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Fetal biochemistry in growth retardation

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Summary

A substantial proportion of fetuses with severe early onset growth retardation are chromosomally abnormal and in these cases detailed ultrasound scanning will often demonstrate the presence of fetal anatomical defects. Chromosomally normal SGA fetuses with no biochemical abnormalities are likely to be normal small fetuses and seem to develop normally. SGA fetuses with evidence of impaired placental perfusion such as altered fetal cardiovascular dynamics and disturbances in biochemical, haematological, metabolic and endocrine status are at increased of neurodevelopmental delay.

Although incomplete, the data collected so far suggest the biochemical changes may be caused by reduced placental transfer of nutrients (e.g. oxygen, glucose and essential amino-acids) and subsequent reduced fetal metabolism leading to high levels of substrates (e.g. triglycerides and non-essential amino-acids) and low levels of tissue products (e.g. thyroid hormone, insulin, platelets and white cells).

Key words: cordocentesis; fetal biochemistry; growth retardation

Introduction

Small fetal size is not a diagnosis but a physical sign associated with an increased risk of several diseases such as inadequate placental function (about 15% of cases) and fetal abnormality (about 5%) but most small fetuses are normal (about 80%). This paper reviews (1), cytogenetic studies; (2), blood gas and acid-base status; (3), haematology; (4), glucose metabolism; (5), lipid metabolism; (6), protein metabolism; (7), adrenal steroids; and (8), thyroid function.

The results have been obtained by studying the blood from 449 small-for-

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gestational-age (SGA) (abdominal circumference below the 5th centile for gestational age) fetuses undergoing cordocentesis (ultrasound guided needle aspiration of umbilical cord blood) over the last 6 years. The gestation at cordocentesis was 20–39 (mean = 29) weeks. Maternal supine hypotension, hyperventilation and sedation were avoided and after sampling the umbilical vessel was identified as an artery or vein by injecting a small volume of normal saline and observing the direction of turbulence produced ultrasonically. The procedure-related risk of fetal death after cordocentesis is approximately 1%.

1. Cytogenetic studies

A chromosomal abnormality was found in 17% of our cases and these included (expressed as a percentage of the whole SGA group) triploid (7%), trisomy 18 (6%), trisomy 21 and 13 (1% each) and others (translocation or deletions) (2%). It has been suggested that chromosomal abnormality can be predicted by the fetal head to abdomen ratio; should the abdomen be more stunted than the head this would be in favour of placental failure and if the fetus is symmetrically small it has been suggested that a chromosomal abnormality is more likely. This should not be used as a reliable guide since the most asymmetrical SGA fetuses are those with the chromosomal abnormality — triploidy, and even cases with autosomal trisomy can have a large head/abdomen circumference ratio.

Detailed ultrasound scanning before sampling demonstrated the presence of structural abnormalities (ultrasound 'markers') in 122 fetuses and 80 (66%) of these were chromosomally abnormal.

In contrast, only 1% of the group with no structural defects (4 of 327) had chromosomal abnormalities. The presence of markers provides a useful guide to patients considering karyotyping but their absence still leaves a risk of about 1 in 100 which is a high enough risk for some patients to request cordocentesis.

SGA fetuses with normal karyotype

2. Blood gases and acid-base status

Many chromosomally and structurally normal SGA fetuses are hypoxic and acidotic [1] and our recent results are shown against reference ranges in Fig. 1.

When SGA fetuses are acidotic there is a mixed respiratory and metabolic acidosis with high levels of both P_{CO_2} and lactate. The cause of the fetal hypoxia may be reduced utero-placental blood flow since hypoxia in SGA fetuses is associated with high resistance pattern Doppler waveforms in the uterine arteries [2] and histopathological studies have shown a failure of the normal development of maternal placental bed arteries into low resistance vessels [3]. Fetal hypoxia and acidosis are also associated with abnormal blood velocity waveforms in the fetoplacental circulation [4] and a possible explanation for this observation is the association of abnormal Doppler studies with histological changes in the chorionic villi [5].

The human fetus, like the sheep, responds to chronic hypoxia by a redistribution of its blood flow to the brain, heart and adrenals, which may maintain tissue oxygenation to those organs at the expense of other organs such as the lungs,

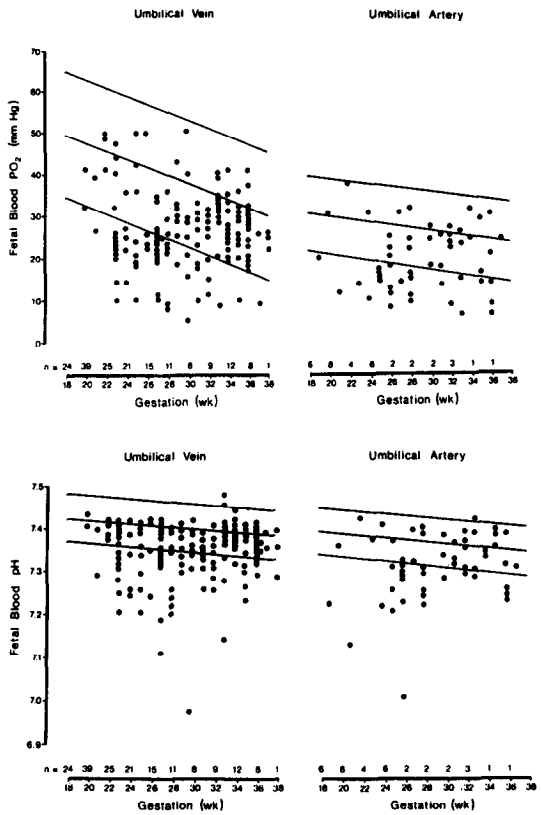

Fig. 1. Umbilical venous and arterial Po_2 and pH of the SGA fetuses plotted on the appropriate reference range.

gastrointestinal tract and kidneys. A high resistance pattern in the descending aorta is associated with neonatal complication in the ischemic organs, such as necrotising enterocolitis [6].

3. *Haematology*

Erythropoietin concentration and erythroblast count. In normal pregnancy the fetal plasma erythropoietin concentration rises with advancing gestational age but in SGA fetuses erythropoietin also increases in proportion to the degree of fetal acidaemia [7]. This suggests a fetal compensatory response to tissue hypoxia and there is an associated increase in erythroblast count [1].

Platelet and leucocyte counts. In normal pregnancy the fetal platelet and leucocyte counts increase with gestational age but severely growth retarded fetuses can be thrombocytopenic [8] and leucopenic [9]. This may be due to (1), impaired haemopoiesis (the result of tissue hypoxia and acidosis and/or deficiency of essential nutrients), (2), stem cell differentiation to erythropoiesis at the expense of other cell lines in an attempt to maintain tissue oxygenation; or (3), a fetal consumptive

coagulopathy and platelet destruction. Fetal thrombocytopenia in other conditions (e.g. allo-immune thrombocytopenia) is associated with cerebral haemorrhage before birth and poor neurological outcome.

4. Glucose metabolism

In normal pregnancy, the major source of glucose in fetal blood is across the placenta from the mother and the umbilical venous plasma insulin concentration and the fetal insulin to glucose ratio increases exponentially with gestation [10]. Some SGA fetuses are hypoglycaemic [1] due either to impaired placental transfer or increased glycolysis in anaerobic metabolism to lactate. Furthermore, there is hypoinsulinaemia which is more severe than accounted for by the degree of hypoglycaemia, suggesting pancreatic b-cell dysfunction [10].

5. Lipid metabolism

In normal fetuses, plasma triglyceride concentration decreases exponentially with gestational age reflecting increased deposition into adipose tissue [11]. Some SGA fetuses have high triglyceride levels, reflecting reduced triglyceride oxidation or less incorporation into body fat [11].

6. Protein metabolism

In normal pregnancies the fetal plasma concentration of amino acids is higher than in the mother due to active transport across the placenta [12]. In growth retardation there are low levels of the essential amino acids and also serine, tyrosine, taurine and ornithine. It is possible that the biosynthetic pathways for these amino acids may not be fully established in intrauterine life so they may be essential substrates for the fetus. Some non-essential amino acids, such as glycine or alanine, have increased levels possibly as a result of tissue breakdown or decreased utilisation for protein synthesis, oxidation or gluconeogensis.

The high ratio of non-essential to essential amino acids is similar to that of children with protein-calorie malnutrition.

7. Adrenal steriods

Cortisol and adreno-cortico-trophic hormone (ACTH) appear not to change significantly with gestational age in normal pregnancies but in some SGA fetuses there are high cortisol but low ACTH levels. The low ACTH seems to exclude a physiological response to stress and the high cortisol could relate to the increased adrenal blood flow [13]. Hypoxic SGA fetuses also have high levels of noradrenaline [14].

8. Thyroid function

In normal fetuses, serum thyroid stimulating hormone (TSH), total and free thyroid hormones increase with gestational age. In some SGA fetuses, TSH concentration is increased and thyroid hormone concentrations are reduced (Fig. 2) [15].

This derangement in the pituitary-thyroid axis is related to the degree of fetal hypoxaemia and acidaemia. Although low thyroid hormone concentrations may slow the metabolic rate and prolong survival in conditions of reduced placental

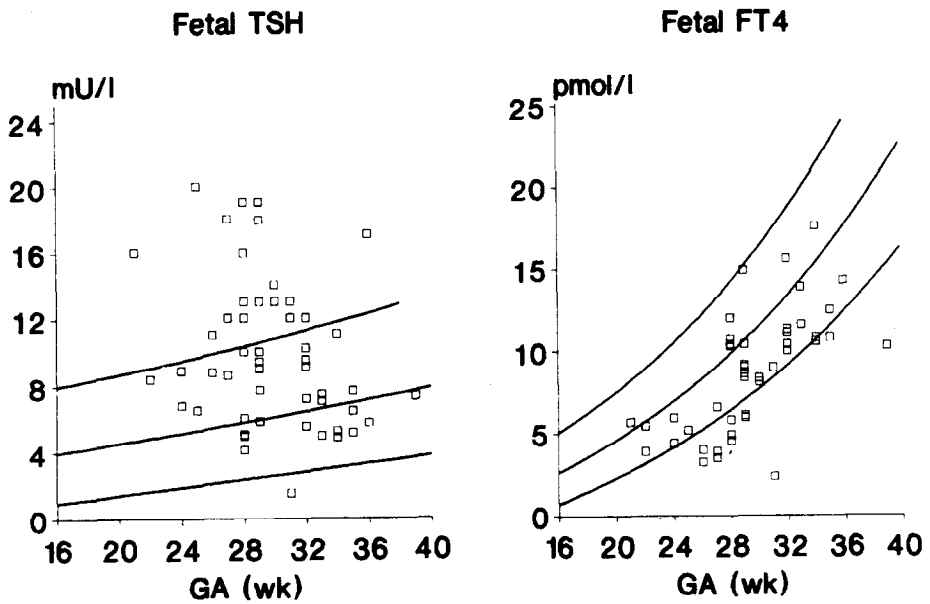

Fig. 2. Plasma TSH and free thyroxine in the SGA fetuses plotted on the appropriate reference range [15].

transfer ('in utero hibernation'), prolonged fetal hypothyroidism could have an adverse effect on brain development. Indeed, some children with congenital hypothyroidism even when treated shortly after birth have reduced subsequent neuro-development so it is likely that fetal hypothyroidism can damage the developing brain.

Fetal outcome

The most important determinate of whether a SGA fetus with normal chromosomes will survive is gestational age (e.g. even severely acidotic growth retarded fetuses survive after 32 weeks). The appropriate end point to assess our care of mature SGA fetuses must therefore be perinatal morbidity, although this is much more difficult to define than mortality. The neuro-development at 1–4 years of the children who were SGA fetuses has been assessed using a Griffith's score and a significant correlation between the degree of fetal acidaemia at cordocentesis and neuro-developmental stages was found (Fig. 3) [16].

The association between acidaemia at cordocentesis and subsequent neuro-development does not establish that acidaemia was the damaging factor (e.g. fetal hypothyroidism or thrombocytopenia could cause developmental delay). To improve timing of delivery, we need to develop techniques that identify poor placental function early in the disease process and research into the sequence of associated secondary effects. Similarly, for pregnancies that are too premature for delivery, attempts to improve the intra-uterine environment must be evaluated. Until this is

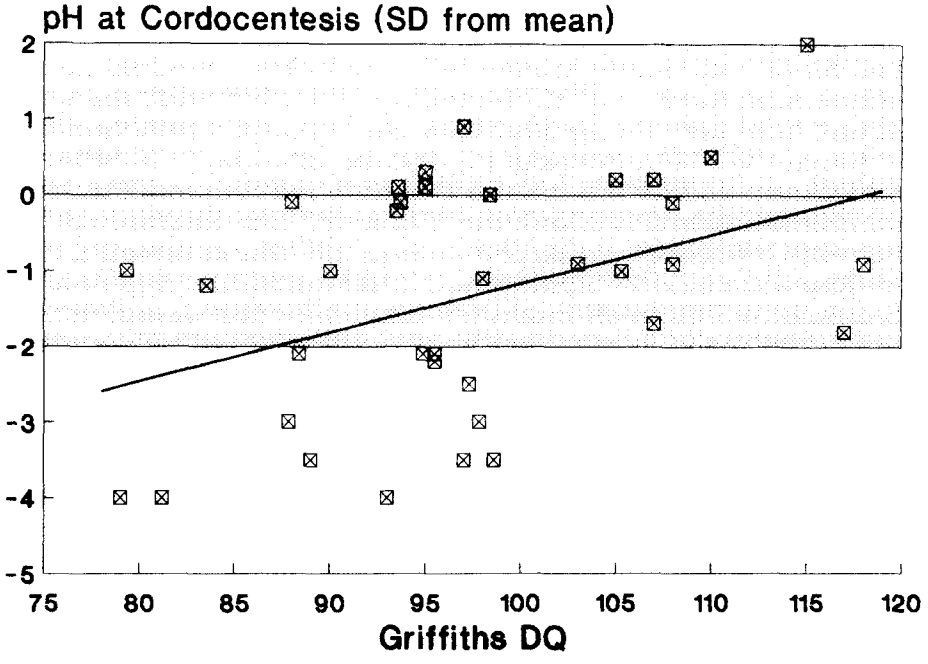

Fig. 3. Relationship between acidaemia at cordocentesis and subsequent neuro-development (Griffiths score) modified from [16].

achieved, logical delivery decisions will require an understanding of the risk of morbidity or mortality to the fetus of remaining undelivered and comparison with the risks of prematurity.

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