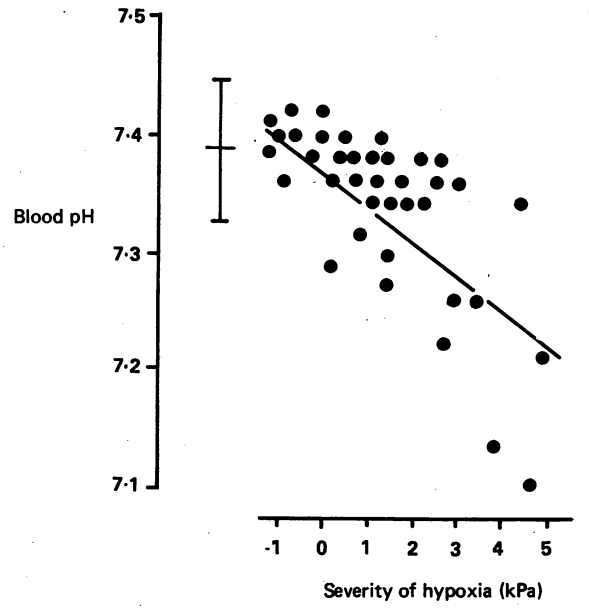

FIG 2—Relation between umbilical venous blood pH and severity of hypoxia (normal mean oxygen tension for gestational age minus observed value) in growth retarded fetuses (r=−0·72, n=38, p<0·0001). Vertical bar indicates mean (2 SD) in normal fetuses.

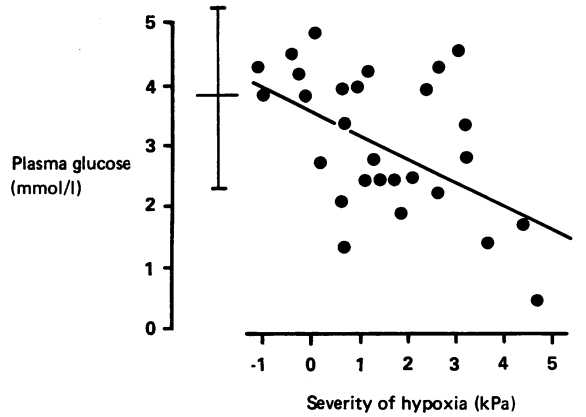

FIG 3—Relation between umbilical venous blood glucose concentration and severity of hypoxia (normal mean oxygen tension for gestational age minus observed value) in growth retarded fetuses (r=−0·58, n=28, p<0·002). Vertical bar indicates mean (2 SD) in normal fetuses.

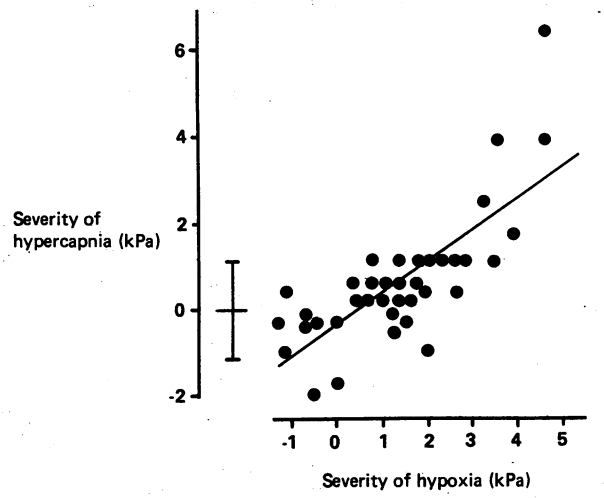

FIG 4—Relation between severity of hypercapnia (observed carbon dioxide tension minus normal mean value for gestational age) and severity of hypoxia (normal mean oxygen tension for gestational age minus observed value) in growth retarded fetuses (r=0·77, n=38, p<0·0001). Vertical bar indicates mean (2 SD) in normal fetuses.

The oxygen tension of the 38 fetuses with intrauterine growth retardation was significantly lower than that of the 150 normal fetuses ($F_{2,185}$=46·1, p<0·0001), and 14 of the 38 fetuses had an oxygen tension below the lower limit of the 95% confidence interval for normal pregnancies (fig 1). The severity of hypoxia had significant negative correlations with pH (r=−0·72, n=38, p<0·0001; fig 2) and glucose concentration (r=−0·58, n=28, p<0·002; fig 3) and significant positive correlations with hypercapnia (r=0·77, n=38, p<0·0001; fig 4), hyperlacticaemia (r=0·60, n=28, p<0·001; fig 5), and nucleated red cell count (r=0·58, n=31, p<0·001; fig 6). The haemoglobin concentration and the severity of growth retardation did not correlate significantly with the severity of hypoxia (r=0·1, n=38, and r=0·27, n=38, respectively).

Discussion

Chronic intrauterine hypoxia, hypercapnia, acidosis, hyperlacticaemia, hypoglycaemia, and erythroblastosis occurred in some of the growth retarded fetuses studied. These findings support the concept that fetal reserves may be reduced before labour and that hypoxia and acidosis at delivery are not necessarily the result of intrapartum events.[11]

The causes of intrauterine growth retardation may be environmental or genetic (low growth potential), and many pregnancies

with this complication would not be expected to have abnormal placental function.[12] Some of the fetuses we studied were not hypoxic and presumably had other causes of growth retardation. Furthermore, the absence of a significant correlation between the severity of growth retardation (abdominal circumference adjusted for gestation) and hypoxia indicates that fetuses stunted by poor placental function are not necessarily smaller than those stunted for other reasons.

It has been suggested that the cause of hypoglycaemia in growth retarded neonates is depletion of liver glycogen stores.[13] Our finding of intrauterine hypoglycaemia suggests, however, that the low glycogen stores at birth may be the result rather than the cause of the low blood glucose concentrations. Possible causes of fetal hypoglycaemia are reduced placental perfusion (inadequate maternal supply), inadequate placental transfer, decreased gluconeogenesis, and increased consumption of glucose. We are currently investigating these mechanisms.

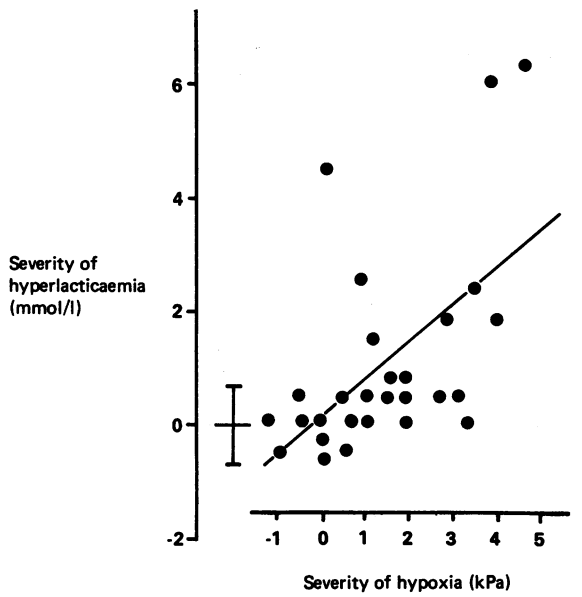

FIG 5—Relation between severity of hyperlacticaemia (observed plasma lactate concentration minus normal mean value for gestational age) and severity of hypoxia (normal mean oxygen tension for gestational age minus observed value) in growth retarded fetuses ($r=0{\cdot}60$, $n=28$, $p<0{\cdot}001$). Vertical bar indicates mean (2 SD) in normal fetuses.

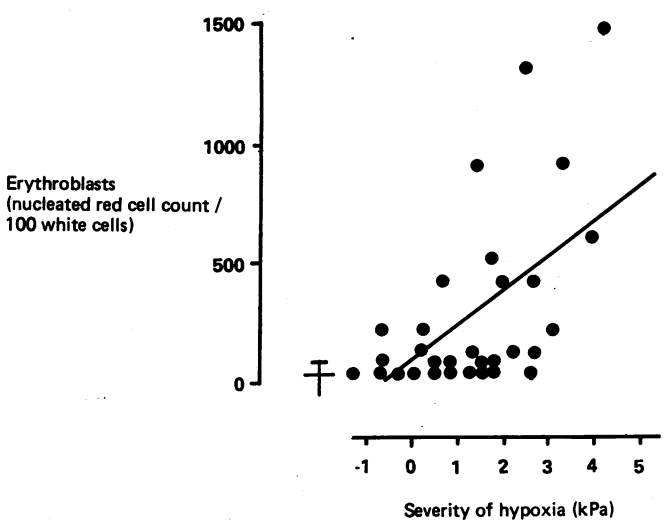

FIG 6—Relation between umbilical venous erythroblast (nucleated red cell) count/100 white cells and severity of hypoxia (normal mean oxygen tension for gestational age minus observed value) in growth retarded fetuses ($r=0{\cdot}58$, $n=31$, $p<0{\cdot}001$). Vertical bar indicates mean (2 SD) in normal fetuses.

In animals intrauterine growth retardation can be produced by ligation of an umbilical or uterine artery, microsphere embolisation of the placenta, surgical reduction of the number of placental cotyledons, or induction of maternal hypoxia.[14] Fetal hypoglycaemia has been reported in several of these studies, which agrees with our findings. In the animal studies, however, plasma lactate concentration was reported as being low[15] or normal,[16] which contrasts with our finding of hyperlacticaemia in some fetuses. Hyperlacticaemia has also been found in human fetuses with severe anaemic hypoxia due to rhesus disease.[17] Such a discrepancy may be the result of differences between species in the response to fetal tissue hypoxia or in the severity or nature of the disease. Similarly, in animal studies the decrease in oxygen tension was small, delayed, or transient and there was no accompanying acidosis or hypercapnia.

In normal human fetuses, despite a physiological fall in oxygen tension with advancing gestation the oxygen content of umbilical venous blood remains constant because of a compensatory rise in haemoglobin concentration.[10] The positive correlation between hypoxia and nucleated red cell count in these fetuses indicates an erythropoietic response, which would tend to maintain blood oxygen content; polycythaemia has been reported in both small for dates neonates[4] and animal studies of intrauterine growth retardation.[18] The lack of a correlation between hypoxia and haemoglobin concentration in our study was therefore surprising. A possible explanation is that the severity and duration of hypoxia required to produce polycythaemia may be detected by the traditional methods of fetal assessment, such as cardiotocography, and that delivery prevented referral for sampling of fetal blood.

Our findings show that "birth asphyxia" is not necessarily due to the process of birth. As samples were taken from the fetuses only once in the antenatal period we cannot define the chronicity or sequence of the abnormalities detected; serial sampling would permit this and might help delivery to be timed to achieve the best postnatal prognosis. Blood sampling would also identify which growth retarded fetuses were not hypoxic and might help reduce unnecessary antenatal admission to hospital and premature delivery.

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