

Significance of raised immunoglobulin M levels in cord blood of small-for-gestational-age infants

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SUMMARY Cord IgM values were determined in small-for-gestational-age infants born at Hammersmith Hospital during a 5½-year period. 121 (12·5%) infants had levels >0·2 g/l; in 92 these were between 0·21 and 0·3 g/l. In only 18 (14·8%) was a level of 0·4 g/l exceeded, and 5 proved cases of intrauterine infection—rubella (2), syphilis (2), and toxoplasmosis (1)—were in this group. The factor most often associated with cord IgM >0·4 g/l was prolonged rupture of the membranes. There was an increased incidence of blood group B among the mothers, probably reflecting the greater number of nonCaucasian women giving birth to small-for-gestational-age infants. Determination of cord IgM did not help significantly in diagnosis.

Realisation of the development of immune competency in the fetus during the latter half of pregnancy (Silverstein, 1962) has led to immunoglobulin M (IgM) levels being estimated in cord blood to help in the diagnosis of intrauterine and perinatal infections (Alford *et al.*, 1967). As IgM does not normally cross the placenta, any present in cord blood is presumed to have been produced by the fetus and it has been suggested there is a close correlation between its circulating level at birth and fetal infection (Alford *et al.*, 1967; Sever, 1969). However, the incidence of abnormal cord IgM levels, >0·20 g/l, varies from 4% of all deliveries in North America (Alford, 1971) to 60% in urban Peru (Lechtig and Mata, 1971), and the value of these estimations as a screening procedure is still not established. Some infants with proved intrauterine infections may have normal values (Alford, 1965), while apparently normal babies have raised levels for which no cause can be found. We have tried to assess whether routine measurement of cord IgM in small-for-gestational-age (SGA) infants has been helpful in management, and to relate raised values to pregnancy details.

Patients and methods

Cord immunoglobulin levels were measured in infants born in Hammersmith Hospital between January 1971 and July 1976 inclusive, whose birthweights were below the 10th centile for gestational age. Gestational age was based on the mother's

menstrual date and the birthweight standards were those of Thomson *et al.* (1968). The immunoglobulin assay used a modified automated immunoprecipitin technique on a Technicon Autoanalyser II (Larson *et al.*, 1972). The limit of normal values was considered to be 0·20 g/l (20 mg/100 ml) based on the estimate of 2 SDs above a mean cord value (Alford *et al.*, 1967). Cord IgA and IgG levels were also estimated by similar methods.

Serology and viral culture techniques, if appropriate, were used for further screening of infants with raised cord IgM values; they aimed to exclude congenital toxoplasmosis, rubella, cytomegalovirus, and syphilis infections (although all mothers had been serologically screened for the last during pregnancy). Screening to exclude ECHO, Coxsackie, and herpes simplex viral infections was also carried out in a few cases. Some infants whose cord IgM values were slightly raised (0·21-0·25 g/l), and who were clinically normal and thriving, had no further investigation.

An analysis was made of maternal illness and certain other features of pregnancy, including drug treatment in mothers of infants with raised cord IgM levels. Prolonged rupture of the membranes was diagnosed when the rupture delivery interval exceeded 24 hours. Chorioamnionitis was assumed to be present when maternal pyrexia was associated with prolonged membrane rupture, when other causes had been excluded, but was not necessarily confirmed histologically. Maternal urinary infection was diagnosed in the presence of >10⁵ organisms/ml on urine culture.

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Results

During the 5½-year period there were 9229 live births of whom 969 (10.5%) were SGA. 121 (12.5%) of the SGA, of whom 12 were preterm or less than 37 weeks' gestation, had cord IgM levels >0.20 g/l and the following details relate to this group.

Mothers. The relative frequency of maternal infection after 20 weeks' gestation is shown in Table 1. Urinary tract infections, predominantly coliform, and trichomonal vaginitis were those most commonly associated with a raised IgM level in cord blood. Four mothers developed a fever in pregnancy, all associated with urinary infection.

In 10 mothers the time between membrane rupture and delivery was prolonged and 9 of these women had an associated pyrexia during labour suggesting chorioamnionitis. Cord blood IgM values in the infants born to these mothers comprised the majority of those in excess of 0.4 g/l.

The frequency of recorded maternal drug ingestion (excluding oral haematinics) in the latter half of pregnancy is illustrated in Table 2. Drug ingestion appeared to be relatively uncommon and consisted chiefly of antibiotics and chemotherapeutic agents.

Substantial antepartum haemorrhage occurred after 20 weeks' gestation in 14 (11.5%) cases, corresponding to the expected incidence of this complication in a group with a high proportion of preterm labours.

28% of the 121 mothers were of blood group B, almost double the proportion of this group generally found in antenatal patients at the hospital. Two-thirds

of the group B mothers were nonCaucasian and nonCaucasians represented just over one-third of the whole sample.

Infants. Of 121 infants, 55 were boys and 66 girls. In most the rise in cord IgM level was small—between 0.21 and 0.3 g/l in 92 (75%) infants (Figure). In only 18 (14.8%) did the value exceed 0.4 g/l. Cord IgA values were raised in 14 (11.5%) cases, but did not correlate closely with the IgM level. Although several infants, mainly preterm, were ill in the neonatal period, illness or abnormality could not be linked with raised cord IgM. Two neonatal deaths occurred, a mortality of 16.5 per 1000: the causes of death were hyaline membrane disease and intrapartum pneumonia. Cord IgM levels in these 2 infants were 0.27 and 0.33 g/l respectively.

Among the 18 infants in whom cord IgM was 0.4 g/l or above (Table 3) there were 5 cases of proved intrauterine infection: rubella (2), syphilis (2), toxoplasmosis (1). The cases of syphilis were

Table 1 *Antenatal infection after 20 weeks' gestation*

Diagnosis	No.	% total
Urinary tract infection	14	11.5
Trichomonal vaginitis	13	10.7
Gonorrhoea	3	2.4
Syphilis	2	1.6
Toxoplasmosis	1	0.8

Table 2 *Drugs taken after 20th week of pregnancy**

	No.	% total
Total pregnancies where drugs ingested	30	25
Chemotherapeutic agents/antibiotics	20	16.5
Intravenous iron infusions	6	4.9
Sedatives	5	4
Antihypertensives	5	4
Corticosteroids	4	3.3
Beta sympathomimetics	4	3.3
Narcotics (heroin addiction)	1	0.8

*Excluding oral haematinics.

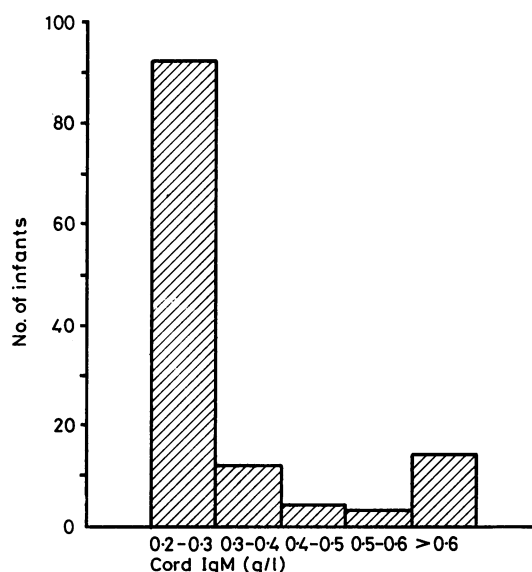


Figure *Cord IgM levels in 121 infants.*

Table 3 *Infants with cord IgM >0.4 g/l (n=18)*

	No.	% total
Maternal membrane rupture to delivery interval prolonged	10	56
Severe Rhesus haemolytic disease	2	11
Congenital rubella	2	11
Maternal syphilis (treated in pregnancy)	2	11
Congenital toxoplasmosis	1	5.5
Maternal heroin addiction	1	5.5

detected by maternal serological screening and treatment was completed before delivery, while rubella and toxoplasmosis were diagnosed retrospectively because of suggestive clinical findings in the infant confirmed by the presence of specific immunoglobulin.

Other ill infants in this group included 2 severely affected Rhesus babies, one of whom had received intrauterine peritoneal transfusions 2 and 4 weeks before delivery. 10 of the remaining 11 infants were born to mothers after a prolonged membrane rupture to delivery interval; the other was born to a heroin addict. None of these 11 infants had clinical features that could readily be associated with a raised cord IgM.

Discussion

Many SGA infants are born to underprivileged mothers, who as a group are more susceptible to certain infections in pregnancy (Naeye and Blanc, 1970; Stern and Tucker, 1973). If screening of cord IgM were, therefore, to prove helpful but could not be applied on a large scale for economic reasons, selection of SGA infants as the group at greatest risk might prove a satisfactory compromise. Mellits (1971) stated that estimation of cord IgM is not an effective device for identifying children who will have an abnormal outcome. Hardy (1971), however, considered that very low and very high values both appeared significant for neonatal and late abnormality.

The mean cord IgM is decreased by prematurity (Yeager, 1973) and increased by postmaturity (Papadatos *et al.*, 1974). One in 8 of SGA infants born in Hammersmith Hospital during the period had raised values. As proved intrauterine infections were comparatively rare in this series (5 cases, 4.1%), other antenatal stimuli would seem of greater importance in inducing IgM production. In particular, foreign antigens other than infecting agents may have crossed the placenta to initiate an immune response. Maternal pyrexia whether from urinary infection or chorioamnionitis has been proposed as a potent fetal immune stimulus (Hardy, 1971).

Many drugs, including antibiotics, taken by mothers in pregnancy attain high fetal tissue levels (Tuchmann-Duplessis, 1975), but it has not been determined which agents, if any, can promote a fetal immunoglobulin response. Although 30 (24.8%) mothers in this study had recorded drug ingestion in the latter half of pregnancy (Table 2), this probably represents an underestimate because many agents, especially simple analgesics, may have been forgotten. Morselli *et al.* (1975) found that 4 to 5 drugs were taken in the average pregnancy. It is unfortunately beyond the scope of our investigation

to say to what extent this group of 121 mothers differed in details of their pregnancy from the majority of mothers of SGA infants where cord IgM values were <0.20 g/l.

When mothers' and infants' blood groups were examined twice as many mothers as expected were of group B compared with the overall antenatal population attending the hospital. This is most likely to be a reflection of the greater number of non-Caucasian women giving birth to SGA infants, as blood group B is more commonly found in non-Caucasians (Race and Sanger, 1975). Both infants with Rhesus haemolytic disease in the study group had cord IgM levels >0.4 g/l and had undergone repeated amniocenteses and, in one case, intrauterine transfusion with donor blood.

The group of infants with cord IgM values >0.4 g/l contained all those SGA infants with proved intrauterine infection. However, most (55%) were born more than 24 hours after rupture of the membranes in the absence of other adverse factors and, in all but one, clinical evidence of chorioamnionitis was present in labour. These infants were treated as potentially infected but other controlled studies have failed to show a higher incidence of invasive infection in such a group (Habel *et al.*, 1972; Reid *et al.*, 1972). Our findings would suggest that their intrapartum environment was sufficient to induce a rise in circulating IgM. Chorioamnionitis due to prolonged membrane rupture thus appeared to be a more significant cause of raised cord blood IgM than infections such as rubella and toxoplasmosis. Inapparent infections with these organisms and others such as cytomegalovirus could have been missed however, because further investigation was not usually performed in infants with IgM levels <0.25 g/l if clinical examination was negative. Only long-term follow-up study of this group with matched controls with normal IgM cord values could determine the significance of these minor increases.

We have to conclude that determination of cord IgM in SGA infants born at our hospital has not helped significantly with their clinical management in the neonatal period. In no case in almost 1000 SGA infants did later knowledge of a raised cord IgM estimation lead to a diagnosis that had not already been made.

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