CURRENT TOPIC

Causes and consequences of fetal acidosis

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The fetus depends on the mother for placental exchange of oxygen and carbon dioxide. This in turn relies on adequate maternal blood gas concentrations, uterine blood supply, placental transfer and fetal gas transport. Disruption of any of these can cause fetal hypoxia, which, despite compensatory mechanisms, may lead to acidosis. When severe and acute (lasting hours), but especially if prolonged (days or weeks), hypoxia and therefore acidosis, are associated with significant morbidity and mortality with potential long term sequelae. Whether this damage is primarily due to reduced cell energy availability, as a result of hypoxia, or secondary to cell poisoning, as a result of acidosis, is unclear and indeed acidosis could simply be a marker of the cause and severity of the hypoxia.

The very different aetiologies of acute *vs* chronic acidosis and the possible consequences will be reviewed, whether directly caused by the acidosis or indirectly by the hypoxia

What is acidosis?

Acidosis means a high hydrogen ion concentration in the tissues. Acidaemia refers to a high hydrogen ion concentration in the blood and is the most easily measured indication of tissue acidosis. The unit most commonly used is pH, which is log to base 10 of the reciprocal of the hydrogen ion concentration. Whereas blood pH can change quickly, tissue pH is more stable. The cut off taken to define acidaemia in adults is a pH of less than 7.36, but after labour and normal delivery much lower values commonly occur in the fetus (pH 7.00), often with no subsequent ill effects. Studies looking at the pH of fetuses from cord blood samples taken antenatally and at delivery have established reference ranges. Other indices sometimes used to assess acidosis are the base excess or bicarbonate. Neither of these is measured by conventional blood gas machines but is calculated from the measured pH and pCO_2.

The major sources of hydrogen ions in the fetus are carbonic and lactic acids from aerobic and anaerobic metabolism, respectively. The removal of CO_2 (and so carbonic acid) from the fetus depends almost entirely on the placenta. Unlike in sheep, lactate does not normally seem to be an important substrate for the human fetus and lactic acid is usually either further metabolised or excreted transplacentally. The latter has been shown by analyses of arterial and venous cord blood samples from human fetuses with low blood oxygen content due to anaemia secondary to severe Rhesus isoimmunisation. Lactate concentration was higher in the umbilical artery than the umbilical vein. The increased lactate is explained by increasing production from anaerobic metabolism and the difference in concentration between the umbilical artery and vein suggests that the placental circulation clears lactate from the fetal blood so helping to "repay" a fetal oxygen debt.[1]

The causes of fetal hypoxia and therefore acidosis can be divided into maternal, placental, or fetal. The consequences of acidosis depend on its severity and duration and also the condition of the fetus before the insult, and we classify the causes of fetal acidosis into acute (hours) or chronic (days). In postnatal medicine acidosis is often described as respiratory (predominantly due to increased pCO_2) or metabolic (predominantly due to increased lactic acid). However, while acute fetal acidosis is almost always initially respiratory, this is quickly followed by mixed respiratory and metabolic acidosis if there is no improvement in oxygenation. Furthermore, the chronic acidosis of fetal life is also mixed,[2] (fig 1) and we therefore prefer to use the terms acute and chronic.

Aetiology

ACUTE

Maternal

Anything that causes hypotension or hypovolaemia such as haemorrhage, a vasovagal attack, or epidural anaesthesia will reduce the maternal blood supply and so oxygen delivery to the uterus. Uterine contractions can also interrupt the uterine blood flow by a pressure rise and if prolonged, as in hypertonus, may cause hypoxia and so acidosis.

Placental

Abruption can disrupt the utero-placental circulation by separating and so tearing the uterine spiral arteries from the placenta.

Fetal

Blood flow from the placenta to the fetus is often affected during labour and delivery by umbilical cord compression and this can sometimes happen before labour if there is reduced liquor or a true knot in the cord. Animal

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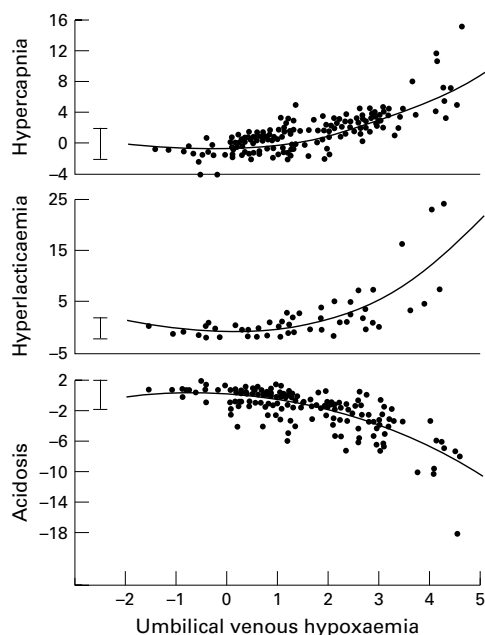P W Soothill

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*Figure 1   Relations between umbilical venous hypoxaemia (pO₂) and umbilical hypercapnia (pCO₂), hyperlacticaemia (blood lactate), or acidosis (pH); these are all expressed in multiples of SD from the appropriate mean for gestational age). Reproduced with permission from Nicolaides et al. Am J Obstet Gynecol;1989;**161**:996-100.*

experiments have shown that there is significant reserve because the fetus can compensate by increased oxygen extraction,[3] meaning blood flow to the fetus must be reduced by at least 50% to cause hypoxia.[4]

CHRONIC
Maternal
Maternal causes of chronic fetal acidosis include reduced oxygenation of maternal blood, such as in severe respiratory or cardiac disease, or reduced blood flow to the placenta as in connective tissue diseases—for example, systemic lupus erythematosus—and pre-eclampsia.

Placental
Antenatal fetal blood sampling by ultrasound guided needle aspiration from the umbilical cord (cordocentesis) in pregnancies with fetal growth restriction (FGR) has shown hypoxia as a result of impaired placental transfer of oxygen.[5] This is thought to result from inadequate trophoblast invasion of the myometrium in early pregnancy,[6] leading to reduced perfusion of the intervillous spaces. In animal experiments, like acute cord compression studies, utero-placental blood flow also needs to be reduced by at least 50% to produce fetal hypoxia.[7] This indicates that the reduction in placental transfer seen in human FGR must be substantial to produce the hypoxia and acidosis found at cordocentesis in such cases.

Fetal
Even with normal placental function, conditions within the fetus can cause acidosis. Anaemia from rhesus disease, parvovirus infection, α-thalassaemia or feto-maternal haemorrhage, when severe enough to reduce fetal haemo-

globin concentrations below 40 g/l (equivalent to an oxygen content below 2 mmol/l), can lead to a fall in pH.[8 9] Arterio-venous shunting in fetal tumours, serious cardiac structural abnormalities, or arrhythmias are other conditions which can lead to chronic acidosis by decreased oxygenation as a result of reduced feto-placental blood flow.

Diagnosis of acidosis
ANTENATALLY
The use of ultrasound imaging to assess fetal size and wellbeing, Doppler studies of the fetal circulation, and cordocentesis have helped us to understand some of the mysteries of life before birth. During the 1980s cordocentesis was used to study the acid base status of the fetus and create reference ranges for umbilical arterial and venous blood gases in the second and third trimesters (fig 2).[2 10] These studies provided the first direct evidence of chronic acidosis.[5] However, cordocentesis carries a procedure related risk of 1% and cannot therefore be used routinely or repeatedly for monitoring. To overcome this, fetal medicine specialists have searched for non-invasive techniques to detect acidosis.

In acute situations where severe hypoxia and acidosis are suspected, the non-invasive techniques used are fetal heart rate monitoring or biophysical profile score (fetal breathing/movements, gross body movement, tone and amniotic fluid volume). However, in pregnancies with placental dysfunction before labour, the onset of hypoxia and acidosis is more gradual and results of these tests are often normal until a preterminal stage[11] where urgent delivery is required to prevent an intrauterine death.

An important breakthrough in antenatal surveillance was the demonstration that increased resistance in placental vasculature in pregnancies with hypoxia and acidosis due to

Key points
- The causes and consequences of *acute* (minutes or hours) and *chronic* (days or weeks) fetal acidosis are different
- In the past much attention has been paid to acute acidosis during labour, but in previously normal fetuses this is *rarely* associated with subsequent damage
- In contrast, chronic acidosis, which is often not detected antenatally, is associated with a significant increase in neurodevelopmental delay
- The identification of small for gestational age fetuses by ultrasound scans and the use of Doppler waveforms to detect which of these have placental dysfunction mean that these fetuses can be monitored antenatally
- Delivery before hypoxia has produced chronic acidosis, may prevent subsequent damage and good timing of delivery remains the only management option at present.
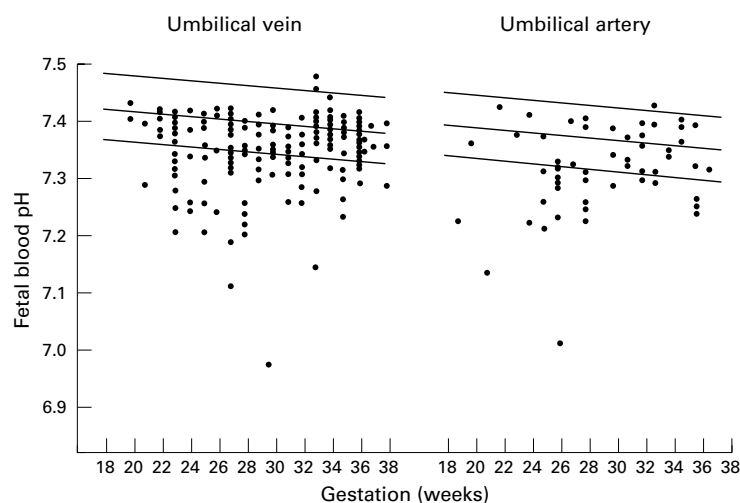
Figure 2 Reference ranges (mean and 95% confidence intervals), of umbilical venous and arterial pH with gestation. Dots represent pH values from FGR fetuses, many with chronic acidosis. Reproduced with permission from Nicolaides et al. Am J Obstet Gynecol. [2]

placental dysfunction caused abnormal flow patterns in the umbilical artery, demonstrable using Doppler ultrasonography. Umbilical artery Doppler velocimetry is a sensitive and specific non-invasive way of detecting chronic acidosis. This was confirmed by the demonstration of significant associations between umbilical artery Doppler waveforms and blood gases at delivery.[12] [13] Further work has also shown a characteristic pattern of redistribution of blood flow to the most essential organs at the expense of the peripheral ones. This occurs with increasing acidosis, and is followed by progressive cardiac dysfunction, leading to abnormal venous blood flow patterns. Doppler is now the most widely used technique to detect chronic acidosis in expert UK clinical practice.

INTRAPARTUM
Fetal heart rate monitoring during labour can give us an indication of fetal hypoxia and acidosis, but although sensitive, this method is not very specific. Measurements of acid base status intrapartum obtained from sampling fetal blood from the presenting part after cervical dilatation and rupture of membranes help decrease operative deliveries following false positive fetal heart rate traces.[14] In contrast to antenatal blood gas results, the value of a single result in labour is limited as the acid base interactions are dynamic and may change quickly, and repeated samples are often needed. Several methods of continuous blood gas monitoring using an electrode attached to the fetus sub- or transcutaneously have been tried for pO_2,[15] pCO_2, and pH.[16] Intrapartum fetal oxygen saturation monitoring by pulse oximetry is being developed and seems to be a good predictor of pO_2 and acid base status,[17] and this has important implications for monitoring in labour.

Fetal pH falls during normal labour but this is found earlier in pregnancies affected by complications such as pre-eclampsia and growth restriction.[18] We believe this result is not only because of "reduced reserve" for

labour but that some of these cases are acidotic before labour onset (as described above).

AT DELIVERY
Studies of acid base status in cord blood at birth have provided normal ranges.[19] As in labour, neonates from pregnancies with antenatal (growth retardation) or intrapartum (meconium staining) complications, are more likely to be hypoxic[20] and acidotic at birth. In our view the important distinction is whether the acidosis resulted from chronic (present before labour) or acute hypoxia. The difference in umbilical artery and vein gases may give further information on its duration. In placental dysfunction where hypoxia is due to reduced placental transfer, umbilical artery and vein values will both be abnormal and similar, whereas in acute cord compression or fetal bradycardia the hypoxia and acidosis will be predominantly in the umbilical artery, leading to a large arteriovenous difference. This is because a slow passage of blood through the placenta allows time for maximum gas exchange despite reduced total blood flow.

Consequences of acidosis
Acidosis occurs as a result of tissue hypoxia and it is unclear whether the consequences of this process are due primarily to the acidosis or the hypoxia. What has become clear over the past decade is that the consequences of hypoxia/acidosis are very different, depending on whether this is acute or chronic. The normal human fetus is adapted to survive labour and has compensatory mechanisms that allow it to withstand even severe hypoxia and acidosis for short periods of time. Several studies have looked at the neurological outcome of neonates who were severely asphyxiated at delivery.[21–24] Although the cutoff of pH used to define severe acidosis and the age at follow up varied, conclusions were similar from all the studies: although mortality may be slightly increased, the predictive value of acidosis at birth for neurological sequelae, especially in term neonates, is poor.

In contrast, the fetus exposed antenatally to chronic hypoxia and acidosis is much more at risk of associated long term morbidity. In 1994 Low *et al* reported a study of neonates following respiratory or metabolic acidosis at delivery.[25] Umbilical arterial buffer base was used and they found that complications were not increased with a pure respiratory acidosis but they were with metabolic acidosis, and these neonates were more likely to have passed meconium and have had instrumental deliveries. An increased proportion of undiagnosed chronically acidotic fetuses in this group could explain this. In a large study of the antecedents of cerebral palsy in 1986 Nelson *et al* concluded that antenatal events were much more important than intra- or postpartum ones.[26] This was supported by a study by Adamson *et al* in 1995 where all term, singleton neonates born over an 8 month period with a well defined diagnosis of encephalopathy within the first week of life were identified prospectively and matched with a well neonate.[27]
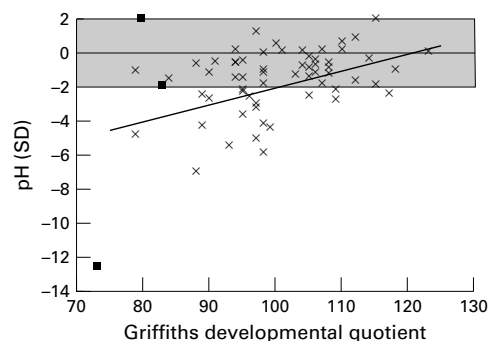
Figure 3   Fetal blood pH (expressed in multiples of SD from the normal mean) at cordocentesis in chromosomally normal small for gestational age fetuses and subsequent Griffiths neurodevelopmental quotient (DQ); r= 0.41, n = 65, p= 0.0008. Squares indicate three children with cerebral palsy. Reproduced with permission from Soothill et al. Eur J Obstet Gynaecol Reprod Biol, 1995;59:21-4.

Antenatal and intrapartum factors in both groups were compared and only 6% of cases had intrapartum risk factors alone. They concluded that in most of their cases intrapartum acidosis was not the cause and events occurring in the antenatal period were more often implicated. Further evidence for this association comes from a follow up study of infants with acid base status assessed as fetuses by cordocentesis. To remove the complications of extreme prematurity only cases delivered after 32 weeks were studied. Neurodevelopmental assessment showed a reduction in developmental quotient following chronic fetal acidaemia (fig 3).[28]

Conclusion

Prevention of severe acute acidosis depends on good labour ward monitoring and care. Prevention of chronic fetal acidosis, which is probably a much more common cause of damage, depends on detection of placental dysfunction antenatally by clinical fetal growth assessment, ultrasound scanning and Doppler ultrasonography. There is still no overall consensus on the best balance between keeping the fetus in an hypoxic/acidotic environment or very premature delivery.[29] In fetuses with abnormal Doppler waveforms delivery should usually be by Caesarean section to avoid acute on chronic acidosis. Much current research is concentrating on improving placental transfer to develop a future in utero treatment for this group.

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