FETAL AND NEONATAL EDITION

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Annotations

Perinatal asphyxia in less developed countries

In less developed countries perinatal asphyxia remains a major cause of death and disability. The pattern of risk factors, the nature of sequelae, and the options and priorities for intervention (both preventive and therapeutic) are significantly different than in the industrialised world. From a public health perspective perinatal asphyxia presents a formidable range of problems to health professionals and policymakers.

Size of the problem

Seven million perinatal deaths occur each year, mostly in developing countries.[1] Nearly 4 million newborns suffer moderate to severe birth asphyxia, with 'at least 800 000 dying and at least an equal number developing sequelae such as epilepsy, mental retardation cerebral palsy and learning disabilities'.[2] A recent community based study in Zimbabwe which audited perinatal mortality showed the commonest single cause was perinatal asphyxia and an avoidable factor was detected in 76% of cases.[3] In another population based study in Bangladesh,[4] which showed a perinatal mortality rate of 75 per 1000 births (37 stillbirths, 38 first week deaths), the major causes of early neonatal death were attributed to a small size at birth (54%), birth asphyxia (26%), and tetanus (8%). In Bangalore, South India a prospective hospital based study of 4572 births showed a perinatal mortality of 43/1000. Using Wigglesworth's classification[5] 24% were considered due to birth asphyxia, even after exclusion of the premature group.[6]

All these studies used indirect and less reliable measures of intrapartum asphyxia such as case note review and Apgar scores. Criteria for the assessment of asphyxia in many studies have been non-specific, for example in the largest follow up study in the USA the correlation between Apgar scores and long term outcome was poor.[7] Early onset neonatal encephalopathy (generally regarded to be due to intrapartum hypoxic/ischaemic injury) is probably the most specific method for assessing asphyxia in the newborn period.[8] Hypoxic-ischaemic encephalopathy (HIE) is known to be associated with marked derangement of cerebral energy metabolism[9] and is also more predictive of outcome. A meta-analysis of studies in developed countries in which HIE was classified as mild, moderate, or severe showed that 25% of moderate and 90–100% of severe cases suffered major neurodevelopmental sequelae.[10] Studies in the UK and other developed countries have shown that the incidence of HIE is approximately six per 1000 livebirths[11] and accounts for up to 25% of perinatal mortality in fullterm infants.[5]

There are few reliable data about the epidemiology or natural history of neonatal HIE in high risk populations of less developed countries. Studies of birth asphyxia using other criteria for diagnosis suggest that HIE could be a much more common problem, especially among low birthweight babies.[12] For example, among 13 900 deliveries in the maternity hospital in Kathmandu in 1992 there were 1873 admissions to the special care baby unit of which 27% were attributed to asphyxia alone, 33% to low birth weight, and 30% to caesarean births. Asphyxia certainly also contributed to both the latter groups of admissions. A study from a tertiary centre in Nigeria found an incidence of HIE of 26·5 per 1000 livebirths with nearly half the cases in the severe category.[13] Babies with intrauterine growth retardation were 10 times more likely to suffer HIE and Apgar scores did not correlate closely with clinical presentation. Twenty one per cent of infants with HIE in this study had good Apgar scores recorded by the midwives at birth including five out of 41 infants who went on to develop severe HIE.

If the incidence of HIE is significantly higher in developing countries this may present heavy social and economic costs. It may present a particular burden for women both in terms of caring for handicapped children and, if the affected infant dies, exposure to the risk of another pregnancy with a short birth interval.[14] The traditional spacing mechanisms of breast feeding and abstinence are halted by the death of a newborn infant.

Risk factors

In less developed countries more information is needed about the nature and timing of events leading to HIE, and about risk factors that are potentially preventable. Decisions about implementing interventions to reduce exposure of pregnant women to a risk factor in countries with severe resource constraints must be informed by clear evidence about the potential costs and benefits these interventions will bring.

Prenatal risk factors such as multiparity, heavy work, and poor maternal nutrition increase the risk of asphyxia and poor pregnancy outcome largely by increasing the risk of low birthweight infants. But interventions to change the social and nutritional status of women are complex and usually linked to long term economic development. Large scale food supplementation trials have rarely been considered cost effective.[15] Micronutrient deficiencies are more amenable to 'magic bullet' interventions. Maternal anaemia is widespread in many developing countries affecting one half to two thirds of pregnant women. There is disturbing evidence of an upward trend in many parts of sub-Saharan Africa and south Asia over the past decade.[16] Even moderate anaemia increases the risk of premature delivery, fetal distress, and perinatal mortality. Treatment of malaria and iron and folate supplementation is of proved value in reducing maternal morbidity.[17]

Intrapartum risk factors for asphyxia are often unpredictable, for example cord prolapse and maternal haemorrhage, and can only be addressed if there is access to trained birth attendants and secondary level referral facilities which can deal with obstetric complications (see later). Postnatal complications may convert a mild-moderate asphyxial insult into a severe one. We have previously shown that the prevalence and occurrence of hypothermia and hypoglycaemia in the first 24 hours among routine uncomplicated infants is 4–5 times greater in Nepal than the UK[18] but whether these problems lead to higher rates of neonatal encephalopathy is unknown. Infants suffering repeated episodes of mild-moderate hypoglycaemia have a substantially increased relative risk of neurodevelopmental sequelae.[19] Known risk factors for hypoglycaemia include low birth weight, asphyxia, and hypothermia.

An interesting research question still to be answered is whether the potentially damaging effects of hypothermia – hypoglycaemia, metabolic stress, and apnoea especially in low birthweight infants – outweigh the suggested benefits of controlled hypothermia as a useful therapy in reducing the sequelae of asphyxia.[20] The links between hypothermia and HIE in less developed countries need further investigation.

Sequelae

Even if the incidence of HIE is significantly higher in less developed countries the contribution it makes to neurodevelopmental sequelae needs to be clarified. Birth asphyxia is estimated to contribute to 3–21% of cerebral palsy in the industrialised world.[21] No studies from less developed countries have yet been reported as to whether an expected higher incidence of HIE translates into a higher incidence of neurodevelopmental sequelae at 1 year and whether survivors indeed have higher mortality rates in infancy than controls. These studies would allow an estimate of the potential benefit in terms of disability prevented which could be achieved if HIE was reduced.

It is important to remember that sequelae should not only be measured in terms of cerebral palsy and learning disabilities. Perinatal asphyxia also contributes, or predisposes, to a much wider range of problems in the neonatal period: feeding intolerance,[22] septicaemia,[23] hepatic damage,[24] hypoglycaemia,[25] transient hyperinsulinism,[26] acute renal failure,[27] conjunctivitis,[28] myocardial dysfunction leading to changes in cerebral blood flow,[29] diminished splenic function,[30] consumption of coagulation factors,[31] thrombocytopenia,[32] necrotising enterocolitis,[33] and changes in cortisol and dihydoxyepiandrosterone concentrations which may have secondary effects on immune function.[34] Later additional sequelae may include growth hormone deficiency,[35] complex partial seizures,[36] cortical visual impairment,[37] and blindness.[38]

Interventions – prevention and treatment

Interventions to reduce perinatal asphyxia in less developed countries may be the most cost effective methods for achieving further reductions in infant mortality and preventing future disability. The provision of good antenatal care to identify and target those mothers at highest risk and to treat preventable risk factors, and the provision of accessible safe delivery (both geographically and economically) are the highest priorities. The effects of recession and economic structural adjustment programmes in many developing countries over the past decade have had precisely the opposite effect. There is clear evidence for reduced utilisation of antenatal and perinatal services by vulnerable groups in many communities where user charges have been introduced[39] with reversals in trends for maternal mortality rates and the incidence rates for low birth weight.[16]

Until recently the only option for most mothers in the developing world was domiciliary delivery. Training of traditional birth attendants was considered the most appropriate policy for improving safe delivery and reducing asphyxia in the community. But evaluation of training programmes for traditional birth attendants has shown they work best when supported closely by a referral facility. In urban areas (of Asia especially) there has been a sharp increase in demand for institutional delivery, although the quality of service is often poor and rarely audited.[40]

Resuscitation plays a significant part in safe delivery.[41] The cost effectiveness of training programmes in resuscitation for traditional birth attendants is still in question even though evaluation of such training has shown that their knowledge and practices related to resuscitation may change in the short term.[42]

Prevention is not the only priority. Many asphyxiated babies might profit from appropriate and timely treatment. While trials of some potentially low cost treatments such as lidocaine,[43] naloxone,[44] thiopentone,[45] and paraldehyde,[56] have been of doubtful benefit there is reason to hope that new trials using free radical scavengers (vitamin E), nitric oxide blockers, excitatory amino acid antagonists (for example magnesium ions which block glutamate receptors[20]; M Levene, personal communication) or calcium channel blockers could reveal potentially cost effective interventions.

Future research

Finally there remain important questions for perinatal health service research in less developed countries. Which predisposing risk factors are most amenable to cost effective intervention? How can guidelines for the optimum management of labour at primary and secondary levels be implemented? To what extent do preventable postnatal insults like hypothermia and hypoglycaemia contribute to and exacerbate asphyxial mortality and morbidity? Does the higher incidence of perinatal asphyxia in developing countries lead to a higher incidence of neurodevelopmental sequelae or simply an increase in mortality? Is it cost effective to train community based midwives and birth attendants in neonatal resuscitation? Should they be given a simple bag and mask or trained in mucous extraction? And, most important of all, how can the various levels of perinatal services, both community

based and institutional, be audited and changed in the context of severe resource constraints, and demoralised staff?

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1 Costello AM de L Perinatal health in developing countries. *Trans R Soc Trop Med Hyg* 1993; **87:** 1–2.
2 World Health Organisation. *Child health and development: health of the newborn.* Geneva: World Health Organisation, 1991.
3 De-Muylder X. Perinatal mortality audit in a Zimbabwean district. *Paediatr Perinat Epidemiol* 1989; **3:** 284–93.
4 Fauveau V, Wojtyniak B, Mostafa G, Sarder AM, Chakraborty J. Perinatal mortality in Matal, Bangladesh: a community-based study. *Int J Epidemiol* 1990; **19:** 606–12.
5 Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. *Lancet* 1980; ii: 684–6.
6 Raghuveer G. Perinatal deaths: relevance of Wigglesworth's classification. *Paediatr Perinat Epidemiol* 1992; **6:** 45–50.
7 Nelson KB, Ellenberg JK. Apgar scores as predictors of chronic neurological disability. *Pediatrics* 1981; **68:** 36–44.
8 Volpe J. *Neurology of the newborn.* 2nd Ed. Philadelphia: Saunders, 1987.
9 Roth SC, Edwards AD, Cady EB, *et al.* Relationship between cerebral oxidative metabolism following birth asphyxia, and neurodevelopmental outcome and brain growth at one year. *Dev Med Child Neurol* 1992; **34:** 285–95.
10 Levene MI, Bennett MJ, Punt J. *Fetal and neonatal neurology and neurosurgery.* Edinburgh: Churchill Livingstone, 1988.
11 Levene MI, Kornberg J, Williams THC. The incidence and severity of postasphyxial encephalopathy in full-term infants. *Early Hum Dev* 1985; **11:** 21–8.
12 Daga AS, Daga SR, Patole SK. Risk assessment in birth asphyxia. *J Trop Pediatr* 1990; **36:** 34–9.
13 Airede AI. Birth asphyxia and hypoxic-ischaemic encephalopathy: incidence and severity. *Ann Trop Paediatr* 1991; **11:** 331–5.
14 Acsadi GTF, Johnson-Acsadi G. Childbearing patterns affecting infant and early childhood mortality. *Optimum conditions for childbearing.* London: International Planned Parenthood Federation, 1986: 13–37.
15 Waterlow JC. Prevention of protein-energy malnutrition. In: Waterlow JC, ed. *Protein energy malnutrition.* London: Edward Arnold, 1992: 376–80.
16 Garcia M, Mason J. *Second report on the world nutrition situation.* United Nations ACC Subcommittee on Nutrition. Lavenham, Suffolk: The Lavenham Press, 1992.
17 Fleming A. Iron deficiency in the tropics. *Clinics in Haematology* 1982; **11:** 365–88.
18 Anderson S, Shakya KN, Shrestha LN, Costello AM de L. Hypoglycaemia is a common problem among uncomplicated newborns in Nepal. *J Trop Pediatr* 1993; **39:** 273–7.
19 Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988; **297:** 1304–8.
20 Palmer C, Vannucci RC. Potential new therapies for perinatal cerebral hypoxia-ischemia. *Clin Perinatol* 1993; **20:** 411–32.
21 Nelson KB. What proportion of cerebral palsy is related to birth asphyxia? [Editorial]. *J Pediatr* 1988; **112:** 572–4.
22 Berseth CL, McCoy HH. Birth asphyxia alters neonatal intestinal motility in term neonates. *Pediatrics* 1992; **90:** 669–73.
23 Antia-Obong OE, Utsalo SJ, Udo JJ, Udo KT. Neonatal septicaemia in Calabar, Nigeria. *Cent Afr J Med* 1992; **38:** 161–5.
24 Saili A, Sarna MS, Gathwala G, Kumari S, Dutta AK. Liver dysfunction in severe birth asphyxia. *Indian Pediatr* 1990; **27:** 1291–4.
25 Singhal PK, Singh M, Paul VK, Deorari AK, Ghorpade MG, Malhotra A. Neonatal hypoglycemia – clinical profile and glucose requirements. *Indian Pediatr* 1992; **29:** 167–71.
26 Schultz K, Soltesz G. Transient hyperinsulinism in asphyxiated newborn infants. *Acta Paediatr Hung* 1991; **31:** 47–52.
27 Jayashree G, Dutta AK, Sarna MS, Saili A. Acute renal failure in asphyxiated newborns. *Indian Pediatr* 1991; **28:** 19–23.
28 Pandey KK, Bhat BV, Kanungo R, Srinivasan S, Rao RS. Clinico-bacteriological study of neonatal conjunctivitis. *Indian J Pediatr* 1990; **57:** 527–31.
29 Van-Bel F, Walther FJ. Myocardial dysfunction and cerebral blood flow velocity following birth asphyxia. *Acta Paediatr Scand* 1990; **79:** 756–62.
30 McKay JG, Hermansen MC, Maley BE. Diminished splenic function in asphyxiated term infants. *J Perinatol* 1990; **10:** 12–5.
31 Andrew M, O'Brodovich H, Mitchell L. Fetal lamb coagulation system during birth asphyxia. *Am J Hematol* 1988; **28:** 201–3.
32 Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. *J Pediatr* 1986; **108:** 749–55.
33 Boo NY, Goon HK. Epidemiology of necrotising enterocolitis in Malaysian neonates. *Singapore Med J* 1989; **30:** 444–8.
34 Procianoy RS, Giacomini CB, Oliveira ML. Fetal and neonatal cortical adrenal function in birth asphyxia. *Acta Paediatr Scand* 1988; **77:** 671–4.
35 Gao TS, Shi YF, Gao SM. Evaluation of adult idiopathic growth hormone deficiency with other pituitary hormones deficiency. *Chung Hua Nei Ko Tsa Chih* 1990; **29:** 205–9.
36 Pratap RC, Gururaj AK. Clinical and electroencephalographic features of complex partial seizures in infants. *Acta Neurol Scand* 1989; **79:** 123–7.
37 Roland EH, Jan JE, Hill A, Wong PK. Cortical visual impairment following birth asphyxia. *Pediatr Neurol* 1986; **2:** 133–7.
38 Goggin M, O'Keefe M. Childhood blindness in the Republic of Ireland: a national survey. *Br J Ophthalmol* 1991; **75:** 425–9.
39 Owa J, Osinake AV, Costello AM de L. Charging for health services in developing countries. *Lancet* 1992; ii: 340.
40 Bhargava SK, Singh KK, Saxena BN, eds. *A national collaborative study of identification of high risk families, mothers and outcome of their offsprings with particular reference to the problem of maternal nutrition, low birth weight, perinatal and infant morbidity and mortality in rural and urban slum communities.* New Delhi: Indian Council of Medical Research, 1990.
41 Joseph R. Resuscitation at birth. *Singapore Med J* 1990; **31:** 166–70.
42 Raina N, Kumar V. Management of birth asphyxia by traditional birth attendants. *World Health Forum* 1989; **10:** 243–6.
43 Hellstrom-Westas L, Svenningsen NW, Westgren U, Rosen I, Lagerstrom PO. Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion. *Acta Paediatr* 1992; **81:** 35–9.
44 Chernick V, Manfreda J, De-Booy V, Davi M, Rigatto H, Seshia M. Clinical trial of naloxone in birth asphyxia. *J Pediatr* 1988; **113:** 519–25.
45 Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986; **61:** 1084–9.
46 Koren G, Butt W, Rajchgot P, *et al.* Intravenous paraldehyde for seizure control in newborn infants. *Neurology* 1986; **36:** 108–11.