European Journal of Clinical Nutrition (1998) 52, 351–355

http://www.stockton-press.co.uk/ejcn

Iodine status, thyroid function and pregnancy: study of Swedish and Sudanese women

B Elnagar[1], A Eltom[2], L Wide[3], M Gebre-Medhin[2] and FA Karlsson[1]

[1]*Department of Medicine,* [2]*Department of Paediatrics, and* [3]*Department of Clinical Chemistry, University Hospital, Uppsala, Sweden*

Objective: To examine and compare the effects of pregnancy on the thyroid hormone homeostasis in two different populations with variable iodine supply.
Design: A longitudinal prospective cohort study throughout pregnancy involving Swedish and Sudanese pregnant women.
Setting: The subjects were enrolled consecutively during their antenatal follow-up at health centres at Nyby in Uppsala, Sweden and Omdurman in Sudan.
Subjects: Fifty-one apparently healthy women from Uppsala, Sweden and twenty-eight pregnant women from Omdurman, Sudan were recruited during pregnancy. The mean age and weight of the Swedish women at the beginning of pregnancy were 29.9 ± 5.4 y and 66.3 ± 12.9 kg respectively. The corresponding figures for the Sudanese women were 28.0 ± 4.9 y and 64.8 ± 9.4 kg respectively.
Methods: Blood samples were drawn on four occasions from the Swedish group at 11–13, 24, 32, and 38 weeks of pregnancy, and on three occasions from the Sudanese group at 10–12, 20–24, and 36–39 weeks. Twenty-four hour urine samples were collected from the same subjects and on the same occasions as blood sampling. The urine samples were kept in a refrigerator until the volumes were measured, after which 20 mL aliquots were taken and kept frozen until analysed.
Main outcome measures: Twenty-four hour urinary iodine output, TSH, FT4 and T3.
Results: The 24 h urinary iodine output at the different times during gestation were higher among the Swedish women, with mean values (95% confidence interval) of 1.40 (1.19–1.61), 1.33 (1.14–1.51), 1.45 (1.06–1.84) and 1.14 (0.88–1.39) μmol/d, than among the Sudanese cohort, with corresponding values of 0.49 (0.27–0.72), 0.29 (0.19–0.39), 0.56 (0.25–0.88) μmol/d. No significant changes in daily urinary iodine loss were observed in the two groups with progression of pregnancy. However, in the Swedish women the mean free T4 concentration fell from 11.81 pmol/l at the beginning of pregnancy to 8.82 pmol/l and the mean TSH rose from 1.11–1.95 mU/l between the beginning and end of pregnancy. Such changes were not detected among the Sudanese women, who had significantly lower mean TSH values than the Swedish women in weeks 36–39 of pregnancy ($P < 0.02$), and significantly higher FT4 values than the Swedish women both in weeks 20–24 and in weeks 36–39 ($P < 0.005$ and $P < 0.001$) respectively.
Conclusions: The study suggests that determination of urinary iodine alone gives inadequate information about the capacity of an individual to utilize an available iodine supply and it also shows the existence of different patterns of thyroid response during pregnancy. The history of iodine availability prior to and during pregnancy seems to be an important determinant of the mechanism of thyroid gland response to ensure the extra iodine needed by the growing fetus.
Sponsorship: Financial support for this work was provided by the Swedish Medical Research Council and InDevelop AB, Uppsala University.
Descriptors: iodine; thyroid function; pregnancy; Sweden; Sudan

Introduction

Thyroid hormones are critical for early development in fetal life (Hetzel & Hay, 1979; Paroah *et al*, 1971; Thilly *et al*, 1978). These hormones reach the fetus through placental transfer, as evidenced by the near-normal T4 levels in cord blood of children with congenital inability to synthesize thyroid hormone (Vulsma *et al*, 1989). The fetal thyroid is capable of producing hormones from 11 weeks of gestation (Thorpe-Beeston *et al*, 1991).

Marked changes in the maternal serum levels of thyroid hormones take place during pregnancy. Human chorionic gonadotrophin (HCG) produced by the placenta has a weak thyroid stimulatory effect and the rapid rise in HCG in early pregnancy is often accompanied by some alterations in serum thyroid hormone and thyrotropin (TSH) levels (Braunstein & Herhman, 1976; Yoshkawa *et al*, 1989; Pekonen *et al*, 1988). Also, the marked increase in the synthesis of thyroxine-binding globulin resulting from the increasing oestrogen levels affects the thyroid hormone homeostasis by expanding the thyroid hormone binding compartment (Glinoer *et al*, 1990; Ericsson & Threll, 1986; Amino *et al*, 1981). Further the extra need of iodine imposed by pregnancy can serve to unmask a mild iodine deficiency as reflected in a relative hypothyroxinaemia and increasing maternal TSH levels (Glinoer *et al*, 1990).

No detailed study of changes in thyroid hormone levels has been carried out on pregnant women in Sweden in recent years, a country where iodine supplementation of

Correspondence: Dr M Gebre-Medhin, Department of Paediatrics, Unit for International Child Health—ICH, University Hospital, S-751 85 Uppsala, Sweden.
Received 16 April 1997; revised 21 January 1998; accepted 31 January 1998

salt was introduced in the 1930s and the iodine intake is assumed to be sufficient. The high frequency of goitre that was seen in certain areas of Sweden prior to salt iodisation has virtually disappeared (Sjöberg & Sundlöf, 1971). In 1933 the Swedish health authority recommended that 10 mg of potassium iodide should be added to each kg of table salt. This recommendation was increased to 50 mg per kg in 1966. Today, the total intake of iodine per day is considered to be approximately 1.58 μmol, with a large part of this intake derived from milk and dairy products. Only limited systematic studies of iodine intake and excretion, however, have been conducted in modern times. The urinary iodine excretion was examined in 1974 in a study of 102 adults in a community in Eastern Sweden. The mean daily urinary iodine excretion among 38 males was 1.01 μmol and among females it was 0.75 μmol. Thirty percent of the women had values below 0.55 μmol while less than 10% of the males had levels below this value (Järnerot & Karlberg, 1974; Gustafsson *et al*, 1977; Sjöberg, 1972; Karlsson, 1993).

In contrast, iodine deficiency is still prevalent in many parts of Sudan and the goitre frequencies are high (Eltom, 1984). Various measures to provide iodine have been undertaken. Iodine-containing capsules (Elnagar *et al*, 1995), iodine fortification of sugar (Eltom *et al*, 1995) and iodination of water (Elnagar *et al*, 1997) have been tried in defined areas of the country. In Khartoum, the goitre frequency among school children and the low urinary iodine output have indicated the presence of moderate iodine deficiency (Eltom, 1984).

The purpose of the present investigation was to examine and compare the effect of pregnancy on thyroid hormone homeostasis in Swedish and Sudanese women, by measurements of urinary iodine concentrations, thyroid hormone levels and TSH.

Subjects and methods

The Swedish women

Fifty-one apparently healthy pregnant women from Uppsala, Sweden were enrolled at Nyby Health Centre, Uppsala, between July 1993 and March 1995. At their initial presentation at the Health Centre, the women gave their informed consent to take part in the study, which had first been approved by the Ethical Committee of Uppsala University, Sweden. The mean age and weight of the women at the beginning of pregnancy were 29.9 ± 5.4 y (range 22–40) and 66.3 ± 12.9 kg (range 53–101), respectively. The women were recruited during the 11th and 13th weeks of pregnancy.

Nineteen subjects did not complete the study for personal reasons ($n = 8$) or because of miscarriage ($n = 3$), or change of residence ($n = 8$). The analysis is thus based on 32 subjects who completed the sampling. Although no systematic dietary survey was carried out among the women, they were all known to consume ordinary Swedish food. In Sweden both iodinated (50 ppm) and non-iodinated salt is available.

The Sudanese women

Twenty-eight pregnant women from Omdurman, an urban area in Sudan were enrolled between September 1993 and March 1995. At their initial presentation at the Health Centres, the subjects gave their informed consent. The women were apparently healthy but lived in an area considered to represent mild to moderate iodine deficiency. However, none of those who consented to take part in the study had goitre. Their mean age and weight were 28.0 ± 4.9 y (range 20–35) and 64.8 ± 9.4 kg (range 45–84), respectively. The women were recruited during the 10th and 12th weeks of pregnancy. Three subjects did not complete the study because of miscarriage ($n = 2$), or because they were not available at the time of sampling ($n = 1$). The analysis is thus based on 25 women, who completed the study. Iodination of salt is not yet established in Sudan.

Sample collections

Venous blood samples were collected from the Swedish and the Sudanese pregnant women at routine check-up visits to the antenatal clinics. Blood samples were drawn on four occasions from the Swedish group at 11–13, 24, 32, and 38 weeks of pregnancy, and on three occasions from the Sudanese group at 10–12, 20–24, and 36–39 weeks. Blood samples were taken from the cubital veins into acid-resined vacutainers. Blood was allowed to coagulate at room temperature, before the sera were separated by centrifugation and kept at −20°C. Twenty-four-hour urine samples were collected from the same subjects and on the same occasion as blood sampling. The urine samples were kept in a refrigerator until the volumes were measured, after which 20 mL aliquots were taken and kept frozen until analysed. The deep-frozen samples from Sudan were transported by flight from Khartoum to Stockholm. On arrival the samples were kept frozen in a central store along with the Swedish samples at −20°C.

Analytical methods

Urine iodine concentrations were determined in both the Swedish and the Sudanese samples in duplicate by one and the same experienced laboratory technician in Uppsala, Sweden, by a modified Sandell–Kolthoff method (Sandell & Kolthoff, 1935), using a Hitachi U-2000 spectrophotometer (Tokyo, Japan). The coefficient of variation for duplicate standard samples was less than 3%. The within-series coefficient of variation was less than 8% and the between-series variation was less than 10%. The conversion factor from SI units is 1 μmol/L = 12.7 μg/dL. Serum triiodothyronine (T3) and free thyroxine (FT4) were measured with solid phase time-resolved fluoroimmunoassays (TR-FIA) (Delfia™, Wallac Oy, Turku, Finland). The reference range in Swedish adult non-pregnant subjects for T3 is 1.2–2.8 nmol/L and for FT4 9–21 pmol/L. TSH was measured with a sandwich TR-FIA (Delfia™ hTSH Ultra, Wallac Oy, Turku, Finland). The reference range in Swedish adult non-pregnant subjects is 0.3–4.0 mU/L. For eleven Sudanese samples we were unable to measure T3 and TSH values. In three of these we were also unable to measure FT4, because of lack of serum for these assays.

Statistical analysis

Basic statistical methods were used to reveal significant differences between the groups, as well as over time, in the variables studied. Within the groups *t*-tests for dependent samples (paired *t*-test) were performed for time 1 (10–13 weeks) versus each of the successive times. Between the groups (countries) *t*-tests for independent samples (unpaired *t*-test) were used for all variables at all comparable times. Further analysis of variance (ANOVA) on each parameter was used and showed differences between the countries for urine volume, UIC and FT4 and differences over time for TSH and FT4.

Results

The 24 h urine volumes (mean ± s.d.) on the different occasions ranged from 1.80 ± 0.64 to 1.92 ± 0.78 L in the Swedish women and from 1.08 ± 0.23 to 1.19 ± 0.21 L in the Sudanese group. The Swedish women produced higher mean 24 h urine volumes than the Sudanese women on all sampling occasions ($P < 0.001$; $P < 0.001$; and $P < 0.001$). The changes in the 24 h urinary iodine loss in relation to weeks of pregnancy in both the Swedish and the Sudanese women are illustrated in Figure 1. The mean 24 h urinary iodine loss for the Swedish subjects during follow-up ranged between 1.14 and 1.40 μmol/d, and for the Sudanese subjects between 0.29 and 0.56 μmol/d. Both the Swedish and the Sudanese subjects showed a relatively stable 24 h urinary iodine loss throughout pregnancy. However, the Swedish women had significantly higher 24 h urinary iodine loss than the Sudanese women in all sampling occasions ($P < 0.001$; $P < 0.001$; and $P < 0.001$).

The mean urinary iodine concentrations (UIC) values did not change with progression of pregnancy were found in either the Swedish or the Sudanese women. However, the Swedish women had significantly higher UIC than the Sudanese women at all stages of pregnancy ($P < 0.001$, $P < 0.001$ and $P < 0.001$). No Swedish subjects had UIC below 0.16 μmol/L (According to the WHO classification (WHO/UNICEF/ICCIDD Indicators for Assessing Iodine Deficiency Disorders IDD). Document WHO/NUT/94.6), the percentages of subjects with urinary iodine concentrations of less than 0.39 and 0.79 μmol/L (namely 5 and 10 μg/dL) should be less than 20% and 50%, respectively, for the population to be regarded as iodine sufficient. In earlier classifications 2 μg/dL (namely 0.16 μmol/L) was also employed as a discriminatory level), at any time during pregnancy, whereas 25%, 30% and 9% of the Sudanese women had UIC values below 0.16 μmol/L on the three measurement occasions, respectively (Table 1).

The proportion of Swedish women with UIC less than 0.79 μmol/L increased from 60% in weeks 11–13 to 71% in week 38 of pregnancy, and that of Sudanese women from 86% in weeks 10–12 to 96% in 20–24 and 91% in weeks 36–39.

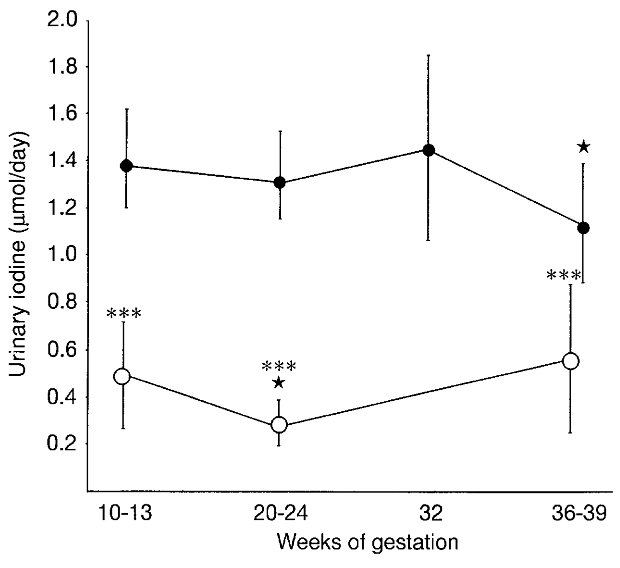

Figure 1 Changes in 24 h urinary iodine output (mean and its 95% confidence interval) in relation to weeks of pregnancy in the Swedish (●) and Sudanese (○) women, measured in 32 and 25 women, respectively. ★, $P < 0.05$, compared to values at 10–13 weeks. (***), $P < 0.001$, compared to the Swedish group.

Table 1 Percentage of subjects with urinary iodine concentrations (UIC) of less than 0.16, 0.39 and 0.79 μmol/L, respectively, during the study period

		Weeks of gestation			
	UIC (μmol/L)	*10–13*	*20–24*	*32*	*36–39*
Sweden	< 0.79	60	61	69	71
	< 0.39	10	8	8	23
	< 0.16	0	0	0	0
Sudan	< 0.79	86	96	—	91
	< 0.39	68	87	—	59
	< 0.16	25	30	—	9

Table 2 Percentage of subjects with serum free thyroxine (FT4) within and outside the reference range during the study period

		Weeks of gestation			
	FT4 (pmol/L)	*10–13*	*20–24*	*32*	*36–39*
Sweden	> 21	0	0	0	0
	9–21	98	42	38	45
	< 9	2	58	62	55
Sudan	> 21	0	0	—	0
	9–21	77	60	—	86
	< 9	23	40	—	14

There was a significant decrease in mean serum FT4 in the Swedish population between weeks 11–13 and all other sampling occasions ($P < 0.001$; $P < 0.001$; and $P < 0.001$). The percentages of subjects with FT4 values below the reference range for non-pregnant individuals increased throughout the follow-up from 2% in week 11–13 to 58% in week 24, 62% in week 32 and 55% in week 38 (Table 2). No subject showed FT4 values above the reference range at any time during pregnancy (Figure 2).

In contrast to the Swedish values, the Sudanese mean FT4 values showed no significant changes during pregnancy. However, the number of subjects with FT4 values below the reference range varied from 23% in week 10–12 to 40% in week 20–24 and 14% in week 36–39. No subject showed FT4 values above the reference range. The Sudanese women had significantly higher FT4 values than the Swedish women both in weeks 20–24 and in weeks 36–39 ($P < 0.005$ and $P < 0.001$).

The mean TSH values in the Swedish subjects increased

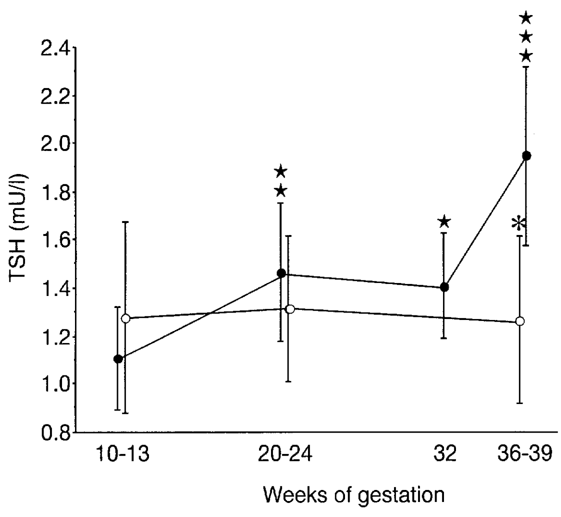

Figure 2 Changes in serum thyroptropin (TSH; mean and its 95% confidence interval) in relation to weeks of pregnancy in the Swedish (●) and Sundanese (○) women. ★ $P < 0.007$, ★★ $P < 0.004$, ★★★ $P < 0.001$, compared to values at 10–13 weeks (*), $P < 0.02$, compared to the Swedish group.

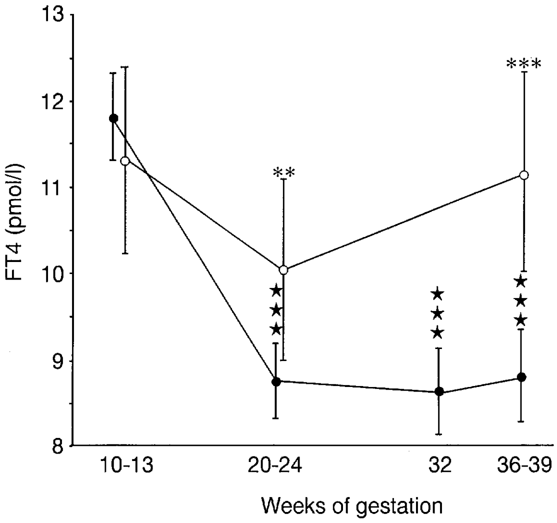

Figure 3 Changes in serum free thyroxine (FT4; mean and its 95% confidence interval) in relation to weeks of pregnancy in the Swedish (●) and Sudanese (○) women. ★★★ $P < 0.001$, compared to values at 10–13 weeks. (**) $P < 0.005$, (***) $P < 0.001$ compared to the Swedish group.

steadily throughout pregnancy (Figure 3) and this increase was statistically significant on all occasions in relation to the weeks 11–13 mean value ($P < 0.004$; $P < 0.007$ and $P < 0.001$). No subject had a TSH value above the reference range at 11–13 weeks, while 3%, 0% and 7% had values above this range in weeks 24, 32 and 38, respectively. The percentages of subjects with TSH values of more than 4 mU/L during the study period are shown in Table 3. In contrast to the values in Swedish women, the Sudanese values displayed a relatively stable pattern throughout pregnancy. No Sudanese subject had a TSH value above the reference range. The Swedish women had significantly higher mean TSH values than the Sudanese women in weeks 36–39 of pregnancy ($P < 0.02$).

The mean value for T3 at the beginning of pregnancy in the Swedish women was 2.49 ± 0.66 nmol/L and the mean T3 values later in pregnancy remained constant at around 2.70 nmol/L. The Swedish subjects showed a stable pattern and there were no significant differences between the values on the different sampling occasions. The mean T3 value at the beginning of pregnancy in the Sudanese women was 2.75 ± 0.98 nmol/L and the values later in pregnancy were 2.87 ± 0.76 and 2.57 ± 0.43 nmol/L, respectively. There were no significant differences between Swedish and Sudanese groups.

Discussion

The urinary iodine excretion pattern observed in the present study illustrates that the two groups of women differed in their iodine status. The iodine outputs were lower throughout pregnancy among the Sudanese women than among the Swedish women, in accordance with previous reports of an increased goitre frequency among people living in Khartoum. In this present study the Swedish pregnant women had a somewhat higher urinary iodine output than Swedish non-pregnant adult individuals in a previous study (Sjöberg, 1972). This could be either due to higher iodine intake or due to the effects of pregnancy in these women. The Sudanese women consistently produced lower urinary volumes than their Swedish counterparts, presumably as a result of a lower water intake and a higher degree of perspiration. Twenty-four-hour urine volumes are admittedly difficult to obtain in a reliable and reproducible way. However, the observed distribution of volumes in the two groups contradicts a possibility of significant methodological differences in urine sampling in Sweden and Sudan. Besides, the differences between the Swedish and the Sudanese women is maintained irrespective of whether urinary iodine concentration or 24 h urinary iodine loss are used in the comparison. The loss of iodine through extra-renal routes is reportedly minor. Thus, the concentration of iodine in sweat has been estimated at 0.29 ± 0.04 μmol/L (Mao *et al*, 1990), and about 5% of the body's iodine loss occurs in the stools (Choufoer *et al*, 1963). We therefore consider it likely that the Sudanese women had a lower iodine intake than the Swedish women. The differences between the two groups in loss of total iodine through sweat or faeces could only be small.

In many African countries with notable iodine deficiency, subjects may occasionally encounter iodine in their diet. The thyroidal economy is thus subjected to both iodine restriction and occasional iodine supply in a reproducible manner. Thus, such an irregular and sporadic iodine supply is unlikely to be reflected in iodine excretion levels. The little iodine available will mainly have been stored in the thyroid gland because of avid thyroidal iodine uptake. However, to the best of our knowledge no iodine supplementation of any kind was ongoing in the study area.

Several studies of thyroid hormone changes as well as of changes in thyroid volume during pregnancy have been carried out in Europe in recent years. In a series of illustrative investigations in Belgium (Glinoer *et al*, 1990; Glinoer *et al*, 1995), it was shown that the FT4 levels tend to decrease and the TSH levels to increase, but remain within the reference ranges of non-pregnant individuals. Several reports indicate an increase in thyroid volume during pregnancy (Glinoer *et al*, 1990; Rasmussen *et al*, 1989; Glinoer *et al*, 1995). Precise determinations of thyroid volume need thyroid ultrasonography. For practical reasons we were unable to monitor the thyroid volume in the present study. However, as stated above under Subjects, none of the Sudanese women who took part in the study had visible or palpable goiter. It is evident that we have, unknowingly selected women with a particularly efficient thyroidal machinery that is capable of handling available iodine in a manner that is different from the case of the average woman. This fact must be kept in mind when interpreting our data. Such extremely efficient thyroid glands are some of the explanations forwarded regarding why some subjects residing in severely iodine deficient areas do not develop goiter.

We found an inverse relationship between TSH and FT4 values in the Swedish group. The mean free T4 levels fell from mid-pregnancy onwards, and the mean TSH levels rose. These changes confirm earlier reports indicating that pregnancy is associated with a decrease in FT4 and an increase in TSH among mildly iodine-deficient women (Glinoer *et al*, 1995), and that pregnancy unmasks relative iodine-deficiency. The Sudanese women did not show such

Table 3 Percentage of subjects with serum thyrotropin (TSH) within and outside the reference range

		Weeks of gestation			
	TSH (mU/L)	*10–13*	*20–24*	*32*	*36–39*
Sweden	> 4.0	0	3	0	7
	0.3–4.0	88	97	100	93
	< 0.3	12	0	0	0
Sudan	> 4.0	0	0	—	0
	0.3–4.0	89	100	—	100
	< 0.3	11	0	—	0

changes, probably because of thyroid gland adaptation through an increased volume and an enhanced capacity to absorb iodine by the thyroid, gut or kidneys or to mobilise stores. The response among the Sudanese women confirms the pattern of changes observed in moderate iodine deficiency during pregnancy (Silva & Silva, 1981). Although the mean urinary iodine output in the Swedish group was significantly higher than in the Sudanese group, the Swedish women, on the average, had lower FT4 levels than the Sudanese group in weeks 20–24 and 36–39. Furthermore, the mean TSH value in weeks 36–39 was significantly higher in the Swedish women than in the Sudanese.

The effects of administration of iodine to pregnant women have been studied in a number of iodine-deficient areas (Glinoer *et al*, 1995; Romano *et al*, 1991; Pederson *et al*, 1993). In general such iodine supply leads to stabilisation of serum TSH, and a significant reduction in the increase in thyroid size, while no marked change in FT4 is produced. Administration of iodine combined with L-thyroxine (Glinoer *et al*, 1995) has been found to improve all thyroid function parameters. Glinoer (Glinoer *et al*, 1995) have suggested that goitre in pregnancy without iodine deficiency should be treated with L-thyroxine, and goitre in the presence of iodine deficiency with iodine supplementation alone. A question may be raised concerning the need for supplmentation of pregnant women living in an area with mild iodine deficiency: Should thyroxine or iodine only, or iodine combined with thyroxine, be given? The alterations in thyroid-related hormones and urinary iodine output observed among the Swedish group might raise a question of iodine supplementation. However, further studies involving a larger sample on thyroid function based on biochemical markers such as T3/T4 ratios, serum thyroglobulin as well as changes in thyroid volume on thyroid function during pregnancy are needed in both Sweden and Sudan. Such studies could also investigate the effects of iodine supply on these populations as well as their newborns. The history of iodine availability prior to and during pregnancy seems to be an important determinant of the mechanism of thyroid gland response to ensure the extra iodine needed by the growing fetus. Therefore, the study of the effects of correction of mild or moderate iodine deficiency on the overall thyroid function during pregnancy would be of particular interest.

Conclusions

Our data suggests that determination of urinary iodine alone gives inadequate information about the capacity of an individual to utilize an available iodine supply. This study also shows the existence of different patterns of thyroid response during pregnancy.

Acknowledgements—Financial support for this work was provided by InDevelop AB, Uppsala University, and the Medical Research Council. We wish to thank Gunilla Sparell for excellent technical assistance and Göran Granath for review of the statistical material. The help of the staff at Nyby Health Centre in Uppsala is gratefully acknowledged.

References

Amino N, Yabu Y, Miki T, Morimoto S, Kumahara Y, Mori H, Iwatani Y, Nishi K, Nakatani K & Miyai K (1981): Serum ratio of triiodothyronine to thyroxine, and thyroxine-binding globulin and calcitonin concentrations in Graves' disease and destruction-induced thyrotoxicosis. *J. Clin. Endocrinol. Metab.* **53**, 113–116.

Braunstein JG & Hershman JM (1976): Comparison of serum pituitary thyrotropin and chorionic gonadotropin concentrations throughout pregnancy. *J. Clin. Endocrinol. Metab.* **42**, 1123–1126.

Choufoer JC, Rhijn M van, Kassenaar AA & Querido A (1963): Endemic goiter in Western New Guinea: iodine metabolism in goitrous and nongoitrous subjects. *J. Clin. Endocr.* **23**, 1203–1217.

Crooks J, Tulloch MI, Turnbull AC, Davidson D, Skulason T & Snaedal G (1967): Comparative incidence of goiter in pregnancy in Iceland and Scotland. *Lancet* **2**, 625–627.

Elnagar B, Eltom M, Karlsson FA & Gebre-Medhin M (1997): Control of iodine deficiency using iodination of water in a goiter endemic area. *Int. J. Food Sci. Nutr.* **4**(2), 119–127.

Elnagar B, Eltom M, Karlsson FA, Ermans AM, Gebre-Medhin M & Bourdoux PP (1995): The effect of different doses of oral iodised oil on goitre size, urinary iodine and thyroid related hormones. *J. Clin. Endocrinol. Metab.* **80**, 891–897.

Eltom M, Elnagar B, Karlsson FA, Thi H, Bourdoux P & Gebre-Medhin M (1995): The use of sugar as a vehicle for iodine fortification in endemic iodine deficiency. *Int. J. Food Sci. Nutr.* **46**, 281–289.

Eltom M (1984): Endemic goiter in the Sudan. Thesis. ACTA Universitatis Uppsaliensis, Uppsala 507.

Ericsson UB & Thorell JI (1986): A prospective critical evaluation of in vitro thyroid function tests. *Acta. Med. Scand.* **220**, 47–56.

Glinoer D, De Nayer P, Bourdoux P, Lemone M, Robyn C, Steirteghem AV, Kinthaert J & Lejeune B (1990): Regulation of maternal thyroid during pregnancy. *J. Clin. Endocrinol. Metab.* **71**, 276–285.

Glinoer D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grun JP, Kinthaert J & Lejeune B (1995): A randomized trial for the treatment of mild iodine deficiency during pregnancy: Maternal and neonatal effects. *J. Clin. Endocrinol. Metab.* **80**,258–269.

Gustfsson R, Sjöberg K-H & Östling G (1977): Jod och koksalt in urin hos ort sbefolkningen och anställda vid Oskarshamns kärnkraftverk. (Iodine and sodium chloride in the urine of the local population and employees at the Ostershamn nuclear power station.) *Läkartidningen* **74**, 3326–3328. In Swedish.

Hetzel BS & Hay ID (1979): Thyroid function, iodine nutrition and fetal brain development. *Clin. Endocrinol.* **11**, 445–460.

Järnerot G & Karlberg B (1974): Jodbrist-alltjämt en realitet? (iodine deficiency—still a reality?) *Läkartidningen* **71**, 1019–1021. In Swedish.

Karlsson FA (1993): The state of iodine nutrition in Sweden. S301-301. In: *Iodine Deficiency in Europe. A Continuing Concern*, eds F Delange, JT Dunn & D Glinoer. NATO ASI series A. Life sciences, New York: Plenum Press.

Mao IF, Ko YC & Chen ML (1990): The stability of iodine in human sweat. *Japan J. Physiol.* **40**, 693–700.

Pederson KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Larsen KR, Eriksen GM & Johannesen PL (1993): Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. *J. Clin. Endocrinol. Metab.* **77**, 1078–1083.

Pekonen F, Alfthan H, Stenman UH & Ylikorkala O (1988): Human chorionic gonadotropin (hCG) and thyroid function in early human pregnancy: circadian variation and evidence for intrinsic thyrotropic activity of hCG. *J. Clin. Endocrinol. Metab.* **66**, 853–856.

Pharoah POD, Buttifield IH & Hetzel BS (1971): Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* **1**, 308–810.

Rasmussen NG, Hornnes PJ, Hegedus L, Feldt & Rasmussen U (1989): Serum thyroglobulin during the menstrual cycle, during pregnancy, and postpartum. *Acta. Endocrinol.* (*Copenh*). **121**, 168–173.

Romano R, Jannini EA, Pepe M, *et al* (1991): The effects of iodoprophylaxis on thyroid size during pregnancy. *Am. J. Obstet. Gynecol.* **164**, 482–485.

Sandell EB & Kolthoff IM (1935): Microdetermination of iodine by a catalytic method. *Mikrochem. Acta.* 232–235.

Silva JE & Silva S (1981): Interrelationships among serum thyroxine, triiodothyronine, reverse triiodothyronine, and thyroid stimulating hormone in iodine deficient pregnant women and their offspring: effects of iodine supplementation. *J. Clin. Endocrinol. Metab.* **52**, 671–677.

Sjöberg K-H (1972): Strumasjukdomarnas profylax och behandling. (Prophylaxis and treatment of goitre diseases.) Nora Boktryckeri AB. Doctoral Dissertation Uppsala. In Swedish.

Sjöberg K-H & Sundlöf G (1971): Strumasjukdomen före och efter jodprofylaxen. *Läkartidningen* **68**, 980–984. In Swedish.

Thilly C, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H & Ermans A (1978): Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *J. Clin. Endocrinol. Metab.* **47**, 354–360.

Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J & McGregor AM (1991): Maturation of the secretion of thyroid hormone and thyroid stimulating hormone in the fetus. *N. Engl. J. Med.* **324**, 532–535.

Vulsma T, Gons MH & de Vijlder JJ (1989): Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to total organification defect or thyroid agenesis. *N. Eng. J. Med.* **321**, 13.

Yoshikawa N, Nishikawa M, Horimoto M, Yoshimura M, Sawaragi S, Horikoshi Y, Sawaragi S, Horikoshi Y, Sawaragi I & Inada M (1989): Thyroid-stimulating activity in sera of normal pregnancy women. *J. Clin. Endocrinol. Metab.* **69**: 891–895.