

Neonatal jaundice - how much do we really know?

It will come as a shock to many to learn that our current practice with jaundiced babies is based on very shaky evidence. Edmund Hey, consultant paediatrician in Newcastle upon Tyne, explains why, in healthy full term babies, jaundice is not nearly as dangerous as we thought. We can safely reduce dramatically the number of babies who undergo phototherapy. Good news for mothers, midwives and budget holders!

This brief overview will concentrate on two questions:

- is jaundice ever severe enough to be dangerous in the term infant in the absence of any evidence of haemolysis?
- should jaundice by itself, in an otherwise well baby, lead us to look for evidence of some unrecognised underlying problem?

Jaundice - is the level dangerous?

The simplest answer to the question 'when should we worry about jaundice?' is 'when the level is abnormally high', and one definition of abnormality is the statistical one.

Any experienced midwife ought to be able to monitor jaundice without ordering lab tests

Using such an approach to define excessive jaundice (hyperbilirubinaemia), 5% of all babies of over 2.5kg were shown to have a total serum bilirubin of 230 μ mol/l at some stage in the first week of life in one carefully documented American study, and 1% had a total serum bilirubin in excess of 284 μ mol/l.¹ This study showed, very clearly, that breastfed babies tended to have higher peak bilirubin values than their bottle fed counterparts, and also remained jaundiced for a longer time. An excellent overview of how breast milk 'causes' more jaundice has just been published.² Basically, it is attributable to:

- low intake due to rigid infrequent early feeding policies
- delayed clearance of meconium in breast fed babies
- enhanced fat absorption (and absorption of unconjugated bilirubin) from the gut in the breast fed baby.

Only 5% of *bottle* fed babies had a peak value in excess of 194 μ mol/l in the American study, but 12% of *breast* fed babies had a bilirubin value that exceeded this threshold (5% having a value that exceeded 246 μ mol/l). A less well known study from Birmingham in the UK published seven years earlier had established similar 'normative' data.³

The data from the American study are now widely quoted as defining what constitutes a 'normal' neonatal

serum bilirubin level. Unfortunately, most of the babies with a bilirubin level above 220 μ mol/l in the American study, and all the babies with a bilirubin level above 310 μ mol/l in the British study, received phototherapy. We simply do not know, therefore, how many normal healthy babies would develop a serum bilirubin level in excess of 250 μ mol/l (c 15mg/dl) or 300 μ mol/l (c 18mg/dl) in the absence of medical intervention. We do know that many factors such as ethnic origin, the use of oxytocin or a bupivacaine epidural anaesthetic in labour, and delayed feeding increase the chance of a baby becoming 'hyperbilirubinaemic'. Babies born even a couple of weeks before term also have an increased chance of becoming significantly jaundiced.

What is normal?

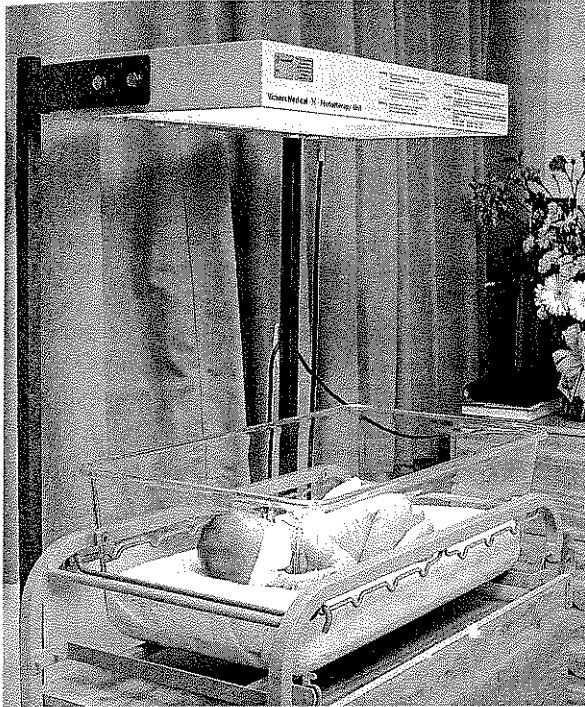
Such high levels are unusual, but does this make them abnormal (whatever that means)? It has been common practice to divide jaundice into 'physiological' jaundice and 'non-physiological' jaundice, but it is difficult to know if such a classification is of any real help. The key question is whether such jaundice is harmful. That is an issue on which there has, until recently, been relatively little information and even less consensus.

The initial experience on which it quickly became conventional to recommend exchange transfusion if the total serum bilirubin level exceeded 340 μ mol/l (20mg/dl) came from a three year review of kernicterus in babies with haemolytic disease of the newborn (HDN) in Boston between 1949 and 1952.⁴ In fact this influential paper contained only very weak evidence in support of this very precise recommendation.

High levels are unusual but does this make them abnormal?

Amazingly, 40 years later, this is still almost the only hard published evidence on which to base clinical practice.⁵ Intervention will usually be appropriate in the term baby with evidence of haemolysis when the total serum bilirubin level exceeds 340 μ mol/l (the old classic threshold of 20mg/dl). At values below this the risks associated with exchange transfusion usually exceed those associated with hyperbilirubinaemia.

Severe jaundice, in the absence of clinical features of kernicterus, has occasionally been associated with



Halving the distance between baby and light would double the dose of phototherapy

disability, including deafness, in babies with severe haemolytic disease,⁶ but all these babies had had severe fetal anaemia. There is no evidence that other causes of jaundice ever cause harm before they cause kernicterus. There are, however, no documented cases of kernicterus developing in an otherwise healthy term baby *in the absence of haemolysis* until the serum bilirubin level exceeds 500 $\mu\text{mol/l}$, and very few until the level exceeds 600 $\mu\text{mol/l}$.⁷ Anxiety has persisted that subtle 'brain damage' including deafness could occur in the healthy full term baby because of jaundice that was not quite severe enough to cause kernicterus, but two recent meticulously conducted reviews of all the available evidence have failed to find any evidence to support these fears.^{8,9} There is fairly clear, but very imprecise, evidence to suggest that the maximum safe level is lower in preterm babies than it is in babies born at term¹⁰ and that the maximum safe level is lower in babies with haemolytic jaundice than in others with 'physiological' jaundice (for reasons that we do not understand at all).

Early or late?

If we need to know whether there are features of a haemolytic process before deciding whether a particular bilirubin level in an otherwise healthy full term baby is safe or not, how is this to be achieved? The classic feature of haemolytic disease is *early* jaundice, ie within a day of birth. Significant haemolytic disease should seldom catch the midwife, or the family, unprepared if a maternal antibody screen has been undertaken in every

woman in late pregnancy. The definitive test, however, is a direct Coombs test after birth to see whether there are antibodies on the baby's red cells. Unfortunately, such a test cannot completely rule out haemolysis due to ABO incompatibility; hazardous jaundice is, however, extremely rare in such babies except where there has been evidence of significant jaundice within a day of birth.

In addition to these causes of haemolytic disease due to isoimmunisation, two other much rarer conditions need to be considered. The dominantly inherited condition congenital spherocytosis may rarely present with severe early jaundice in the absence of any apparent family history. The other condition is glucose-6-phosphate dehydrogenase (G6PD) deficiency. In many communities the condition is of little clinical significance, but in a minority of affected families from Greece, Italy, Singapore and Thailand, a more severe (B-) variant can produce dangerous jaundice at any time in the first two weeks of life, and does not always present with jaundice in the first day of life.

In summary, unless there is a chance that the baby has the B- variant of G6PD deficiency, there seems to be no chance of neonatal jaundice causing deafness or kernicterus in the healthy Coombs-negative term baby until the serum bilirubin level exceeds 500 $\mu\text{mol/l}$. If ABO incompatibility and early jaundice can be excluded then management can certainly be conducted on this assumption.

Staff caring for babies need to 'train their eyes'

Lab results can be inaccurate

In reporting serum bilirubin levels it is important to know that most routine methods of laboratory analysis are not very accurate. In a survey of 67 laboratories in Indiana in America in 1982, total bilirubin levels of between 186 and 410 $\mu\text{mol/l}$ were reported for a single test specimen, with a mean level of 310 $\mu\text{mol/l}$. If a specimen with a total bilirubin level of 340 $\mu\text{mol/l}$ is sent to a laboratory and assayed 100 times most of the results will fall somewhere between 306 and 374 $\mu\text{mol/l}$, but five of the results reported will lie outside this range. Most other types of chemical laboratory tests are much more accurate and reproducible than this.

Training our eyes

What the nurse or midwife needs to know is when to initiate laboratory assessment. From what has already been said there is a clear case for documenting the blood group, getting a Coombs test done, and starting to record serial laboratory total bilirubin levels in any baby showing signs of jaundice within a day of birth.



The icterometer — used by pressing the baby's nose (or gums in the case of black babies) and comparing the skin colour to the shaded stripes

Any experienced midwife ought to be able to monitor early neonatal jaundice in most other term babies clinically without ordering any laboratory tests. Jaundice appears on the face before it appears on the trunk. It is seldom seen over the lower leg and tibia until the total bilirubin level approaches $250\mu\text{mol/l}$.¹¹ Once jaundice appears on the hands and feet it can be assumed to have exceeded this level. This 'cephalopedal' progression of early jaundice has been well attested in a range of studies. Its value as a tool in the assessment of early neonatal jaundice should not be underestimated merely because its cause is not properly understood. Staff caring for babies need to 'train their eyes' and check their ability to replicate these findings both in daylight and under artificial light. The hand-held battery-operated Minolta Jaundice Meter (costing about £1700) can be used by those who are unsure of their clinical acumen,¹² but the simple icterometer described by Gosset in 1960¹³ may be equally effective¹⁴ (see illustration), and this only costs \$20. (The icterometer is currently only marketed by Cascade Health Care Products of Salem, Oregon in the USA). Bilirubin levels in excess of $340\mu\text{mol/l}$ are unlikely to be missed if a laboratory blood sample is obtained whenever the icterometer reads 3.5 or more (unless the baby is already having phototherapy).¹⁵

Uncomfortable questions

If the level of jaundice at which we need to become anxious

is so poorly defined, but also so much higher than is generally acknowledged in term babies without haemolysis, why do paediatricians become so worried about babies with moderate jaundice on the fourth or fifth day of life? Indeed, why do we worry about jaundice at all in the few term babies who are still in hospital five days after birth, but express no concern for the wellbeing of the many five day old babies with a comparable degree of jaundice out in the community? And why, if laboratory bilirubin estimates are so variable, do we have so little faith in our ability to assess the degree of jaundice clinically, and become so concerned to monitor trends and to document serial laboratory bilirubin estimates?

Why do paediatricians become so worried about babies with moderate jaundice on the fourth or fifth day of life?

There are no comfortable answers to these uncomfortable questions, but part of our discomfort must be that we doubt whether phototherapy can really be relied upon to stop the bilirubin level rising further. Much of the fault for this rests on our reluctance to treat the administration of phototherapy seriously.¹⁷ We pay too much attention to colour and too little to intensity. We seldom take the trouble to position the light as close to the baby as we can; halving the distance would double the irradiance. The 'dose' of light we give is often the dose it is easy to administer, not the 'dose' that would work best. There is evidence to suggest that phototherapy for one hour every four hours is as effective as continuous phototherapy.¹⁶ Efficacy can be doubled, however, by increasing the area of skin exposed and placing light below the baby as well as above, an arrangement most easily achieved by placing the baby on a fiberoptic phototherapy blanket.¹⁷ This produces a light intensity of twice that of eight 20W fluorescent tubes placed 35cm above the baby, but still only half the irradiance experienced out-of-doors but in the shade on a bright summer day.¹⁸

Why do we have so little faith in our ability to assess the degree of jaundice clinically?

If we could bring ourselves to believe that *effective* phototherapy will always produce an immediate fall in the serum bilirubin level in the term baby with no evidence of haemolysis we would not need to start phototherapy in the 6-8% of all breastfed babies deemed to merit such treatment on current guidelines¹⁹ when the serum bilirubin level exceeds $285\mu\text{mol/l}$. If we could rid ourselves of the

unsubstantiated fear that the Coombs negative term baby who is not at risk of the more severe genetic variant of G6PD deficiency and who does not present with recognisable jaundice in the first two days of life, is going to come to harm when the serum bilirubin level exceeds 340 μ mol/l (the magical 20mg/dl 'threshold')⁵ we could concentrate on giving effective phototherapy to the one baby in a thousand in whom the level exceeds 430 μ mol/l. In so doing, we would still be initiating treatment well below the threshold for which there is any documented evidence of risk (500 μ mol/l).

Similarly, if we could only bring ourselves to realise that most Coombs-positive babies never develop serious jaundice, and that many babies with early jaundice never develop progressive jaundice, we could further reduce the use of phototherapy (which can all too easily interfere with early discharge home). The bilirubin time-trend graphs, first developed to identify babies with Rhesus isoimmunisation who might require *repeat* exchange transfusion, greatly overestimate the risk of serious jaundice ever developing in babies without Rhesus isoimmunisation.²⁰

Jaundice — should it be investigated?

The crucial facts needed for the safe management of severe jaundice in the term baby are a knowledge of the age of the baby and the total serum bilirubin level.

Early jaundice

Haemolysis must be a real possibility when the bilirubin level exceeds 250 μ mol/l within 48 hours of birth, and for such babies a Coombs Test and a knowledge of the baby's (and the mother's) blood group will influence further management.

Early progressive jaundice remains a neonatal emergency

Tests for congenital spherocytosis and G6PD deficiency will be called for if the threshold of 340 μ mol/l is reached in the absence of any other explanation, especially if there is early, severe (and therefore, presumably, haemolytic) jaundice. Early progressive jaundice remains a neonatal emergency, and needs to be treated as such. Haemolytic jaundice (even in the absence of Rhesus isoimmunisation) can escalate so quickly that kernicterus develops by the time the baby is 36 hours old.

Later jaundice

The investigation of transient, spontaneously-resolving jaundice later in the first week of life in order to come up with a diagnosis, and an 'explanation' for the parents, is seldom fruitful and very expensive.²¹ Sudden

progressive jaundice can be the first sign of septicaemia or of an inborn error of metabolism such as congenital galactosaemia, but these babies will be 'off their food' and ill in other ways. To subject every child developing jaundice after two days to a 'septic work-up' including blood culture and a range of haematological tests cannot be justified.⁶

Screening for low grade urinary tract infection may be easier to justify, although it is rare in babies with early jaundice. One recent estimate¹⁴ suggests that urinary infection will only be encountered once in 4,000 births.

The rapid spot diagnosis of galactosaemia may be life saving, but this recessively inherited disorder is only seen in 1:60,000 births, making routine testing clearly inappropriate unless the child is unwell.

Prolonged jaundice

Protocols have also been proposed for the investigation of jaundice lasting more than 10-14 days,²² looking for evidence of intrauterine infection, alpha-1-antitripsin deficiency, cystic fibrosis and hypothyroidism, especially if there is a raised conjugated bilirubin level (>50 μ mol/l), but the yield is low. Hypothyroidism is now routinely screened for anyway in the UK using the Guthrie screening test, and the only other important and potentially treatable condition that needs to be diagnosed as rapidly as possible if treatment is to be optimised is biliary atresia.²³⁻²⁶ Extrahepatic biliary atresia is rare (1:20,000 births) but the aim must be to get every such baby diagnosed within four weeks, because the operative success rate falls rapidly when surgery is only undertaken more than six weeks after birth. Parents need to be told that prolonged jaundice is common, and entirely normal, especially in the breastfed baby, but that urgent review to rule out biliary atresia is called for if this persists for more than three weeks, particularly if the stools are consistently pale and putty-coloured rather than yellow or green (something that the midwife or health visitor *must* verify for herself by direct inspection).

As long as this one condition is not overlooked, no important treatable condition will be missed by dispensing with further investigations when prolonged low-grade jaundice is encountered in an otherwise vigorous and thriving breastfed term baby. Supplementary water feeds do not lower the initial peak jaundice levels seen in these babies, and may even make matters worse.²⁷ Substituting an artificial milk for 24-48 hours will produce a 'diagnostic' fall in the bilirubin level in most of these babies²⁸ but such a move is quite unnecessary and taking the baby off the breast merely leads the mother to feel she is harming her baby in some way.

Even a short period of low-dose phototherapy is more effective than two days of artificial feeding in lowering the bilirubin level. The rebound after phototherapy (or artificial milk) is stopped is seldom substantial.²⁹

It is a sad indictment of the medical approach to normality that we now define 'normality' by the performance of the average bottle fed baby. As a result we tend to look upon the low enterohepatic recirculation of bilirubin that accompanies the frequent, incompletely digested stool of the bottle fed baby as being more normal than the continuing mild jaundice caused by the very efficient gastrointestinal performance of the breast fed baby.

Summary

Jaundice affects every baby, especially in the first week of life. Very occasionally, however, it can also be the first sign of some serious, but as yet unrecognised, problem.

Jaundice probably only calls for medical intervention in one term baby in a thousand

Forty years ago, it became clear that jaundice could also occasionally, of itself, cause deafness, brain damage and even death in the preterm baby, and in a few babies with haemolytic disease. Policies were quickly formulated to guide the management of severe jaundice in these babies, and these have generally stood the test of time. Their later extrapolation to influence the care of the healthy term baby cannot, however, be supported by any review of the available evidence.

Jaundice probably only calls for medical intervention, in the absence of haemolytic disease, in one term baby in a thousand.

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Hey EN. MIDIRS Midwifery Digest, vol 5, no 1, Mar 1995, pp 4-8.

Original article written for MIDIRS by Edmund Hey, consultant paediatrician (retired). © MIDIRS, 1995.