# Relationship between fetal acidemia at cordocentesis and subsequent neurodevelopment

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## ABSTRACT

*To determine whether there is a relationship between chronic fetal acidemia and subsequent neurodevelopment, a follow-up study was undertaken of 36 children with normal karyotype and morphology, who had prenatal cordocentesis for severe growth retardation. The main outcome measure was the Griffiths neurodevelopmental quotient. The children who had acidemia as fetuses (n = 13) had a significantly lower developmental quotient (mean = 91.8, SD = 6.3) than those with normal (n = 23) fetal blood pH (mean = 100.3, SD = 10.3; t = –2.68, p = 0.011). There was also a significant correlation between developmental quotient and the degree of fetal acidemia (r = 0.41, n = 36, p = 0.012). The pregnancies with acidemic fetuses had similar epidemiological characteristics to those with fetuses with a normal pH, except for a higher incidence of smoking. There was no significant correlation between the degree of growth retardation (birth weight expressed as multiples of SD from the mean for gestational age and sex) and fetal acidemia (r = –0.23, n = 36, NS) or subsequent Griffiths developmental quotient (r = –0.005, n = 36, NS).*

*The results show an association between chronic fetal acidemia and subsequent impaired neurodevelopment. This observation suggests that future preventative interventions may be possible.*

## INTRODUCTION

In labor, fetal scalp blood sampling and measurement of blood pH is an accepted technique for the evaluation of abnormal fetal heart rate patterns; fetal acidemia is taken to indicate the need for urgent delivery in order to reduce the risk of fetal death[1]. A similar approach, the study of pH in fetal blood obtained by cordocentesis, has been advocated for the management of complications occurring before labor[2].

Perinatal mortality has fallen so dramatically that reducing morbidity has become an increasingly important aim of obstetric care[3]. However, there is very little association between acidemia in cord blood at the time of delivery and subsequent impaired neurodevelopment[4]. Nevertheless, there is substantial evidence supporting the concept of Freud and others of a link between complications of pregnancy suspected to cause fetal acidemia before labor and impaired neurodevelopment[5–8]. A possible explanation for this apparent discrepancy is that acidemia at birth is often the result of acute changes in labor occurring in previously healthy fetuses with little if any prospect of long-term damage. The large number of cases of acute acidemia may obscure an association between the less common chronic fetal acidemia and subsequent impaired development.

The aim of this study was to test the hypothesis that chronic fetal acidemia before labor impairs subsequent development, by performing a neurodevelopmental assessment on children, who as fetuses had cordocentesis to establish the cause of severe growth retardation.

## PATIENTS AND METHODS

Neurodevelopmental assessment was carried out in 38 children, aged 12–52 months (mean = 29.1 months, SD 13 months) who as fetuses had cordocentesis and measurement of blood pH for severe fetal growth retardation. Cordocentesis was performed as described previously[2], and the results were made available to the referring obstetricians who decided the timing and mode of delivery. The indications for inclusion in the study were:

**Table 1** A comparison of the characteristics of pregnancies with normal and acidemic fetal pH. Mean ± SD for $t$-test or absolute numbers for non-parametric comparisons are presented

|  | Normal pH (n = 23) | Acidemic (n = 13) | Statistics |
|---|---|---|---|
| *Maternal* |  |  |  |
| Age (years) | 26.9 ± 4.6 | 29.7 ± 6.7 | $t = 1.5$, NS |
| Ethnic (Caucasian, black, Asian) | 17, 4, 2 | 11, 2, 0 | $z = 0.83$, NS |
| Social class (1, 2, 3, 4, 5)* | 1, 7, 10, 2, 3 | 0, 3, 4, 4, 2 | $z = 1.2$, NS |
| Smoker (yes/no) | 5/18 | 9/4 | $z = 2.8, p = 0.005$ |
| Parity | 0.83 ± 1.1 | 0.46 ± 0.6 | $t = -1.1$, NS |
| Weight (kg)† | 63.4 + 11 | 64.3 ± 12 | $t = 0.22$, NS |
| Mode of delivery (vaginal/LSCS)‡ | 7/16 | 1/12 | $z = 1.6$, NS |
| *Neonatal* |  |  |  |
| Cord–del. (days)** | 14.3 ± 20 | 1.1 ± 2.4 | $t = -2.3, p = 0.03$ |
| Gestation at delivery (weeks) | 36.0 ± 2.3 | 34.5 ± 1.7 | $t = -2.1, p = 0.05$ |
| Birth weight (g) | 1824 ± 363 | 1559 ± 397 | $t = -2.1, p = 0.05$ |
| Birth weight (SD from mean) | -2.6 ± 0.6 | -2.8 ± 0.9 | $t = 0.7$, NS |
| Admission to special care baby unit (yes/no) | 16/7 | 9/4 | $z = 0.02$, NS |
| Duration (days) | 12.4 ± 13 | 18.2 ± 15 | $t = 1.2$, NS |
| Sex (M/F) | 11/12 | 9/4 | $z = 1.2$, NS |
| Age at neurodevelopmental test (months) | 28.7 ± 13 | 29.4 ± 14 | $t = 0.15$, NS |

* Social class was derived from the partner's occupation or mother's if she had no partner. Social class 5 includes those who were unemployed; †maternal booking weight; ‡LSCS = lower segment Cesarean section; **cordocentesis to delivery interval; NS = not significant

(1) Gestation at delivery ≥ 32 weeks and birth weight < 2 SD from the mean for gestational age and sex;

(2) Normal fetal karyotype and morphology; and

(3) The children were at least 1 year of age.

Only children delivered after 32 weeks' gestation were included in order to exclude the possible damaging effect of severe prematurity.

The neurodevelopmental assessments were made according to the Griffiths scales[9,10] by the same operator (R. A. A.), who had no knowledge of the fetal pH at cordocentesis. Since all the children were born after 32 weeks' gestation, the developmental quotient scores were not corrected for gestational age at birth. The data from two children were excluded from analysis because a complete Griffiths assessment was not possible; one child would not co-operate and the other only spoke German (aged 3 years), making our assessment of hearing, speech and practical reasoning impossible. Both these children had normal blood gas results as fetuses and were thought to be developing normally.

To evaluate the importance of acidemia, as opposed to reduced fetal growth, the Griffiths developmental quotient of children who had been acidemic growth-retarded fetuses was compared to that of children who were growth-retarded fetuses with a normal pH.

The study was approved by the hospital's Ethics Committee.

**Statistical analysis**

In normal pregnancies, umbilical venous and umbilical arterial blood pH and birth weight change with gestational age[11,12]. Therefore, the measured values in the growth-retarded fetuses were expressed as multiples of standard deviation from the normal mean for gestational age.

Comparison between groups for continuous variables was by the $t$-test (two-tailed) and for non-parametric data by analysis of variance by ranks (equivalent to the $\chi^2$ test with the Yates correction), resulting in a $z$-test[13].

**RESULTS**

At cordocentesis, 13 of the 36 (36%) fetuses were acidemic (blood pH < 2 SD for gestational age). The acidemic group was not significantly different from the non-acidemic group for maternal age, race, social class, parity, weight, mode of delivery, frequency and duration of admission to special care baby units, fetal sex, degree of growth retardation and age at Griffiths assessment (Table 1). However, in the acidemic group there was a higher incidence of maternal smoking, the cordocentesis-to-delivery interval was shorter, the gestational age at delivery was lower and the birth weight was lighter than in the non-acidemic group (Table 1).

At the time of neurodevelopmental assessment, one child (who was severely acidemic as a fetus) had been diagnosed as having ataxic cerebral palsy, but none of the other parents had been given any indication that their children were developing inappropriately. The Griffiths developmental quotient of children who had been acidemic as fetuses (mean = 91.8, SD = 6.3) was significantly lower than those who had a normal fetal blood pH (mean = 100.3, SD = 10.3; $t = -2.68, p = 0.011$). There was also a significant correlation between the degree of fetal acidemia and developmental quotient (Figure 1; $r = 0.41, n = 36, p = 0.012$).
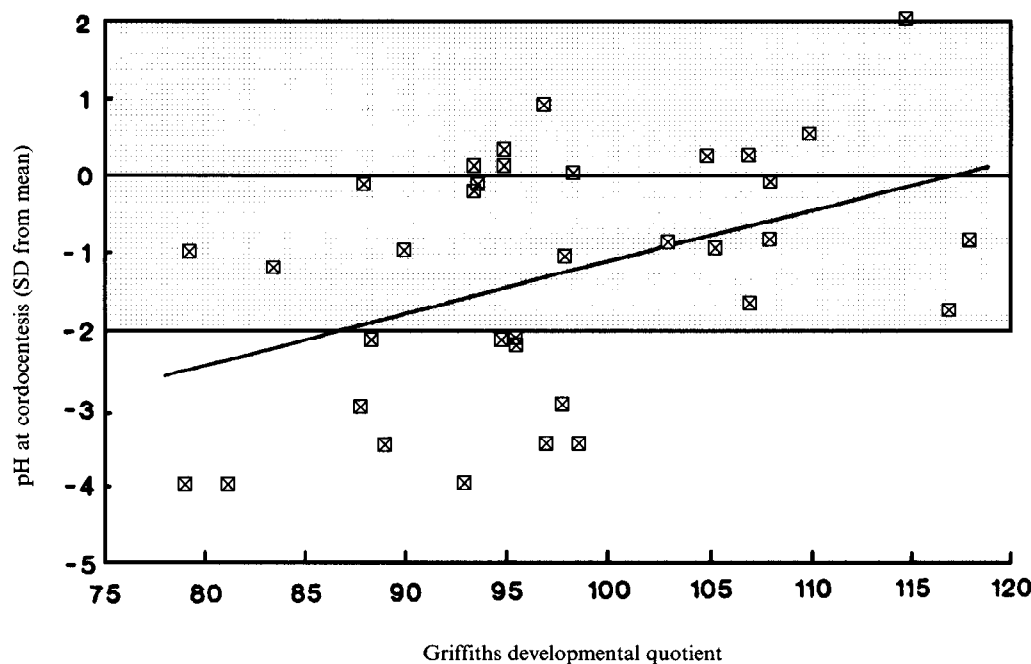
**Figure 1** The relationship between Griffiths neurodevelopmental quotient and fetal blood pH at cordocentesis ($r = 0.41$, $n = 36$, $p = 0.0012$). Since in normal pregnancies fetal pH changes with gestational age, the values from the study cases are expressed as multiples of SD from the normal mean for gestational age

There was no significant correlation between the degree of fetal growth retardation (birth weight expressed as multiples of SD from the mean for gestational age and sex) and the degree of fetal acidemia ($r = -0.23$, $n = 36$, NS) or subsequent Griffiths developmental quotient ($r = -0.005$, $n = 36$, NS).

## DISCUSSION

The significant correlation between the degree of fetal acidemia and the degree of neurodevelopmental impairment does not establish that acidemia was the damaging factor. Inadequate placental function, severe enough to stunt growth and cause fetal acidemia, can have many other nutritional and metabolic effects including hypothyroidism[14] and thrombocytopenia[15] which in themselves could cause developmental delay.

Although there have been several studies of the relationship between fetal growth retardation and subsequent neurodevelopment, they provided conflicting results with some finding severe handicap and others minimal or none[16]. This is not surprising because, as shown in the present study, there is no significant correlation between fetal size for gestational age (birth weight expressed as multiples of SD from the mean) and either fetal acidemia or subsequent neurodevelopment. The findings also support the fear that, despite the great efforts currently made to detect small fetuses, size is not a good predictor of fetal acidemia. Indeed, it is likely that many acidemic fetuses are not detected by any currently used technique of assessing fetal well-being and are born with a birth weight within the normal range.

With the exception of the child with cerebral palsy, the parents were not aware of any developmental problems. Although these children are not clinically handicapped, the prevention of mild or moderate brain damage is important. Damage resulting in children failing to achieve their genetic neurodevelopmental potential may be much more common than currently recognized.

Two possibly complicating factors were identified. The acidemic fetuses were delivered at a slightly earlier gestational age than the non-acidemic. By limiting our study to children who were delivered after 32 weeks' gestation, it is unlikely that the slightly earlier delivery of acidemic fetuses, and their associated slightly lower birth weight, had a significant effect on neurodevelopment. Second, the acidemic fetuses were much more likely to have mothers who smoked during pregnancy and this difference between the groups appeared to be independent of other maternal characteristics such as social class and maternal age. This observation requires further investigation.

The results suggest that, despite the short cordocentesis-to-delivery interval, acidemia may be too late in the disease process to be used as an indication for delivery to prevent handicap. Furthermore, non-invasive tests of fetal well-being can be normal with severe fetal acidemia[2]. To improve timing of delivery, we need to develop techniques that identify such pregnancies early in the disease process and to research into the sequence of associated secondary effects. Similarly, for pregnancies that are too premature for delivery, attempts to improve the intrauterine environment[17] must be evaluated.

If the damage to neurodevelopment is to be reduced, mature fetuses (such as those in this study) may benefit from earlier delivery than is suggested by current testing techniques. In very premature pregnancies, logical delivery decisions will require an understanding of the

risks to the fetus in a hostile intrauterine environment and comparison of this information with the risks of prematurity.

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