Routine immunisation of preterm infants

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SUMMARY Fifty one preterm infants (26–36 weeks' gestation) were enrolled in a study of their immunological responses to diphtheria, tetanus, pertussis, and polio antigens eight to 12 weeks after their primary courses had been completed. Samples from 21 infants born at full term were also analysed. Many infants were able to start immunisation at 3 months of age. Premature infants who are immunised as soon as possible after 3 months of age develop adequate antibody responses.

Immunisation is one of the most effective means we have of protecting children against infection. Preterm infants are a vulnerable group and very preterm infants with long term respiratory problems are particularly at risk from respiratory infections such as pertussis; it is therefore important to protect them from pertussis as early as possible. In the United Kingdom the Department of Health recommends that immunisation programmes start at 3 months of age, and the current guidelines also advise starting immunisation of preterm infants at that age.¹ The practice varies across the country with some authorities starting at three months after the actual delivery date, some at three months from expected date of delivery, and some taking an arbitrary figure in between.² In the United States, it is recommended that preterm infants begin their immunisations at the appropriate chronological age regardless of prematurity, but they comment that there is no research to justify this.³

There are good theoretical grounds for supposing that preterm infants will be able to mount immune responses comparable with those born at full term. Antibody production increases with age, but this is related to duration of exposure to the antigen after birth rather than postconceptional age.^{4,5} Studies on cell mediated immunity suggest that preterm infants behave similarly to those born at full term.⁶ The small amount of work that has been done on routine immunisation of preterm infants supports this view. Smolen *et al* looked at antibody responses to polio virus vaccine after two months and four months in 37 preterm infants; they had similar levels of antibody to those born at full term.⁷ Bernbaum *et al* studied 25 infants from 28 to 34 weeks' gestation given triple vaccine (diphtheria, tetanus, and pertus-

sis) at the ages of 2, 4, and 6 months.⁸ After the first injection fewer preterm infants had satisfactory antibody concentrations, but by the second and third injections there were no significant differences when compared with those born at full term.

In Nottingham the local recommendation is for preterm infants to start the immunisation programme three months from birth, whatever the period of gestation, or as soon as possible after this. We have followed up a series of preterm babies to monitor what actually happens and to look at their immune responses to diphtheria, tetanus, pertussis, and polio vaccines.

Subjects and methods

Preterm infants were selected in the neonatal period while still in hospital. About 20 infants were chosen between 32 and 36 weeks' gestation, and a further 20 between 28 and 32 weeks' gestation. As many babies as possible were recruited who were born at under 28 weeks' gestation. Cord blood was sampled where possible. Parents were asked if they would like to take part in the study and those agreeing were given a written explanation. Consent was obtained from the local ethics committee. The general practitioner and health visitor were informed. The immunisations were carried out as a routine in the normal system, starting at three months where possible, the second dose six to eight weeks later, and the third dose four to six months later. At about eight to 12 weeks after the third dose, a blood sample was taken from the baby for analysis of diphtheria, tetanus, pertussis, and polio antibodies. The sample was separated and serum was stored frozen.

Blood samples taken from children for a variety of reasons in hospital between the ages of 12 months and 24 months that would normally have been discarded as excess were saved in the laboratory to act as controls. Immunisation records of these children were scrutinised to select samples taken at about the same interval after the three immunisations as the preterm infants. Samples were not used if the child was preterm or if there was an illness that might affect the immune response.

LABORATORY ASSAYS

Polio virus antibodies

This assay was performed by mixing 50 µl volumes containing approximately 100 times the median tissue culture infective dose of each of the three Sabin poliovirus types, with an equal volume of a dilution of a serum sample. The samples were diluted in microtitre plates in the range 1/2 to 1/256. The plates containing the serum virus mixtures were incubated at 35°C for two to three hours before adding 0.1 ml of a suspension of 5×10^3 HEp2 cells and reincubating for five days. The end point was expressed as the dilution of serum estimated to neutralise the challenge virus in 50% of the wells in the plates.

Diphtheria and tetanus antitoxin

An enzyme linked immunosorbent assay (ELISA), comparable with that described by Melville-Smith *et al* was used to estimate antitoxin concentrations in international units (IU)/ml.⁹ Human reference serum samples of known potencies previously assayed by *in vivo* neutralisation tests were included in each assay.

Pertussis antibodies

These were estimated by an ELISA similar to that described above but using the supernatant from centrifuged sonicated cells of *Bordetella pertussis* strain W28 at a concentration of 8 ng protein/ml as antigen. The human reference was a serum pool from normal children vaccinated who had been vaccinated against diphtheria, tetanus, and pertussis, which had a nominal concentration of 100 pertussis antibody units/ml. Pertussis antibodies were detected using alkaline phosphatase conjugated antihuman polyvalent immunoglobulins (raised against α , γ , and μ chains).

Results

Fifty preterm infants completed the study (22 from 32–36 weeks' gestation, 19 from 28–31 weeks' gestation, and nine either 26 or 27 weeks' gestation). Twenty one control samples were analysed.

Many of the infants were able to start their immunisations by 12–13 weeks of age (fig 1). There was an inevitable delay with some of the very sick infants. The longest delays in starting immunisation were for social reasons—for instance, difficulty in getting the child to the clinic. One child was delayed while uncertainty about possible fits was being resolved. Five children had their first dose in the neonatal unit, and two of these had all their immunisations in hospital. One child of 33 weeks' gestation, who was immunised at the age of 16 weeks, was described as 'jittery' after the first triple dose, and had pertussis omitted from the second and third doses. No other reactions were reported other than mild fever, irritability, and redness at the injection site.

There were no neonatal contraindications to pertussis vaccine in any of the children despite some having had complicated neonatal courses. All the children started immunisation with the triple antigen. Two children were diagnosed as having cerebral palsy (one probably spastic quadriplegia, one mild hemiplegia). Both these children were born at 27 weeks' gestation and it was thought that the benefit from pertussis immunisation outweighed any possible risk.

Two children (of 27 and 31 weeks' gestation, respectively) had had admissions for asthma in the first year of life. One child (of 26 weeks' gestation) had persistent failure to thrive and feeding difficulties. One child (of 29 weeks' gestation) had necrotising enterocolitis necessitating resection of bowel. One child (of 26 weeks' gestation) had a tracheo-oesophageal fistula and a hand anomaly.

Fig 1 Age of preterm infants at immunisation. The diagonal line indicates estimated date of delivery plus three months.

Table Immunological responses

	Gestational age (weeks)			
	26-27 (n=9)	28-31 (n=19)	32-36* (n=22)	≥37 (n=19)
Diphtheria antitoxin (IU/ml):				
Mean (SD)	4.64 (3.2)	4.26 (3.6)	4.15 (3.1)	5.47 (6.03)
Range	0.42-10.73	0.42-12.97	0.55-12.12	0.49-25.92
Tetanus antitoxin (IU/ml):				
Mean (SD)	2.53 (1.2)	4.67 (3.4)	4.47 (2.2)	5.29 (7.4)
Range	0.59-4.26	0.45-13.6	1.73-9.9	0.40-34.38
Pertussis antibody (units/ml):				
Mean (SD)	31 (25.5)	73 (56)	48 (30)	69 (62)
Range	2-78	16-226	3-102	6-133

*One infant had diphtheria and tetanus only.

Fig 2 Antibody production against polio immunisation, showing that premature infants responded as well as those born at full term.

Fig 3 Antibody production against pertussis vaccine in all infants. The circulating amount varied widely, but did not seem to be related to the infants' maturity at birth.

Forty two of the children had blood samples taken for antibody measurements 8–12 weeks after the third immunisation. One child had the sample taken at one week, seven between 13–17 weeks, and one was 21 weeks after diphtheria, tetanus, and polio and five weeks after the pertussis (the third pertussis injection was delayed because of a question about contraindications). The immunological responses of all children were satisfactory to all antigens compared with the controls (table, fig 2). There was no relation between response and gestational age (individual values for pertussis are shown in fig 3) or the age of starting immunisations.

Cord blood samples were available for 19 children. There was no association between antibody concentrations in cord blood and the infant's response to immunisation, or between cord blood and gestation (though only two cord blood samples were from infants of less than 31 weeks' gestation).

Discussion

Infants born early are at high risk of serious consequences from pertussis because of their immaturity, their limited respiratory reserve, and possible residual damage after lung and brain problems related to their immaturity or neonatal care. Yet it is this group in whom the pertussis vaccine may be omitted from the immunisation programmes because of uncertainty about the contraindications, or in whom the programme is delayed as a deliberate policy or because of the delicate nature of the infants or uncertainty about their well being.

This investigation has shown that premature infants, vaccinated as soon as possible after 3 months of age, develop adequate responses as judged by circulating antibodies (comparable with those found in infants born at full term) and they did not develop more severe local reactions or show adverse systemic reactions. Inevitably the numbers

are small, but they nevertheless support the 1988 DHSS recommendation that preterm infants should be immunised as soon as possible after 3 months.

Individual health staff within the community only rarely have to advise about immature infants. This may lead to a tendency to 'play safe' and postpone immunisation or even omit the pertussis immunisation altogether. A clear recommendation from the neonatal unit on neonatal contraindications to pertussis *and the lack of them*, and advice on the age at which to start, should help to overcome this.

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