Plasma prolactin and clinical outcome in preterm infants

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Abstract

Plasma prolactin was measured weekly in 280 preterm infants. The complex gestational age dependent pattern of postnatal prolactin release has been defined and reference standards provided. Plasma prolactin was higher in girls, with increasing divergence between the sexes from the third week onwards, and higher after two weeks, in infants of mothers with pregnancy related hypertension. Diet, assigned randomly, exerted a major effect on plasma prolactin, with significantly higher values in infants fed donor breast milk or standard formula than in those fed a protein, energy, and mineral enriched preterm formula. After adjusting for confounding factors, infants with the lowest plasma prolactin concentrations (<1000 mU/l, 32·9 µg/l) occurring usually at a nadir between days 5 and 12, showed a 120% increase in the duration of ventilatory assistance required, a 20% increase in the number of days to attain full enteral feeds, and a 30% decrease in length gain.

We suggest preterm birth disrupts the normal perinatal pattern of prolactin release and that those infants who develop relatively low plasma concentration have an adverse outcome. Our data add to the broader debate on whether preterm infants require multiple endocrine replacement treatment.

Prolactin has a central role in stimulating milk production. Numerous and diverse actions for prolactin have been proposed in animals and man, however,[1] [2] and in recent years the possibility has been raised that prolactin is important for developmental events in the perinatal period.[3–7]

High plasma prolactin concentrations are found in the fetal circulation and in amniotic fluid.[5] [8] Plasma values considerably in excess of those seen in adults have been found in neonates and persist up to three months postnatally in full term infants and longer still in infants born preterm.[9–11] Prolactin may be important for lung maturation and surfactant synthesis,[12–17] and the possibility that low plasma concentration might be of aetiological importance in hyaline membrane disease in preterm infants has been suggested and debated by several groups.[7] [12–15] [18–22] Further evidence, also debated, points to a possible role for prolactin in the growth of the gut and its mucosal function[23–25] and the intestinal absorption of fluid and ions.[26]

Because of the uncertainty about the physi-

ological actions of prolactin in early life and its potential importance in preterm neonates, we have studied plasma prolactin concentrations longitudinally in a large cohort of intensively monitored premature infants, taking part in a multicentre feeding trial.[27] Firstly, we have derived standards for plasma prolactin concentrations, taking into account postnatal age, gestation, and sex. Secondly, we have investigated the effect of diet and possible influence of other perinatal factors on prolactin release. Finally, in view of the observations above, we have explored, using regression analysis to adjust for confounding factors, whether postnatal plasma prolactin concentrations relate to selected clinical outcome responses potentially linked to the development of the lung or gut. These outcomes include duration of severe respiratory disease, necrotising enterocolitis, days to attain full enteral feeds, and growth performance.

Subjects and methods

Longitudinal data derived from a large multicentre infant feeding study were analysed.[27] A total of 280 neonates were studied in five centres with a mean (SE) gestational age of 30·3 (0·2) weeks and a mean birth weight of 1330 (18) g. All were less than 1850 g at birth. Extensive data were collected on their biochemical profiles. Growth data were collected as described previously.[27]

In three centres infants whose mothers elected not to˙ provide their own milk were assigned randomly[27] to receive either banked pooled donor breast milk or a preterm formula (Oster-Prem, Farley Health Products) as sole diets (trial 1). When mothers expressed their own 'preterm' milk the infants were assigned randomly to receive either donor breast milk or preterm formula as supplements in volumes according to the mother's success in expressing her milk (trial 2). In the remaining two centres infants were assigned randomly to receive either a standard 'term' formula (Osterfeed, Farley Health Products) as sole diets (trial 3) or as supplements to mothers milk (trial 4). The protein, energy, and sodium contents of the preterm formula were: 2·0 g/100 ml, 0·33 MJ (80 kcal)/100 ml, and 19·6 mmol/l, and of the standard formula: 1·45 g/100 ml, 0·28 MJ (68 kcals)/100 ml, and 8·3 mmol/l, respectively.

In each subject plasma prolactin was measured weekly until discharge from hospital or until a weight of 2000 g was exceeded; the mean (SD) duration in study was 37·3 (20·6) days. Data beyond week 7 are presented as the mean of values from week 8 onwards for each subject

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still in the study. The population of infants remaining in the study fell with postnatal age; of the 280 subjects, 160 remained beyond week 4 and 56 beyond week 8. An additional cross sectional analysis was performed on values obtained within two day blocks of time from days 1–2 up to day 13–14.

Venous samples were collected in cooled heparinised tubes, centrifuged at 4°C, and the plasma fraction stored at −20°C within 30 minutes of sampling. Plasma prolactin concentrations were measured on 1340 duplicate 20 μl samples by radioimmunoassay (CIS France). The percentage cross reactions obtained by the assay were: prolactin 100%, human growth hormone 0·24%, and human placental lactogen, luteinising hormone, follicle stimulating hormone, human chorionic gonadotrophin, and thyroid stimulating hormone×10⁻⁴%. Minimum assay sensitivity was 26 mU/l (0·85 μg/l).
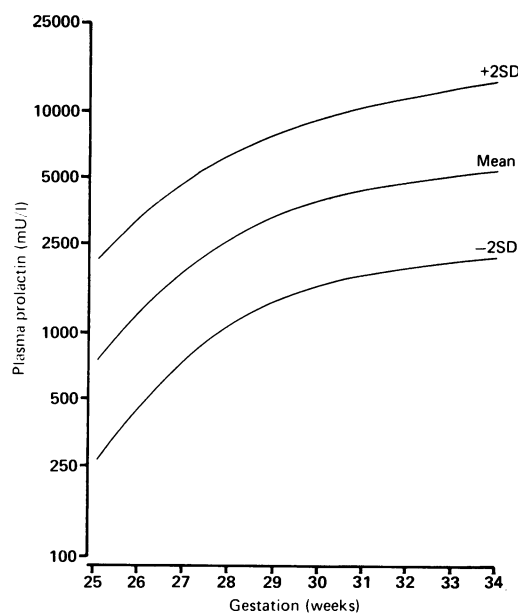

Figure 1   Plasma prolactin (plotted on a logarithmic scale) in preterm neonates during the first 48 hours at gestations from 25 to 34 weeks. Data have been smoothed and represent the geometric mean±2SD. To convert mU/l to μg/l divide by 30·4.

Statistical analyses were performed using Student's t test and χ^2 tests; multiple and logistic regression was used to explore the association between plasma prolactin concentrations and a range of perinatal and neonatal factors. For these analyses, plasma prolactin has been treated either as a dichotomous variable (a value above or below a given threshold) or as a continuous one. In the latter case, as data were postively skewed, they were analysed after log transformation. For presentation, data have been antilogged, providing geometric means with 95% confidence intervals.

Results

REFERENCE VALUES FOR PLASMA PROLACTIN IN PRETERM INFANTS

Plasma prolactin concentrations in the first 48 hours after birth were strongly related to gestation (fig 1 shows a smoothed reference chart). At 25–26 weeks plasma prolactin was 950 mU/l (31·3 μg/l) (95% of values lying between 340 (11·2) and 2660 (87·5)) rising to 5420 (178·3) (2120 (69·7), 13840 (455·3)) mU/l (μg/l) at 33–34 weeks (p<0·001).

Table 1 shows smoothed reference values for plasma prolactin in the first seven weeks according to gestation. Early values, up to 14 days, are for both sexes combined, because as shown below, consistent sex differences do not emerge until later in the neonatal period. In each gestational age group plasma prolactin concentrations fell postnatally to a nadir at a mean of seven to 10 days followed by a rise. The overall trend in plasma prolactin over the first seven weeks depended on gestation (table 1 and fig 2A). In infants under 28 weeks, after an initial fall (p<0·001), values rose progressively over the next six weeks (p<0·001). In contrast (fig 2A) infants of 32–36 weeks' gestation showed overall a major fall in plasma prolactin from birth to week 7 (p<0·001).

Figure 2B shows sex differences in plasma prolactin for the whole cohort. In the first 48 hours, values were lower in boys 2440 (80·3)

Table 1   Plasma prolactin concentrations in mU/l* in preterm infants in the first seven weeks according to gestational age and sex. For the period 1–14 days and in infants under 28 weeks' gestation both sexes are combined. Data were originally log transformed to derive means and SDs; the data here have been antilogged to provide a geometric mean plus or minus 2 SD

Postnatal age	25–27 Weeks' gestation (n=36)			28–31 Weeks' gestation (n=152)			32–36 Weeks' gestation (n=92)		
	−2SD	Mean	+2SD	−2SD	Mean	+2SD	−2SD	Mean	+2SD
Day:†									
1–2	350	1620	7590	870	3020	10470	2240	5370	12880
3–4	270	910	3090	680	2400	8510	1150	2820	6920
5–6	190	630	2140	590	2040	7080	810	2140	5620
7–8	180	580	1860	540	1820	6170	710	2000	5620
9–10	200	630	2000	510	1700	5620	720	2140	6310
11–12	300	830	2290	650	1910	5620	790	2340	6920
13–14	360	980	2690	910	2400	6310	910	2690	7940
				28–36 Weeks' gestation combined‡					
				Boys (n=120)			Girls (n=124)		
Week:									
3	410	1180	3390	760	1910	4790	680	2340	8130
4	510	1480	4270	660	1700	4370	710	2290	7410
5	530	1510	4570	590	1510	3890	780	2340	7080
6	520	1620	5010	490	1320	3550	810	2340	6760
7	550	1700	5250	430	1180	3240	870	2340	6310

*To convert mU/l to μg/l divide by 30·4.
†As subjects provided one sample/week, data for days 1–14 are based only on those subjects who were sampled in each two day time period (about one third of subjects sampled/two day period).
‡From week 3, infants of 28–31 and 32–36 weeks' gestation have been combined as there were no significant differences between these groups after this age.
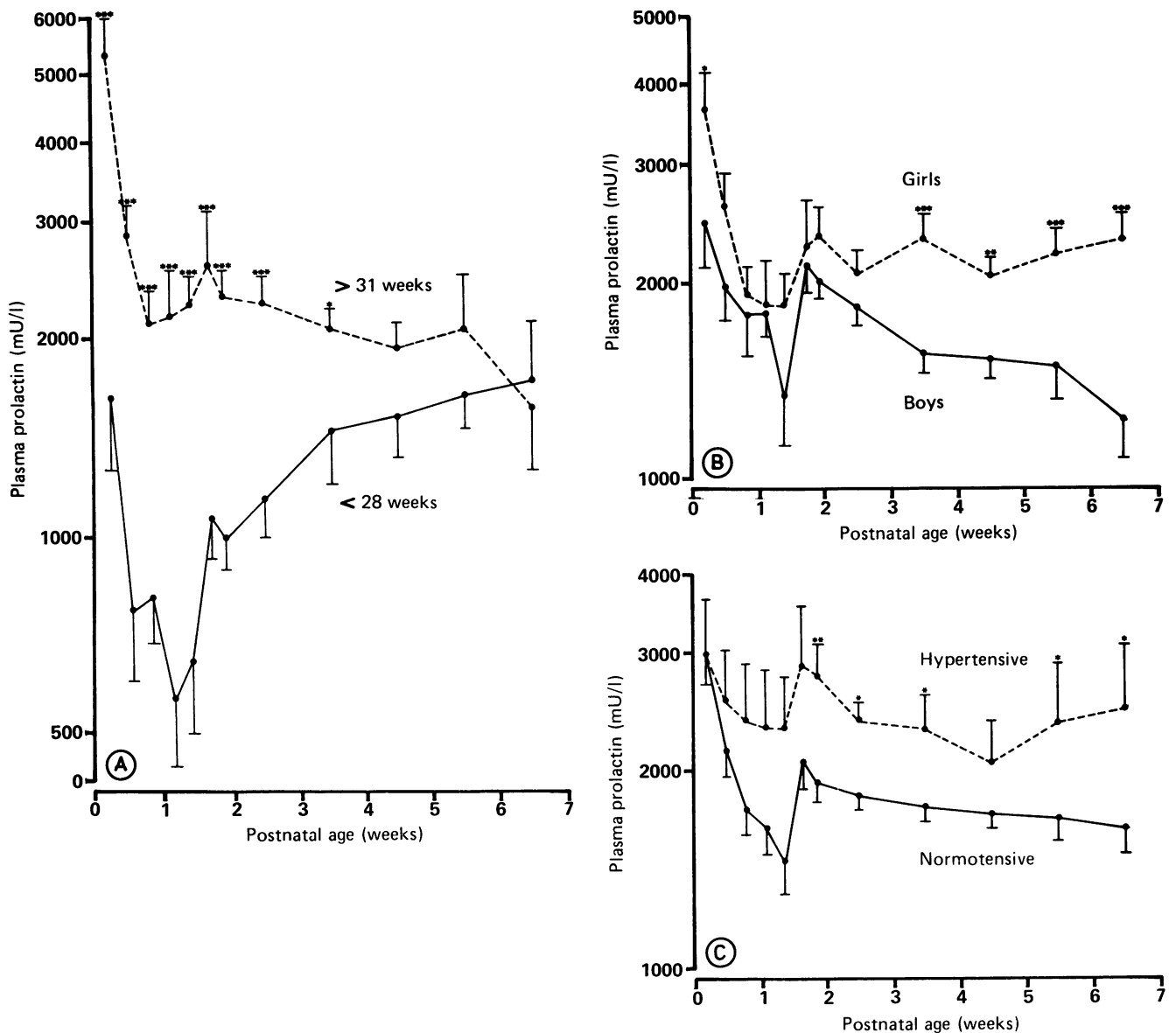
Figure 2 *Plasma prolactin in preterm infants during the first two months: (A) infants under 28 weeks compared with those above 31 weeks' gestation; (B) boys compared with girls; and (C) infants whose mothers had pregnancy related hypertension compared with those with normotensive mothers. Data are geometric mean (SE) ***p<0·001; **p<0·01; *p<0·05. To convert mU/l to µg/l divide by 30·4.*

(620 (20·4) to 9600 (315·8)) mU/l (µg/l) than in girls 3600 (120·4) (1100 (36·2) to 12180 (400·7)) mU/l (µg/l) (p<0·5). This difference did not reach significance again until week 3, after which there was a major and progressive divergence in values between the sexes.

FACTORS RELATING TO PLASMA PROLACTIN CONCENTRATIONS

In addition to gestation and sex, a range of other factors were explored for their association with plasma prolactin.

Effect of diet

Figure 3A shows plasma prolactin in infants in trials 1 and 2. While those fed on breast milk showed no change in prolactin values from the second to seventh week, values in the group fed preterm formula declined progressively and

were significantly lower beyond weeks 3. A similar trend was seen in trials 3 and 4 with lower values on preterm formula. The differences (not depicted) did not reach significance in this much smaller comparison. In fig 3B, however, all four trials have been combined to compare infants fed 'unfortified' diets: banked milk or term formula compared with those fed a 'fortified' preterm formula. As this is a balanced addition of trials, the comparison is a randomised one. In infants fed preterm formula, plasma prolactin concentrations declined linearly (p<0·01) with values progressively diverging from those seen on banked milk or standard formula.

As high prolactin concentrations are found in early milk,[28] we considered that these might contribute to high plasma concentrations in newborn infants. A comparison of infants fed 90% or more of their own mothers early preterm milk with infants fed on mature donor breast
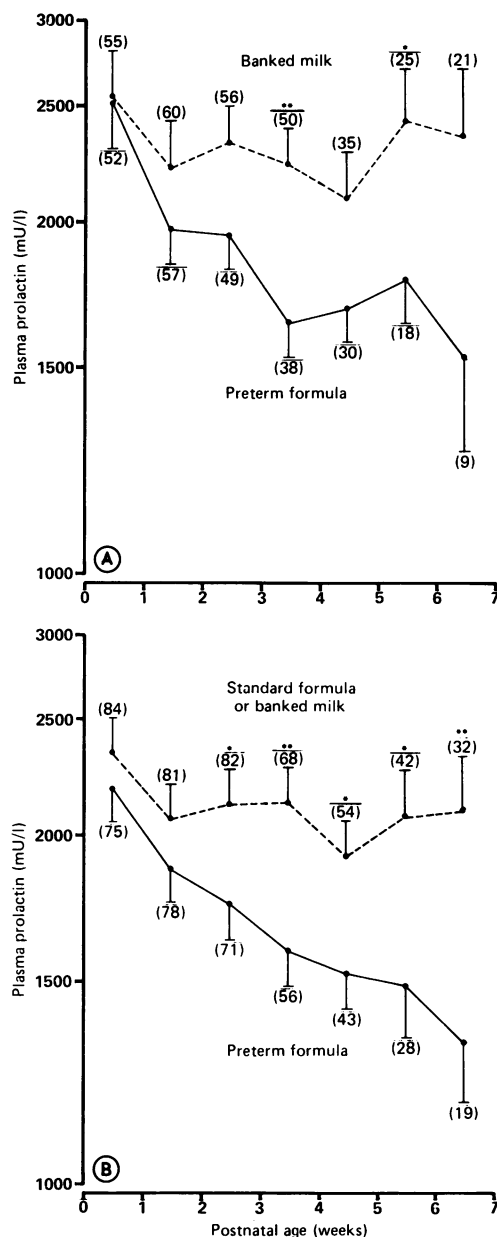
Figure 3 Effect of diet, randomly assigned, on plasma prolactin concentration in preterm infants during the first two months. (A) Banked donor breast milk compared with preterm formula, as sole diets or supplements to maternal milk and (B) standard formula or banked milk ('unfortified diets') compared with preterm formula as sole diets or supplements to maternal milk. **p<0·01, *p<0·05.

milk, however, failed to show any difference in neonatal plasma prolactin (t values for the difference at ages 1–3 days and 4–7 days were 0·02 and 0·71).

Other factors

Using regression modelling, a range of factors have been examined for their independent relationship with prolactin concentration, calculated as the mean of all values for each subject in the first month (dependent variable). Independent variables included the infant's sex, gestation (above or below 28 weeks), birth weight, diet (banked milk or standard formula compared with preterm formula), and fetal growth retardation (birth weight above or below 10th centile). Also included were pregnancy related hypertension (diastolic blood pressure 90 mm Hg or over; or systolic blood pressure 140 mm Hg or over), days of mechanical ventilation (log transformed; plus 1, to avoid log 0), Apgar score at five minutes (below 5 compared with 5 and above), mode of delivery (caesarean compared with vaginal), necrotising enterocolitis, number of days to attain full enteral feeds (defined as 150 ml/kg per day or more), and days of dopamine treatment (only eight cases).

Four factors were independently associated with plasma prolactin: sex (higher in girls, p<0·001), gestation (higher above 28 weeks; p<0·001), pregnancy related hypertension (associated with higher values, p<0·02), and diet (lower on preterm formula, p<0·02). Raw data on the association between these four factors and plasma prolactin (against postnatal age) are shown in table 1 and figs 1, 2, and 3.

Interaction terms were also introduced into the models to explore any interactions between gestation, sex, diet, and hypertension. The only one identified was between gestation and hypertension, demonstrating that a significant rise in plasma prolactin in hypertensive subjects was greatest in infants of low gestation. As babies of hypertensive subjects had a slightly higher mean gestation than those of those who were normotensive (31·7 compared with 30·5 weeks), the data depicted in fig 2C represent an underestimate of the difference that would have been seen if the two groups had had the same mean gestation.

In order to explore the possibility that the dietary effect (above) related to sodium status, mean plasma sodium concentration (in week 1 or month 1) was added to the models. No association between plasma sodium and plasma prolactin emerged, and the dietary effect was unchanged.

It should be noted that in all the longitudinal data described above, sample size diminished when the larger babies were discharged from hospital. Thus after the first month the popula-

Table 2 Raw data on association between the minimum (lowest) plasma prolactin concentration in the neonatal period and respiratory disease, prolonged establishment of enteral feeds, and neonatal linear growth rate

	Minimum plasma prolactin concentration (mU/l)*			
	<1000	1000–1999	2000–2999	≥3000
No (%) infants with respiratory distress syndrome (needing ventilation)	50/67 (75)**	65/128 (51)	26/50 (52)	16/35 (46)
No (%) of infants ventilated >7 days	29/67 (43)***	15/128 (12)	4/50 (8)	2/35 (6)
No (%) infants taking >14 days to full enteral feeds	16/59 (27)*	14/120 (12)	6/49 (12)	4/33 (12)
Mean (SE) length gain (mm/day)	1·09 (0·07)	1·33 (0·06)	1·33 (0·08)	1·33 (0·09)

*To convert mU/l to μg/l divide by 30·4.
†Nineteen of 280 subjects died before attaining full feeds.
***p<0·001, **p<0·01, *p<0·025 for comparison of infants whose minimum plasma prolactin was below 1000 mU/l and all infants whose minimum plasma prolactin was 1000 mU/l and above (last three columns in the table combined).

tion remaining in the study was predominantly infants below 32 weeks' gestation.

ASSOCIATION BETWEEN PLASMA PROLACTIN AND CLINICAL OUTCOME

In a series of regression models, plasma prolactin has been treated as an independent variable to explore its association with the following clinical outcome responses (dependent variables): duration of respiratory disease (days of ventilation), necrotising enterocolitis, days to full enteral feeds (over 150 ml/kg per day), weight gain (g/kg per day), length gain (mm/day), and head circumference gain (mm/day) (the growth rates were assessed from the day of regaining birth weight to discharge from the study). Logistic regression was used for the dichotomous dependent variable, necrotising enterocolitis. Further independent variables were the same as those in the models described in the previous section.

No association was found between mean or the peak (highest) plasma prolactin concentration and any of the outcome responses. After adjusting for confounding factors (above), however, the minimum plasma prolactin concentration, usually occurring between days 5 and 12, was found to be significantly related to duration of ventilation (p<0·005), linear growth (length gain) in the neonatal period (p<0·02), and the number of days of full enteral feeds (p<0·03) (minimum prolactin concentration was log transformed in these models to achieve the best fit).

From inspection of the raw data in table 2, it is apparent that when the minimum plasma prolactin concentration fell below 1000 mU/l (32·9 µg/l) there was a sharp rise in the duration of ventilatory assistance and days to full feeds and a sharp fall in linear growth. Using regression analysis to adjust for confounding factors, a value of 1000 mU/l (32·9 µg/l) again proved to be the best modelled cut off for predicting these adverse outcomes. Plasma prolactin values under 1000 mU/l (32·9 µg/l) in the first week were independently associated with an increase in the number of days of ventilation (p<0·001), the proportion of subjects ventilated for over seven days (p<0·001), neonatal length gain (p=0·018), and the number of days to attain full enteral feeds (p=0·027) (fig 4).

The raw data (table 2) show that the incidence of respiratory disease as well as the duration was related to low plasma prolactin; after

adjusting for confounders (table 3), only the duration was significantly related. Interestingly, despite previous reports that low plasma prolactin at birth relates to the incidence of respiratory distress,[6][7][12] we found no association between plasma prolactin in the first 48 hours and the incidence or duration of respiratory disease. Low plasma prolactin was unrelated to weight gain, head circumference gain, or necrotising enterocolitis.

Discussion

In a large cohort of preterm infants monitored during the early months we have defined the complex pattern of longitudinal changes in plasma prolactin concentration and provided new reference standards. A major effect of diet on plasma prolactin concentration emerged, and after adjusting for other factors the infant's sex and gestation and pregnancy related hypertension in the mother were strongly related to the pattern of prolactin release. Most important, low plasma prolactin in the neonatal period was significantly related to prolonged respiratory disease, an increase in the length of time taken to establish enteral feeds, and reduced linear growth performance, even after adjusting for a wide range of potentially confounding factors.

Several studies describe hyperprolactinaemia in preterm and term infants,[9-11] but the complexity of the postnatal changes and their relation to gestation and sex had not been adequately defined. Cord plasma values have been shown to rise with gestation.[21] Our data show a sixfold increase in plasma prolactin between 25 and 30 weeks' gestation, from a concentration little above the normal adult reference range. High fetal values, which are believed to derive from the fetal pituitary and not the mother, may be induced by maternal oestrogens.[5] This could explain high plasma prolactin we and others have observed in the early days after birth.[9] We showed that regardless of gestation and in all subgroups studied plasma concentrations fell rapidly to reach a nadir at seven to 10 days, followed by a significant rise by the 12th day and possibly a second smaller fall.

Breast milk contains very high prolactin concentrations in the first three days.[28] Our data did not suggest that this contributed to high neonatal plasma prolactin, however, as values were the same whether infants were fed early maternal milk or mature donor breast milk.

It has been argued that hyperprolactinaemia, which even occurs in anencephalic neonates,[5][29] implies a failure of prolactin inhibition, by prolactin inhibitory factor, rather than a stimulation of release. Maturation of the ability to release prolactin inhibitory factor[5][11] could account in part for the progressive decline in plasma prolactin during the early months observed here and described previously. However, our data suggest a more complex explanation. Firstly, in the most immature infants, below 28 weeks' gestation, plasma values rose considerably over a period of weeks from the nadir at seven to eight days; such a *rise* is difficult to reconcile with the explanation of

Table 3 Association between low plasma prolactin (<1000 mU/l) and duration of severe respiratory disease, days to establish full enteral feeds, and linear growth, after adjusting for potentially confounding factors (see text) by multiple regression

Dependent variable	Plasma prolactin <1000 mU/l*	95% Confidence interval	p Value
Days of ventilation†	Increased by 2·2:1	1·4:1 to 3·6:1	<0·001
Days to attain full enteral feeds	Increased by 1·2:1	1·0:1 to 1·4:1	0·027
Length gain (mm)	Decreased by 0·33	−0·08 to −0·74	0·018

*To convert mU/l to µg/l divide by 30·4.
†Log transformed for statistical analyses.

hyperprolactinaemia above. Furthermore, boys showed a much more rapid decline in values during the first two months than that seen in girls.

The sex difference in plasma prolactin in preterm infants, found also after adjustment for potentially confounding factors, was of interest. In adolescence and adulthood, females have higher prolactin values than males, principally early in the menstrual cycle when plasma oestrogen is high.[10] This sex difference has not been described during infancy or childhood. Indeed, in a much smaller sample it was preterm boys who transiently had higher plasma prolactin concentrations during the first week.[10] We found girls had transiently higher values after birth (consistent with a previous observation[15] based on cord blood analyses), and beyond 2 weeks of age when a major and progressive divergence in plasma prolactin between boys and girls was found. It requires exploration whether this difference could contribute to the well described poorer prognosis in boy preterm neonates.[30] [31]

Maternal hypertension has been associated with an increase in plasma prolactin in cord blood.[21] It might be supposed that maternal pre-eclampsia had exerted a transient influence on the metabolic milieu of the fetus. However, our data show, surprisingly, that the association between high plasma prolactin and pregnancy related hypertension persists and increases in magnitude during the first two months (even after adjustment for confounding factors). The possibility is raised therefore that pregnancy related hypertensive disease might induce long term changes in the infant's endocrine state.

Diet was a major factor influencing plasma prolactin. In a strictly randomised comparison infants fed preterm formula developed lower plasma prolactin concentrations than those fed donor breast milk or standard formula (when these diets were used alone or as supplements to mothers' milk). The preterm formula was enriched in protein, energy, sodium, and other minerals. Ertl *et al* showed a significant postnatal decline in plasma prolactin,[32] as seen here in infants fed the preterm formula with sodium chloride supplementation. We found that plasma sodium and plasma prolactin were unrelated. While this does not exclude the possibility that our dietary effect was solely due to differences in salt intake, effects of other nutrients on prolactin release need to be excluded.

Prolactin has been identified as a possible trigger for surfactant synthesis.[12–17] Fetal prolactin secretion rises before surfactant production and there are prolactin receptors in the lung,[16] and after experimental administration of prolactin to fetal rabbits pulmonary lecithin content increases rapidly.[13] Some investigators find that a low plasma prolactin concentration in cord blood relates to the development of respiratory distress[6] [7] [12]; others do not[20] [22] and claim low plasma prolactin is simply a marker for low gestation.[20] Such reports have relied on simple correlative analyses, however, with little adjustment for potentially confounding factors. Moreover, these investigations have related values at birth to the incidence of respiratory

distress and have not examined the association between the subsequent development of low plasma prolactin and the persistence of respiratory disease. Our raw data showed a strong association between the incidence of respiratory disease and minimum plasma prolactin, with a sharp rise in incidence as prolactin values fell below 1000 mU/l (32·9 µg/l). After adjusting for confounding factors, this association was not sustained, casting doubt on some previous observations. Nevertheless, the subsequent development of low plasma prolactin was strongly and independently related to the duration of severe respiratory disease. This relationship held when minimum plasma prolactin was treated as a continuous variable, but data modelling showed that for prognostic purposes, a minimum value below 1000 mU/l (32·9 µg/l) was associated with a major increase in duration of mechanical ventilation. Infants whose plasma prolactin concentration fell below 1000 mU/l (32·9 µg/l) had a more than twofold increase in the number of days of ventilation that they required and were over twice as likely to be ventilated for more than seven days, even after adjusting for birth weight, gestation, fetal growth retardation, sex, pre-eclampsia, low Apgar scores, and other major factors.

After adjusting for the same factors, infants whose plasma prolactin fell below 1000 mU/l (32·9 µg/l) took 20% longer (median three days longer) to attain full enteral feeds and, more important, had a linear growth rate 30% lower than in infants in whom values remained above this concentration. Possibly, these outcomes related in part to slower gut maturation in those with low plasma prolactin.[23–26] It is unlikely that delayed establishment of enteral feeds and reduced linear growth in those with low plasma prolactin simply reflected increased respiratory disease in this group, as adjustment for the presence and duration of severe lung disease did not abolish these associations. Interestingly, low prolactin values only related to reduced linear growth and not reduced weight gain or head growth. Low plasma prolactin might have had a selective effect on nutrient absorption, with reduction in intestinal transport of bone mineral substrate.

This speculation accords with Mainoya's experimental findings in rats that prolactin enhanced jejunal absorption of calcium (and other ions).[26] Furthermore, prolactin has been implicated in regulation of 1-25 hydroxyvitamin D production,[33] and this might also influence bone growth. Indeed in humans with hypopituitarism prolactin treatment promotes skeletal growth.[3]

Preterm birth may disrupt normal endocrine development. Previously we have identified (in the same cohort) low plasma concentrations of two other hormones that may have an important bearing on clinical outcome: low neonatal triiodothyronine concentrations were associated with later reduced developmental scores[34] and low testosterone values in boys with failure of testicular descent.[35] In this study we have presented a further example of an early endocrine disturbance that relates to an adverse outcome: preterm infants, born before the normal rise in

fetal prolactin in the third trimester, may have low plasma prolactin concentrations and these are strongly related to prolonged respiratory disease, delay in establishment of full enteral feeds, and reduced linear growth performance. Collectively, these data are relevant to the important question, requiring further scientific consideration, of whether infants of low gestation require multiple endocrine replacement treatment.

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