Infant feeding, fetal growth and adult thyroid function

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Prolonged breast-feeding in humans is associated with increased low-density lipoprotein cholesterol and higher death rates from ischaemic heart disease in adult life. The reasons for this link are unclear. A possible explanation is that thyroid hormones present in breast milk and absorbed by the sucking infant could, by the process of hormonal imprinting, permanently down-regulate the set point of thyroid homeostasis. Thyroid hormones influence cholesterol metabolism, and could explain the link between infant feeding and the regulation of cholesterol levels in the adult. We therefore investigated whether infant feeding was related to adult thyroid function in 303 women aged 60–71 years who were born in the county of Hertfordshire, UK, where birthweight, the weight at 1 year and the method of infant feeding had been recorded routinely. Free thyroxine (FT_4) concentrations but not free triiodothyronine (FT_3) or thyroid stimulating hormone (TSH) were increased in the women who, as infants, had been breast-fed beyond 1 year of age (p<0.01). In women who were bottle-fed, with or without breast-feeding, serum TSH rose and FT_4 fell with increasing birthweight (p=0.01 and p=0.04, respectively). Although the metabolic significance of these findings is unclear, they suggest that the set point of thyroid function in the adult is determined by fetal growth and infant feeding.

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Recent research has shown that in babies born 70 years ago who were breast-fed and weaned relatively late, a process was established that led to raised serum concentrations of low-density lipoprotein cholesterol and to increased death rates from coronary heart disease in adult life (1). These findings are paralleled by studies in baboons, which show that breast-fed animals weaned on to an atherogenic diet high in cholesterol and saturated fat have higher low-density lipoprotein cholesterol and more atherosclerosis in adult life than animals who were formula-fed before being weaned on to the same atherogenic diet (2).

Differences in the nutrient content of breast milk and formula feeds could account for the differences in later lipid metabolism in the baboons. Breast milk has a higher cholesterol and saturated fat content than formula feeds. However, varying the levels of cholesterol or saturated fat in the formula feeds so as to resemble the amounts found in breast milk did not affect later cholesterol metabolism. This suggests that it was not the nutrient content of breast milk that resulted in the adverse effects on cholesterol levels in the adult (3, 4).

Another possible explanation for the effects of breast-feeding on cholesterol metabolism could be that they are mediated by hormonal programming. Breast milk contains several hormones and growth factors, including thyroid hormones and cortisol (5). There is evidence that some of these hormones are present in sufficient quantity to influence circulating hormone levels in the suckling human neonate and in newborn animals (6, 7). Furthermore, exposure to exogenous hormones, including thyroxine and androgens, in the neonatal period can permanently down-regulate the hypothalamic–pituitary axis (8, 9). Endocrine homeostasis may influence lipid metabolism. Thyroid hormones are implicated in the regulation of plasma lipoproteins and hepatic sterol metabolism (10) and differences in plasma cortisol levels are estimated to account for up to 12% of the variance in plasma low-density lipoprotein cholesterol levels (11).

The present studies were carried out to investigate whether infant feeding affects thyroid function in adult humans. They were based on a group of women born in Hertfordshire, UK, where birthweight, the weight at 1 year and the method of infant feeding was recorded routinely from 1911 onwards. Women rather than men were studied because thyroid disorders are more prevalent among women.

Subjects and methods

In the county of Hertfordshire from 1911 onwards, each birth was notified by the attending midwife and the birthweight recorded. A health visitor saw the child at home periodically throughout infancy and recorded how the baby was fed, using one of three categories: breast-feeding, bottle-feeding or a combination of breast-and bottle-feeding. When the children were 1 year old their weight, whether or not they were weaned, and
how many teeth had erupted were recorded. Weights were measured in pounds (2.2 lb = 1 kg) and as they were often rounded to the nearest half-pound or pound we used the original units. As described previously (1), we traced 514 women who were born in the six districts of East Hertfordshire and still lived there. Of these, 388 agreed to be interviewed and were visited at home by one of four fieldworkers who had not seen the infant data recorded for the women. The women were asked about their medical and social history. After the interview, the women were asked to attend a local clinic to have a blood sample taken; 309 agreed to do so. Free thyroxine (FT4) and free triiodothyronine (FT3) were measured using a solid-phase radioimmunoassay (Diagnostic Products Ltd., Abingdon, UK), and thyrotrophin (TSH) by means of a two-site immunoradiometric assay (Immunodiagnostic systems Ltd., Boldon, Tyne and Wear, UK). The laboratory reference ranges were: FT4, 10–23 pmol/l; FT3, 3–9 pmol/l; TSH, 0.1–3.6 mU/l. The TSH values were transformed logarithmically to normality before analysis and geometric means were computed. Antibodies to the thyroid antigens thyroid peroxidase (TPO) and thyroglobulin (TG) were measured by highly sensitive assays that depend on the direct interaction of labelled TPO or TG with antigen (12). One-way analysis of variance was used to analyse differences between feeding groups.

Results

Adequate sera for analysis were available from 303 of the 309 women who attended the clinic. They were aged 60–71 (mean 64) years. Six (2.0%) of the women were already on thyroxine replacement therapy for spontaneous hypothyroidism. A further 11 (3.6%) were newly diagnosed as being hypothyroid on the basis of a TSH of more than 3.6 mU/l in association with a low FT4 (<10 pmol/l) or a TSH level of more than 10 mU/l. Sixteen of the 17 women with hypothyroidism had detectable TPO antibody and the other had TG antibody.

Of the 303 women, 218 had been breast-fed exclusively, 72 had been both breast- and bottle-fed and 13 had been bottle-fed exclusively: 63 of the 218 women who had been breast-fed exclusively were still receiving breast milk at 1 year. Analysis of thyroid function according to the method of feeding (Fig. 1) showed that the mean FT3 concentration was 16.2 pmol/l in the breast-fed women who were still receiving breast milk at 1 year, 15.0 pmol/l in women who had been breast-fed exclusively but weaned before 1 year of age, 14.8 pmol/l in the women who had been breast- and bottle-fed and 14.0 pmol/l in the women who had been bottle-fed exclusively. Analysis of variance showed that the FT4 levels differed significantly between these feeding groups (F = 3.16, 3 df, p = 0.025). In addition, the mean FT4 concentration in the group who received prolonged breast-feeding was significantly higher than in the other groups combined (p < 0.01). There were, however, no significant differences between groups in either free T3 or TSH levels.

Because the feeding groups differed in their birthweights and infant weights, we examined the effects of birthweight and infant weight on thyroid function. Figure 2a which is based on all 303 women, shows that the serum TSH concentration rose with increasing birthweight (p = 0.025). There was also a weak trend to a falling FT4 concentration (p = 0.34) with increasing birthweight but no discernible relationship with FT3. The FT4, FT3 and TSH concentrations were unrelated to the weight at 1 year of age. A multiple regression analysing the simultaneous relationships of birthweight and weight at 1 year with TSH concentration showed
that only the correlation between TSH and birthweight remained statistically significant (p = 0.03). Although the relationship between TSH and birthweight was evident in the total population of women, it was confined to the 85 who were bottle-fed with or without breast-feeding. In these women, the TSH concentration rose (p = 0.01) and the FT₄ concentration fell (p = 0.04) with increasing birthweight (Fig. 2b) but they were not related to weight at 1 year. Women who received breast milk exclusively showed no trends in either FT₄ or TSH with birthweight (p = 0.62 and 0.63 respectively). Re-analysis of the data after exclusion of the women with hypothyroidism showed that the effects of feeding or birthweight on thyroid function were unaffected by the omission of these women with overt thyroid disease.

**Discussion**

We have studied thyroid function in a group of late middle-aged women whose birthweight, infant growth and method of feeding had been recorded in detail. The FT₄ concentration, but not the levels of the other thyroid hormones, increased with prolonged breast-feeding. In women who were bottle-fed with or without breast-feeding, serum TSH rose and FT₄ fell with increasing birthweight.

The explanation for the high FT₄ concentration in the women who were breast-fed and weaned relatively late is not clear. Babies in Hertfordshire who were not weaned at 1 year would have had prolonged exposure to maternal hormones in milk. Although breast milk
contains thyroid hormones, it is not certain to what extent these affect circulating thyroid hormone levels in the infant. Experimental studies in baboons suggest that breast-fed infants have lower T4 and FT3 concentrations than formula-fed infants at 14 weeks of age (DS Lewis, CA McMahan and GE Mott, unpubl. observations). Effects of breast feeding on thyroid function in the human infant have been reported in some studies (13, 14), but not others (15). Exposure to exogenous thyroid hormone in the neonatal period would be expected to cause a down-regulation of thyroid function in adult life (8). The current findings are, therefore, the reverse of what might be expected. They could not be explained by a relationship between breast-feeding and autoimmune thyroid disease because the prevalence of thyroid autoantibody was similar in the different feeding groups (data not shown). It is also unlikely that the differences in thyroid function between breast- and bottle-fed subjects are the long-term consequences of neonatal iodine deficiency resulting from a low iodine content of either the breast or bottle milk, because a national survey of goitre in schoolchildren indicated that iodine deficiency was not prevalent in Hertfordshire during the 1920s (16). We do not know why some mothers chose to bottle-feed their infants or what was contained in the bottle feeds because this was not specified in the Hertfordshire records. Bottle feeds available 70 years ago included patent preparations of dried cows' milk, unmodified cows' milk, diluted condensed milk and patent feeds made from wheat-flour or arrowroot (1). Modern baby-milk formulas differ from these foods. Consequently, it is difficult to assess whether the same differences would be found between breast- and bottle-fed babies today.

Serum TSH levels increased with increasing birth-weight (Fig. 1). Although this correlation was evident in the total population of women, for reasons that are unclear, it was confined to the group of women who had been bottle-fed with or without breast-feeding. In this group, TSH concentrations rose and FT4 concentrations fell with increasing birthweight but not with weight at 1 year of age, suggesting that an impairment of fetal rather than infant growth influenced thyroid function. These findings based on thyroid function in adults contrast with the data from several observations in both human and animal neonates that fetal growth retardation is associated with lower FT4 and FT3 concentrations (17–20). If our data are confirmed, they would suggest that the relationships between birthweight and thyroid function are different in neonates and adults.

Our findings suggest that there are lifelong, between-individual differences in the set point of thyroid function that are determined by early growth and feeding. The differences in the set point explain some of the between-individual variation in the plasma concentrations of thyroid hormones. These variations are substantial and much greater than the within-individual variations, which are controlled within a narrow range by the pituitary thyrotroph. Although the differences that we report here are within the normal range of thyroid function, minor alterations in plasma thyroxine levels have been shown to affect metabolism and enzyme induction (21–23). Whether these differences in thyroid function could have metabolic consequences in the adult is uncertain.

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References


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