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Factors affecting neonatal jaundice

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SUMMARY Plasma bilirubin was estimated on 690 term infants on about the 6th day of life. Perinatal factors were recorded and the results analysed. Hyperbilirubinaemia was defined as a level >205 μmol/l (12 mg/100 ml) and this was present in 20% of cases. Three factors—epidural analgesia, breast feeding, and poor weight recovery—showed highly significant associations with jaundice. The relative importance of these is discussed and compared with recent reports. Induction of labour, for reasons other than postmaturity, and a gestational age <39 weeks showed a slightly increased incidence of jaundice. There was no correlation with other factors tested including oxytocic drug administration. Despite the high incidence (20%) of hyperbilirubinaemia, only 2.5% infants needed treatment and none required exchange transfusion. Radical changes in obstetric management or infant feeding are not indicated.

Since the claim by Mast *et al.* (1971) and Quakernack and Mast (1971) that oxytocic drugs were related to an increased incidence of neonatal jaundice, reports on this and on other maternal or perinatal factors have shown conflicting results (Ghosh and Hudson, 1972; Davidson *et al.*, 1973; Eden *et al.*, 1974; Gould *et al.*, 1974; Chalmers *et al.*, 1975). It was therefore decided to carry out a prospective study at the Birmingham Maternity Hospital taking into account the recent changes in obstetric and paediatric practice to assess incidence, related factors, and clinical implications.

Method

Two representative lying-in wards at the hospital were chosen. 903 mothers were delivered of live-born infants between September 1974 and July 1975 inclusive, but 180 of these babies were discharged before 6 days and a further 33 were preterm, of low birthweight, Coombs-positive, or delivered by ventouse, and so were excluded. The 180 infants were compared with the remaining 690 and no significant differences were found regarding ethnic group, social class, gestation, or birthweight. There were however rather fewer vertex deliveries and rather more forceps and caesarean births among the infants who stayed the full 6 days. Otherwise the 690 infants studied were representative of term babies delivered at that time in the hospital.

The maternal history, birth details, and infants' data were recorded on a proforma suitable for computer analysis.

Assessment of jaundice. As the plasma bilirubin (PB) level rises and then falls in the normal newborn during the first week, the timing of the samples needs to be as constant as possible to give comparable results. Sampling was therefore arranged to coincide with the metabolic screening test on about the 6th day. Those infants showing clinical jaundice had PB levels measured earlier and 17 infants with PB levels >308 μmol/l (18 mg/100 ml) before the 6th day received phototherapy. In these the highest recorded levels were used in the analysis. PB was measured by a modification of the method of White *et al.* (1958).

Despite a general alertness for jaundice, surprisingly high PB levels were obtained for the first time at the routine 6th day heel prick in some babies. 32 (4·4%) had PB levels >205 μmol/l (12 mg/100 ml) and 9 (1·2%) >256 μmol/l (15 mg/100 ml). These might have been missed, emphasising the need for all infants to have blood samples taken if the true incidence of hyperbilirubinaemia is to be obtained.

Results

A distribution curve for the whole series was plotted

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within 34 μmol/l (2 mg/100 ml) groups (Figure). The interplay of the various factors and the levels of PB were repeatedly analysed on the computer. It was found that a level of 205 μmol/l (12 mg/100 ml) and above showed the most significance, and this was defined as hyperbilirubinaemia. Mean PB levels were also recorded for comparison.

The following factors showed no effect on jaundice: ethnic group, ABO blood group, maternal age, time of year, type of delivery, birthweight, birth rank, vitamin K administration, sex, maternal toxaemia, and social class.

The gestational age of all these infants was >37 weeks and there was a slight increase both of mean PB levels and of hyperbilirubinaemia in those <39 weeks (Table 1). The mean gestational age was taken into account in each subsequent analysis and it showed a similar distribution throughout the different clinical groups.

Six clinical groups remained to be analysed further: previous contraceptive pill taking by the mother, oxytocic drug, labour onset, epidural analgesia, method of feeding, and weight recovery.

Table 2 shows how these clinical groups compared in respect of mean PB levels and percentage of babies with hyperbilirubinaemia. There was no difference in respect of pill taking or oxytocic administration. When induction of labour was analysed for the whole group there was no apparent effect but when the cases were divided into those induced for prolonged pregnancy and those induced for other reasons there were significant differences.

Epidural analgesia, weight recovery, and breast or artificial feeding all gave highly significant differences in respect of percentage jaundice and, the last two, in respect of mean PB levels as well. The clinical groups were therefore analysed a further three ways according to whether the mothers had received epidural analgesia or not, whether the baby regained birthweight above or below 95%, and whether it was wholly breast or artificially fed. Epidural analgesia and weight recovery did not alter the results in Table 2, but taking the 590 wholly breast-fed or wholly bottle-fed babies there were some minor changes. The mean PB level of the breast fed 'pill' group was significantly higher than the 'no pill' but the difference in hyperbilirubinaemia was not. Oxytocic drug and labour onset remained virtually the same. The interrelationships between the three

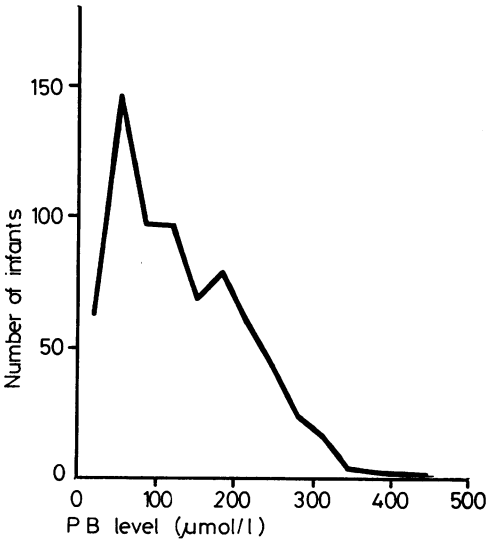

Figure *Frequency distribution of plasma bilirubin levels for 690 infants.*

Table 1 *Jaundice and gestation*

Gestation	*n*	*Mean PB (μmol/l)*	*Hyperbilirubinaemia (%)*
<39 weeks	99	159 ***	27·3
39 to 40 weeks	164	130	18·3
40 to 41 weeks	242	120	18·2
41 weeks and over	125	121	17·6

*** P<0·001.
Conversion: SI to traditional units—1 μmol/l ≈ 0·06 mg/100 ml.

Table 2 *6 clinical groups and the incidence of jaundice*

Group	*n*	*Mean PB (μmol/l)*	*Hyperbilirubinaemia (%)*
All cases	690	130	20·0
Pill			
No	274	123	18·7
Yes	390	135	21·0
Oxytocic drugs			
No	407	133	22·1
Yes augmented	117	127	21·4
Yes induced	290	135	22·4
Labour onset			
Spontaneous	330	125 *	19·1
Induced, prolonged pregnancy	82	111 **	14·6 *
Induced, other	224	143	24·6
Epidural			
No	178	122	11·8 ***
Yes	512	133	22·9
Weight recovery			
≥95%	411	119 ***	14·6 ***
<95%	165	162	33·3
Feeding			
Artificial	268	109 ***	12·3 ***
Breast	312	144 ***	25·3 *
Mixed	110	138	23·6

*P<0·05; **P<0·01; ***P<0·001.
Conversion as in footnote to Table 1.

significant factors is further examined in Table 3. The effect of epidural analgesia on hyperbilirubinaemia was reduced in significance and this was more apparent in the breast-fed than the artificially-fed group, probably because the size of the sample was smaller. Poor weight recovery did not show an effect in the artificially-fed infants so it was concluded that breast feeding itself rather than any concomitant underfeeding was the more important factor.

Discussion

An increasing incidence of neonatal jaundice has been reported by several authors (Campbell *et al.*, 1975; Sims and Neligan, 1975; Smith and Wilson, 1978), while in Birmingham the incidence of hyperbilirubinaemia (>205 μmol/l) has apparently risen from 5·6% (Wood *et al.*, 1962) to 20% in 1975. These figures are not strictly comparable however because in the early years routine blood tests were not done and, as already shown, 4% of babies with significant levels might have been omitted. Despite this, and a recent questionnaire to the contrary (Friedman *et al.*, 1977), it appears that in many centres there has been a real increase, although this may have levelled off since 1972 (Friedman *et al.*, 1978).

The incidence of hyperbilirubinaemia reported from different centres ranged from about 5% in Belfast (McConnell *et al.*, 1973), 8% in Liverpool (Beazley and Alderman, 1975), 9% in Cardiff (Davies *et al.*, 1973), 10% in Edinburgh (Chew and Swann, 1977), 12% in London (Campbell *et al.*, 1975), and 21% in Oxford (Calder *et al.*, 1974), which alone closely approached our own figure of 20%.

The pill and breast feeding. Since the report of Wong and Wood (1971) of a higher incidence of jaundice in breast-fed babies of mothers who had previously taken the pill, the oestrogen content has been much reduced and this may be the explanation (Wong, 1974) for a difference ($P < 0.05$) being seen only in mean PB levels and not in hyperbilirubinaemia in the present series.

Table 3 *Epidural analgesia and weight recovery in breast- and artificially-fed babies*

Group	n	Mean PB (μmol/l)			Hyperbilirubinaemia (%)		
		Breast fed		Artificially fed	Breast fed		Artificially fed
All cases	580	144	†††	109	25·3	†††	12·3
Epidural							
No	152	140	††	98	16·9 *	†	5·3 **
Yes	428	146	†††	114	28·1	†††	15·0
Weight recovery							
>95%	349	132 ***	††	104	20·7 **	††	10·3
<95%	129	174	†	127	39·0	†	17·2

*Vertical differences between clinical groups; †horizontal differences between type of feeding.
*†$P < 0.05$; **††$P < 0.01$; ***†††$P < 0.001$.
Conversion as in footnote to Table 1.

Oxytocic drugs. The dose of oxytocin in this series was low (< 10 units for most labours) which supports the view of Davies *et al.* (1973) and Beazley and Alderman (1975) that the effect, if any, is likely to be dose related. Our results showed no increase in either mean PB levels or of hyperbilirubinaemia whether the oxytocin was given to induce or augment labour.

Labour onset. Only when induction was divided according to its two main indications—prolonged pregnancy, on the one hand, or for obstetric or medical reasons, on the other, was there any difference. Any pronounced increase of preterm induction as a result of individual hospital policy would be liable to increase the jaundice risk, as shown in Table 1. This accords with the findings of Calder *et al.* (1974) and Sims and Neligan (1975) where the concept of enzyme priming in spontaneous labour was raised.

Epidural analgesia. Davies *et al.* (1973), Campbell *et al.* (1975), Sims and Neligan (1975), and Friedman *et al.* (1978) question the use of bupivacaine as a cause of hyperbilirubinaemia, and this study showed a highly significant difference. Whether this was due to the analgesic drug itself or to a related factor is uncertain. It is unlikely to be due to any post-delivery drug administered to the mother and secreted in her milk as it was also shown in the artificially-fed babies. Sims and Neligan (1975) thought that the association of epidural with jaundice in their series was probably because of the need for efficient pain relief during high dose oxytocin infusion after deliberate induction of labour. If this was the explanation in our epidural cases, one would expect that the proportion of deliberately induced babies would be significantly higher in those with hyperbilirubinaemia than in the rest. In fact the percentages were 43 and 38% respectively, showing no significant difference. The forceps rate in epidurals was as expected higher (52·5%) compared with nonepidurals (9%). However the incidence of hyperbilirubinaemia in the epidurals was the same whether they were delivered by vertex (22·6% hyperbilirubinaemia) or by forceps (21·6% hyperbilirubinaemia), again suggesting that the epidural is the relevant factor.

Feeding and weight recovery. From Table 3 it appears that breast feeding is more relevant than poor weight

gain. In Newcastle, Sims and Neligan (1975) also noted such a relationship and felt that it could not be explained by the jaundice causing the weight loss as the lowest weight was usually recorded on the 3rd day while the peak bilirubin level was not reached before the 4th or 5th day. This suggests that some human milk may contain an icterogenic factor but this may not necessarily be an endogenous one.

Other factors. In a comprehensive analysis of some 20 different drugs administered to the mother in labour, Drew and Kitchen (1976) showed that aspirin, barbiturate, and some others lowered the newborn baby's PB level on the 2nd and 3rd days while diazepam and oxytocic drugs raised it. The effect was small and probably only of significance in the at risk infant. It would be interesting to extend that kind of investigation in both breast-fed and artificially-fed infants during the first week of life.

In conclusion it appears that the high incidence of jaundice in this series was probably associated with the frequency of epidural analgesia (74%) and of wholly breast-fed babies (45%). As stated the only other report of a similar incidence of hyperbilirubinaemia was from Oxford (Calder *et al.*, 1974) where 85% of mothers had epidurals and 29% wholly breast fed their infants.

These factors overshadowed the others so that previous pill taking by the mother and oxytocic administration in the relatively low dosage used had no effect. Induction of labour showed its expected effect only if cases induced for postmaturity were excluded.

The question remains as to whether the bupivaine and the breast milk themselves are icterogenic or whether the women concerned received different analgesic or hypnotic drugs from the others and these might be the active agents.

While obvious jaundice in her infant can cause maternal anxiety and may delay discharge from hospital it should be noted that only 17 (2·5%) of the 690 infants had PB levels >308 μmol/l (18 mg/100 ml) at which phototherapy or feed change was instituted. None reached 427 μmol/l (25 mg/100 ml) which was the agreed level for exchange transfusion. Evidence for long-term handicap after nonhaemolytic jaundice of this degree is tenuous. The findings by Boggs *et al.* (1967) and later by Scheidt *et al.* (1977) of delayed psychomotor development at 8 months and one year in infants with neonatal PB levels of about 256 μmol/l made inadequate allowance for gestational age at birth and later reports on these children are still awaited. 17 of 18 children found to be deaf by Fenwick (1975) after similar PB levels had haemolytic disease and, in the 18th, the child's mother had an obscure jaundice. In an earlier series of 371 jaundiced infants reported by us (Culley *et al.*, 1970), full neurological and psychomotor examination at age 5 years showed no ill effects unless PB exceeded 342 μmol/l (20 mg/100 ml).

There is therefore no reason for doctors to reduce their advocacy of breast feeding or to make radical changes in the management of labour until the responsible factors have been more clearly identified.

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