Increased recall rate at screening for congenital hypothyroidism in breast fed infants born to iodine overloaded mothers

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SUMMARY Skin disinfection with povidine-iodine (PVP-I) is widely used in obstetrics. We evaluated the influence of PVP-I in mothers at delivery on the serum thyroid stimulating hormone concentrations of their infants at the time of screening for congenital hypothyroidism. The study covered 4745 infants who were either breast fed (3659, 77%) or bottle fed (1086, 23%); 3086 (65%) of them were born to mothers with no iodine overload (controls) and 1659 (35%) to mothers with iodine overload. Compared with the control group, the breast and bottle fed infants born to mothers with iodide overload had a shift of neonatal thyroid stimulating hormone concentration towards high values. The shift was maximal in the breast fed infants with a 25 to 30 fold increase in the recall rate at screening for congenital hypothyroidism (serum thyroid stimulating hormone >50 mU/l) while in the bottle fed infants, the recall rate was barely modified. In conclusion, the use of PVP-I in mothers at delivery induces a transient impairment of thyroid function in their infants, especially if breast fed. This situation is detrimental to screening for congenital hypothyroidism. Consequently PVP-I is not recommended in obstetrics.

Skin disinfection with povidone-iodine (PVP-I) is widely used in obstetrics in epidural anaesthesia or caesarean section. This procedure results in iodide overload of the mother due to cutaneous absorption of iodine.¹ Iodide readily crosses the placenta² and is actively concentrated in the mammary gland.³ Consequently, newborn infants born to mothers treated with PVP-I are also exposed to iodine overload, especially if breast fed.⁴

The thyroid gland of newborns is highly sensitive to the blocking effect of excess iodide on thyroid hormone synthesis, and a raised concentration of serum thyroid stimulating hormone is the most reliable index of impairment of thyroid function.⁵ The objective of the present work was to evaluate the influence of cutaneous application of PVP-I in mothers at delivery on the concentrations of thyroid stimulating hormone in their infants at the time of screening for congenital hypothyroidism. In order to appreciate the specific role of the iodine contained in breast milk, a comparative study was performed between breast and bottle fed infants.

Patients and methods

The study included 4745 (96%) of the 4923 infants born in our maternity ward during a two year period. Of the 178 infants who were not included in the study, three were omitted because they had permanent congenital hypothyroidism due to thyroid agenesis with an appreciably raised serum thyroid stimulating hormone concentration and a low thyroxine concentration at screening and diagnosis. One hundred and seventy five (45 full term and 130 premature infants) were omitted because they were neither breast nor bottle fed: they were severely ill and received total parenteral nutrition until at least the fifth day of life. None of these 175 infants had a serum thyroid stimulating hormone concentration >50 mU/l at the time of screening for congenital hypothyroidism.

The 4745 infants under study were investigated on the fifth day of life at the time of screening for congenital hypothyroidism. As shown in table 1 they were distributed in several groups on the basis of the

Table 1 Definition of the groups of newborn infants under investigation

	Breast fed	Bottle fed	Total (%)
No iodine overload	2358	728	3086 (65)
Epidural anaesthesia	980	283	1263 (27)
Caesarean section	321	75	396 (8)
Total (%)	3659 (77)	1086 (23)	4745 (100)

type of feeding and the absence or presence of iodine overload: 3659 (77%) of the infants were breast fed and 1086 (23%) were bottle fed; 3086 (65%) were born to mothers with no iodine overload, 1659 (35%) were born to mothers with iodine overload due to the cutaneous application of PVP-I at delivery for epidural anaesthesia or caesarean section. In the former, a cutaneous surface of about 900 cm² was covered by one single application of PVP-I. In the latter, the whole abdominal wall was covered by three applications of PVP-I. The 10% solution of PVP-I used contained 10 mg of iodine/ml.

All the newborn infants were submitted to systematic neonatal screening for congenital hypothyroidism; serum thyroid stimulating hormone concentration was used as the primary screening test. When thyroid stimulating hormone concentration was above 20 mU/l serum thyroxine was measured in a second step from the initial blood spot. The criteria used for recalling an infant under suspicion of congenital hypothyroidism were a serum thyroid stimulating hormone concentration of >50 mU/l or a thyroid stimulating hormone concentration between 20 and 50 mU/l associated with a serum thyroxine concentration of <64 nmol/l.⁶ Further investigation included clinical, biological, and radiological assessments, and when necessary the infants were scanned. Serum thyroid stimulating hormone and thyroxine were measured in duplicate by specific radioimmunoassay: at screening on blood spots dried on filter paper (the sensitivity was 40 mU/l for thyroid stimulating hormone and 13 nmol/l for thyroxine) and at recall on serum (the sensitivity was 0.4 mU/l for thyroid stimulating hormone and 13 nmol/l for thyroxine).⁷

Statistical analyses determined the frequency distribution of serum thyroid stimulating hormone concentrations in the whole infant population under study and compared this distribution in the different groups. The frequency distributions were compared by χ^2 tests.

Results

The frequency distribution of serum thyroid stimulating hormone concentration in the 4745 infants

studied is shown in fig 1. The distribution was asymmetrical and skewed towards low values: 4311 (91%) of the values were <10 mU/l, 388 (8%) were moderately raised between 10 and 50 mU/l, and as many as 46 (1%) of the infants had a serum thyroid stimulating hormone >50 mU/l and were thus recalled. None was recalled on a basis of a thyroid stimulating hormone concentration between 20 and 50 mU/l associated with a thyroxine concentration <64 nmol/l.

The frequency distributions of serum thyroid stimulating hormone concentrations in the different groups of infants considered are shown in fig 2: in the breast fed infants born to mothers treated with PVP-I, there was a clear cut shift of serum thyroid stimulating hormone towards high values.

The recall rate increased from 0.1% in the absence of iodine overload to 3.2% in case of epidural anaesthesia and 2.7% in case of caesarean section. Serum thyroxine concentration at screening and at the time of recall for control examinations was normal in all infants. In the bottle fed infants, there was also a slight shift towards raised thyroid

Fig 1 Frequency distribution of the serum thyroid stimulating hormone concentration (mU/l) on day five in all newborn infants under investigation (n=4745).

Fig 2 Comparison of the frequency distributions of the serum thyroid stimulating hormone concentration (mU/l) on day five in the different groups of newborn infants considered. The numbers on the dotted lines represent the cumulated frequencies of the serum thyroid stimulating hormone concentrations included in the arrows. The levels of significance both in breast and bottle fed infants refer to the comparison with the group with no iodine overload; *= $p<0.05$; **= $p<0.01$.

stimulating hormone concentrations in the iodine contaminated groups. The shift was much less pronounced, however, than in breast fed infants and the recall rate was barely modified.

Discussion

The present work shows that one cutaneous applica-

tion of PVP-I in mothers at the time of delivery results in a shift of neonatal thyroid stimulating hormone towards raised concentrations both in breast fed and bottle fed infants. The shift is much more important in the case of breast feeding, where there is a 25 to 30 fold increase in the recall rate.

The cause of the shift in breast fed infants is

obviously iodine overload. We have previously reported that there was a two and 12 fold increase in the iodine content of breast milk after the use of PVP-I for epidural anaesthesia and caesarean section respectively (table 2).⁴ The shift in bottle fed infants probably results from moderate fetal iodine overload occurring between skin disinfection with PVP-I and delivery because of a transfer of iodine across the placenta.

Chabrolle and Rossier have shown that the application of PVP-I directly on the skin of infants occasionally increases their serum thyroid stimulating hormone concentrations.⁸ Our results indicate that the same phenomenon occurs when PVP-I is used in the mother before delivery.

In our study, all infants with moderately or appreciably raised serum thyroid stimulating hormone concentrations at screening had normal thyroxine at screening and all further investigations were also normal. Consequently, the raised serum thyroid stimulating hormone indicates a very transient state of compensated or subclinical hypothyroidism which, most probably, will not affect the long term development of the infants.⁵⁻⁹ Our study, however, underlines the public health importance of these transient alterations. In the newborn population under study, the recall rate was 1% instead of 0.2% in our screening programme.¹⁰ In addition, there was a clear cut increase in the frequency of moderately raised thyroid stimulating hormone between 10 and 50 mU/l, which also indicates some impairment of thyroid function, although the infants were not recalled.

This high recall rate is detrimental to the screening programme and increases its cost because of the further investigations needed. It also appreciably increases the frequency of so called 'false positives' at screening; this is an unfavourable situation for a screening programme.¹¹ Finally, but of major importance, the high recall rate causes unnecessary psychological stress in many families. Long term effects of this recall on the mother-infant relationship have been well documented; these adverse effects

were present even when the results of the control examinations were normal.¹²

In conclusion, the use of PVP-I in mothers at delivery can result in a mild Wolff-Chaikoff effect in the infant, especially if breast fed. Impairment of thyroid function is transient and probably without major consequences. It unnecessarily increases the recall rate, however, and consequently the cost of the screening and stress on families. Therefore PVP-I is not recommended in obstetrics.

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See letter from Chanoine *et al* in Correspondence column p. 1297.

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Table 2 Iodine content of maternal milk at the fifth postnatal day with and without iodine overload. (Modified from Chanoine *et al*⁴)

	Mean (SD) iodine concentration (µmol/l)
No iodine overload	0.75 (0.05)
Iodine overload after:	
Epidural anaesthesia	1.26 (0.11)
Caesarean section	9.98 (3.31)