IMPACT OF IODINE DEFICIENCY ON THYROID FUNCTION IN PREGNANT AFRICAN WOMEN - A POSSIBLE FACTOR IN THE GENESIS OF 'SMALL FOR DATES' BABIES

Santosh C. Das¹, Uche P. Isichei², Aminu Z. Mohammed³, Abraham A. Otokwula² and Abiodun Emokpae¹

1 Department of Chemical Pathology, 3. Department of Pathology, Aminu Kano Teaching Hospital, Kano, Nigeria

2 Department of Chemical Pathology, University of Jos, Jos, Nigeria

ABSTRACT

The effect of iodine deficiency (ID) on thyroid function in African women during pregnancy and postnatal period was examined, for which very limited information is available. Serum T_4 , T_3 , TSH, TBG, thyroxine binding capacity (TBK), free thyroxine index ($FT_4I = T_4/TBK$) and T_4/TBG were determined by ELISA technique in 32 pregnant women (resident of Plateau state, Nigeria - an ID zone) through pregnancy upto term delivery, and in 5 women up to 6 weeks post delivery. Urinary iodide level was measured at delivery to determine the degree of iodine deficiency. Results were matched with a non pregnant control comprising 44 subjects. 5555 birth weights (BW) of term babies in the region were analysed to determine the prevalence of 'small for dates' (SFD) babies in the population. Results show that the level of serum FT_4I was elevated very significantly at late gestation ($P < .001$) but the women were not hyperthyroid, suggesting a marked disturbance in binding of T_4 with TBG during pregnancy. Five women with SFD babies were found in 'compensated hypothyroid state' and showed a significant depression ($p < .01$) in serum T_4/TBG , T_4 , FT_4I and T_3 levels to a low normal range, with a concurrent significant rise ($p < .001$) in TSH level (above normal range) throughout pregnancy. Incidence of SFD babies was higher ($p < .001$) in ID zone (Bassa 15.2%) compared to control zone (Jos 9.8%). It is concluded that a state of maternal 'subclinical (compensated) hypothyroidism' during pregnancy possibly plays an important role in the aetiopathogenesis of SFD babies in Africans. A normal reference range for thyroid parameters at various stages of pregnancy in healthy African women is established for the first time.

KEY WORDS

Africans, Iodine deficiency, Pregnancy, Thyroid function.

INTRODUCTION

In normal human pregnancy, an increased serum concentration of T_4 -binding globulin (TBG) results in changes in several parameters of thyroid function (1). In earlier studies with equilibrium dialysis which is a standard reference method for measuring free hormones, the serum concentration of free thyroxine (FT_4) during pregnancy has been reported decreased (2), normal (3) and increased (4). Similarly, the serum free thyroxine index (FT_4I) was found to be normal (5) or high (6) in pregnancy. Serum ratio of T_4 to TBG (T_4/TBG) was similarly reported to be either normal or high

(6). Based on the results obtained using commercial test kits serum FT_4 levels have been found to remain either low or normal in women with normal pregnancy (7-10). The proportion of FT_3 (free triiodothyronine) is also reportedly increased (11) but there is some evidence that FT_3 levels fall below normal and remain low until term (11). Recent studies have shown that there is a mild rise in serum free T_4 level in early pregnancy and this has been attributed to the early surge in HCG during pregnancy (12-15). The changes in serum TSH levels have not been widely studied during pregnancy but have been reported to vary from normal (16) to slightly elevated levels (11, 12). Studies carried out so far in this regard were largely confined to the populations of white north Americans, Caucasians, Asians and Australians. Very little information is available with respect to the variation of thyroid function parameters in African women with progressive pregnancy. It is interesting to note in this regard that the normal serum TBG levels in some black African communities have been reported to be

Author for Correspondence :

Professor S.C. Das
Department of Chemical Pathology,
Aminu Kano Teaching Hospital,
P.M.B. 3452, Kano 700 001,
Nigeria

higher than their Caucasian counterpart (17-20). The present study examines the pattern of changes in thyroid function profile during progressive pregnancy and postnatal period in African women living in an iodine deficient (ID) region of Plateau state, Nigeria. An estimated 1/5th of the world population (nearly 1 billion) are currently reported to be at risk of ID and its consequences (21).

MATERIALS AND METHODS

Thirty two pregnant Nigerian women (age range 16-36 years) attending the ante-natal clinic (ANC) of Jos University Teaching Hospital, Jos, Nigeria were assessed serially in a follow up manner through first (12-16 weeks) second (24-28 weeks), and third (32-36 weeks) trimesters, up to the delivery. Five women were further seen at 6 weeks post partum. The women who delivered at the completion of term pregnancy (40 weeks of gestation) only were included in this study. Women delivering premature babies (<40 weeks) were excluded, and their serum thyroid profiles determined were not included in this study. Our previous studies (22-25) carried out in Plateau state, Nigeria have clearly demonstrated that Bassa local government council (LGC) of the state is a marked ID region with widespread distribution of various environmental and dietary goitrogens (goiter prevalence (GP) in school children 25% and in adult 42% (22,23); urinary iodide excretions (UIE) in children $90.4 \pm 57 \mu\text{g/l}$ (22, 23); drinking water iodide (DWI) 0.0048 ppm (23); urinary thiocyanate (SCN^-) in children $239 \pm 182 \text{ mg/dl}$ (22, 24) and an increased hardness of water (Ca^{++} and Mg^{++} and CO_3^{--}) (22, 23) while Jos metropolis, the state capital, is a relatively iodine sufficient zone (GP 0.4% in school children, <5% in adults (22, 23); UIE $153.4 \pm 75 \mu\text{g/l}$ in children; DWI 0.041 ppm; urinary SCN^- $150 \pm 52 \text{ mg/dl}$ in children (24) and a relatively less amount of Ca^{++} , Mg^{++} and CO_3^{--} in the water (23, 25). Out of a total of 32 women assessed, 9 were residents of Jos and 23 were from the Jengere locality of Bassa region (about 50 km away from Jos), from where they were coming to attend ANC in Jos. Some notable common features seen frequently in pregnant African women such as malaria, sickle cell disease and trait, malnutrition, hypertension, venereal disease, anaemias of different proportion and alcohol and smoking habits etc. (26) were ruled out while selecting the subjects for the present study through appropriate clinical and laboratory examinations, which are conducted routinely on the women attending ANC. About 10 ml of blood was collected from the subjects at the respective trimesters and at 6 weeks post delivery period. The unhaemolysed serum samples separated through centrifugation ($5000 \times g$) were subjected to the measurement of various thyroid function parameters by 'ELISA' technique. The use of this technique has been reported by us in our previous studies (18, 22).

The measurement included thyroxine (T_4), triiodothyronine (T_3), thyroid stimulating hormone (TSH), thyroxine binding globulin (TBG) and thyroxine binding capacity (TBK). Serum TBK reflects the binding capacity of TBG molecules with T_4 (Boehringer). The serum level of free thyroxine index (FT_4I) was determined by dividing the serum values for T_4 with those of TBK ($\text{T}_4/\text{TBK} = \text{FT}_4\text{I}$) (27). Similarly, the serum T_4/TBG quotient was determined arithmetically and the results multiplied by 10 (as per SI unit).

The commercial test kits used in these assays were obtained from the manufacturer 'Boehringer Mannheim Immuno-diagnostics' Mannheim, Germany (27). The samples were run in batches and the accuracy of the results were monitored by the inclusion of international control serum sample 'Precinorm U' (also supplied by the same manufacturer) in each batch of the sample analysis. The intra and interbatch variation (imprecision) was less than 8% CV. Serum total protein and albumin levels were measured at 1st trimester by standard Biuret and dye-binding Bromo-Cresol (BCG) methods (22) respectively to eliminate the cases of malnutrition. Urinary iodide level was measured in 32 urinary samples obtained at delivery by standard 'ceric ion-arsenous ion' method (22) to detect the degree of iodine deficiency. The results obtained were compared with those observed at the various stages of pregnancy and post partum periods (in which the subjects themselves were used as control) as well as with those obtained from a group of 44 non-pregnant normal Nigerian women (age range 17-38 years) taken as a second control. In addition, the Birth weight (BW) of a total of 5555 term babies born in Bassa (1196) and in Jos (4359) regions were analysed to determine their distribution pattern, and the prevalence rate of 'small for dates' (SFD) babies (i.e. babies born with BW <2.5 kg at term) (26) in the local population. Except for UIE, all the results were found to have normal 'Gaussian' distribution and therefore student "t" test was employed to determine the degree of significance between the groups. For UIE a Mann-Whitney U test was performed. The 'p' values less than 0.05 were considered significant.

RESULTS

The results of the present investigation are outlined in Tables 1 and 2, and in Figs 1-3.

The mean serum level of T_4 was found to be progressively raised through 1st trimester ($p < .005$ vs non-pregnant control), 2nd trimester ($p < .01$ vs 1st trimester) and 3rd trimester ($p < .05$ vs 2nd trimester). The level then began to decline through delivery ($p < .01$ vs non-pregnancy), reaching close to the non-pregnant level ($94.6 \pm 17.1 \text{ nmol/l}$) at 6 weeks post delivery (Fig 1). Serum T_3 also showed a similar

Table 1. A Comparison of major thyroid parameters determined in the present study with those obtained by Amino *et al.* (Values are in mean±SD and those shown in brackets are in old units)

Present study	Non pregnant control n = 44	1 trimester n=32	2 trimester n = 32	3 trimester n = 32	Delivery n = 32	6week post partum n= 5
Serum						
T4nmol/l	94.6±17.1	127.2±32.6 ^a	148±36.2 ^b	170±41.7 ^c	123.5±18.4 ^{a*}	84.4±21.3
FT4l	91.4±21.8	95.2±23.6	107.1±29.5 ^{a**}	123.2±32.5 ^b	112.8±30.5	93.8±32.2
TBG nmol/l	292.3±51.8	369.4±113.2 ^{a*}	473±41.5 ^b	513±120.6 ^a	386±76.8 ^{a*}	305±96.4
TSH mU/l	2.27±0.88	3.0±1.67	3.16±2.37	2.97±2.43	2.78±2.7	4.9±3.1 ^{a**}
T4/TBG(x10)	3.28±0.32	3.34±0.33	3.05±0.29	3.23±0.31	3.18±0.28	2.86±0.41
TBK	1.07±0.09	1.34±0.24 ^a	1.36±0.22 ^a	1.39±0.26 ^a	1.06±0.24	0.91±0.31
Urinary I µg/l	152±31	-	-	-	163±31	
Amino <i>et al</i> ¹⁴ n = 10						
n = 10						
n = 10						
n = 10						
1 month post partum n = 10						
Serum						
T4 nmol/l	96.5±14.2	150±33.5 ^a	140.3±34.7 ^b	180.2±28.3 ^b	101.7±16.7	
(µg/l)	(75±11)	(117±26) ^a	(109±27) ^b	(140±22)	(79±3)	
FT4 ug/dl	1.56±0.21	1.79±0.45	1.42±0.14	59±0.16	1.4±0.20	
TBG nmol/l	416.5±61.3	584.5±77 ^c	754.3±117.3 ^c	882±87.5 ^c	495.3±75.5 ^b	
(µg/ml)	(23.8±3.5)	(33.4±4.4) ^c	(43.1±6.7) ^c	(50.4±5) ^c	(28.3±4.2) ^b	
TSH mU/l	2.41±1.07	2.19±0.59	2.66±1.41	2.56±0.41	2.32±1.23	
T4/TBG(x10 ⁻³)	3.20±0.47	3.0±0.76	2.53±0.39 ^a	2.78±0.35 ^b	2.81±0.26 ^b	
P values						
Present study: vs non pregnancy a<0.005, a*<0.01, a**<0.05; vs 1 trimester b<0.01; vs 2 trimester c<0.05 Amino <i>et al</i> ¹⁴ : vs non pregnancy a<0.05, b<0.01, c<0.001						
Local non pregnant reference range:						
T4 = 60-126 nmol/l, T3 = 1-3 nmol/l, TSH = 0.5-5 mU/l, TBG = 172-371 nmol/l, FT4l = 47-143, T4/TBG = 2.6-3.85, TBK = 0.17-1.31						
Values previously expressed in older units by Amino <i>et al</i> have been converted to SI units for comparison as follows:						
T4 µg/l x 12.87 = nmol/l, TBG µg/ml x 17.5 = nmol/l						

progressive rise but with less dramatic variation (see Fig 1). During the entire course of pregnancy, the mean serum TSH level was found to be virtually unchanged except at 6 weeks post delivery where it showed a significant rise (mean 4.92±3.1 mU/l; p<.05) compared to the non-pregnant level (mean 2.27±0.88 mU/l).

Serum TBG, similarly, showed a progressive rise through 1st, 2nd and 3rd trimester (mean 513±120.6 nmol/l) when compared to the level seen in non-pregnant group (mean 292.3±51.8 nmol/l). At post delivery the level dropped drastically to a mean value

of 305±96.4 nmol/l. Although the level of serum TBK was found to be progressively elevated through pregnancy reaching a peak at 3rd trimester (see Table 1 and Fig 1), the elevation seen was, however, not proportionate to that seen for TBG or T₄ levels. The free thyroxine index (FT₄I = T₄/TBK) was, therefore, elevated very significantly, particularly around 3rd trimester (mean 123±32.5; p<.01 vs 1st trimester) compared to that in non-pregnant control group (mean 91.4±21.8). Eleven subjects (34%) at this point even showed values outside the upper limit of the normal non-pregnant range (47.4-143). In contrast, the serum

Fig. 2. A comparison of serum T_4/TBG ratio and TSH levels during advancing pregnancy between the mothers carrying 'SFD' babies ($n=5$) and those carrying normal babies ($n = 27$). The shaded areas indicate the non-pregnant reference range

Table 2. A comparison of the results of thyroid parameters determined in mothers carrying 'SFD' babies (n = 5) (mean BW of babies 2.3± 0.11 kg) and those carrying normal babies (n =27) (mean BW 3.8 ± 0.26 kg) (Results are in mean ± SD)

Serum parameters	Trimesters			Delivery	6 weeks post partum n = 5
	1	2	3		
T4nmol/l	84.2±15.2 ^e (129.1±34.1)	107.6±18.1 ^e (157.2±38.2)	121.4±23.3 ^e (173.1 ± 42.3)	88.2±16.3 ^e (139.6 ±35)	-(84.4±21.3)
T3 nmol/l	1.9±0.36 ^e (2.6±0.48)	1.96±0.42 ^d (2.7±0.62)	2.4±0.68 (2.91±0.51)	2.1±0.41 ^a (2.7±0.52)	-(1.61±0..53)
TSH mu/1	2.9±0.89 (2.7±0.9)	7. 9±2.1 ^e (2.12±1.6)	8.2±2.9 ^e (2.29±2.1)	7.4±2.0 ^e (3.1±1.9)	-(4.92 ± 3.1)
TBG nmol/1	325±21 ^e (381±59.2)	471±112.2 (489±114)	510 ±101 (526±109)	398±59 (439±101)	-(305 ±96 .4)
TBK	1.21±0.19 (1.38±0.25)	1.56±0.31 (1.41±0.29)	1.53±0.32 (1.39±0.28)	1.26±0.21 (1.39±0.26)	-(0.91±0.31)
FT4l	74.2±19.8 ^b (99.1±21.3)	69.1±17.2 ^e (114±19.1)	76.6±16.1 ^e (127.2±21.2)	72±15.3 ^e (119±21)	-(93.8±32.2)
T4/TBG(x10)	2.9±0.32 ^c (3.36±0.34)	2.61±0.28 ^e (3.41±0.41)	2.69±0.26 ^e (3.46±0.39)	2.7±0.21 ^c (3.2±0.28)	-(2.86±0.41)
Urinary I µg/l	-	-	-	79±24 ^e (188±39)	-
Reference range values in normal pregnant women (n = 27)					
T4 nmol/l	61-197	85-233	89-257	70-210	
T3 nmol/l	1.7-3.5	1.86-3.54	1.9-3.94	1.66-3.64	
TSH mU/l	0.5-5.0	0.5-5.0	0.5-5.0	0.5-5.0	
TBG nmol/l	263-499	261-713	308-744	257-641	
TBK	0.88-1.87	0.83-1.99	0.83-1.95	0.87-1.91	
FT4l	57- 49	76-152	85-169	77-161	
T4/TBG (x10)	2.64-4.0	2.61-4.2	2.80-4.38	2.64-3.68	
Urinary I/ig/l	-	-	-	110 -266	
P values vs normal mothers: a <0.05, b<0.02, c <0.01, d <0.005, e<0.001					
Values in the brackets indicate the results derived from the normal mothers with normal babies.					

T₄/TBG ratio was found to be virtually unchanged throughout the entire course of pregnancy (see Table 1 and Fig. 1). Serum T₃/T₄ ratio also did not show any significant change throughout (see Fig 1).

Table 2 shows that the level of serum T₄, FT₄l, T₄/TBG ratio and T₃ were all significantly depressed at 1st trimester (p<0.02), 2nd trimester (p<0.001), 3rd

trimester (p<0.001) and at delivery (p<0.01) to a low-normal range in the group of 5 mothers delivering 'SFD' babies, in comparison to the corresponding mean and range values seen in the respective stages of pregnancy in the normal group of 27 mothers carrying normal babies (Fig 2). Serum TSH in 'SFD' group was in contrast, significantly elevated (p<0.001) at 2nd and 3rd trimesters and at delivery, showing mean

Fig. 3. The percentage distribution of Birth Weights of term babies (n=5555) in Jos (control zone) and in Bassa district (iodine deficient zone) of Plateau State, Nigeria.

values outside the upper normal limit seen in non-pregnant women (0.5 - 5 mU/l) (Table 2 and Fig. 2). Mean UIE in 'SFD' group was significantly lower ($p < 0.001$) than that in normal group of women.

DISCUSSION

Previous pregnancy studies carried out among Africans were largely limited to the evaluation of thyroid function at delivery stage (maternal - neonate) only (28). In the present investigation we provide a thyrometabolic study during advancing pregnancy and post natal period among African women. In recent studies carried out among British, Asians (Japanese) and white north Americans (12-16) a mild rise in serum FT_4 level has been reported during early pregnancy, and this has been attributed to the early surge in chorionic gonadotrophin seen around the period which is believed to possess some thyrotropic activity. The TSH level has also been found to be suppressed during this period (29). By contrast, in the present investigation we have failed to observe this phenomenon in African women with uncomplicated pregnancy. Rather, we found a very significant rise in free thyroxine index ($FT_4I = T_4/TBK$) at 3rd trimester; 34% of the subjects assessed showing level outside the normal range (47.4-143). The serum T_4/TBK ratio, is useful marker of thyroid status during pregnancy, however, did not show any rise at this stage in the

present group of women, nor was there any suppression of serum TSH during this period confirming the earlier work of Smith *et al.* (30) who also did not observe any suppression in TSH level during pregnancy, suggesting that the women during this stage (although showed a rise in FT_4I levels) were probably not hyperthyroid. None of the pregnant women assessed in this study showed any clinical evidence of hyperthyroidism, at any stage.

We therefore, believe that with the advancing pregnancy and particularly around 3rd trimester, the binding of T_4 with the rising TBG molecules is significantly disturbed by the presence of some unknown metabolites arising from the pregnancy, which can displace and bind T_4 molecules (competitively or otherwise) from the rising TBG molecules. The displaced and bound- T_4 moiety, thus becomes physiologically ineffective. This would, therefore, cause a less proportionate rise in the level of serum TBK in comparison to the marked rise seen in TBG level as has been observed in the present study (see Table 1 and Fig. 1). This displacement phenomenon, therefore, tends to constitute a rise in serum free thyroxine index level (measured as $T_4/TBK=FT_4I$) in the pregnant women of the present investigation without causing any clinical hyperthyroidism.

Our study further shows that out of 32 women assessed 5 (15.6%) delivered 'SFD' babies at term, with a mean BW of 2.3 ± 0.11 kg. Mothers carrying these babies, in a retrospective look, showed significant depression in serum T_4/TBK (best indicator of thyroid status during pregnancy in the absence of FT_4), FT_4I , T_4 and T_3 levels to a low-normal range, in association with a mild but significantly ($p < 0.001$) elevated TSH level (reaching above the upper normal limit) at the various stages of pregnancy, in comparison to the corresponding mean and range values seen at the corresponding stages of the pregnancy in the rest of 27 normal mothers with normal babies (mean BW of babies 3.8 ± 0.26 kg) (see Table 2 and Fig 2). The UIE in these 5 women were significantly reduced (mean 79 ± 24 $\mu g/l$; $p < 0.001$) compared to the level seen in the 27 normal pregnant women with normal babies (mean 188 ± 39 $\mu g/l$), suggesting that the women with 'SFD' babies in the present investigation were iodine deficient and were in a state of 'subclinical or compensated hypothyroidism'. In one of our earlier related studies we found a significant number of pregnant women from the iodine deficient Bassa region of the state (the present study area) in a 'compensated hypothyroid state' with reduced UIE (22). Thilly *et al.* (28) also reported a similar group with subclinical (compensated) hypothyroidism among the pregnant women population from the iodine deficient Ubangi region of Zaire, Central Africa. Strikingly, in the present study

out of 5 women with 'SFD' babies assessed 4 were from Bassa (an ID zone) and 1 from Jos (non ID zone).

Analysis of BW of term babies carried out in the region (Fig. 3) further shows a significant drop ($p < 0.001$) in BW among the babies from Bassa group (mean 2.87 ± 0.54 kg) compared to that in Jos group (mean 3.24 ± 0.46 kg), with a clear 'shift to the left' in the percentage distribution pattern of BW in Bassa region (see Fig. 3). This BW analytical study was hospital based, and the subjects studied belonged to the similar socio-economic and nutritional groups (without any selection bias) for both the Bassa and Jos regions. The incidence of 'SFD' babies, in this assessment, was found to be 15.2% (182/1196) in Bassa and 9.8% (427/4359) in Jos, confirming the earlier reported incidence (of 10.6% in Jos) obtained by previous workers (31).

These observations tend to suggest that there is a possibility that apart from the various established maternal causes of 'SFD' babies in a population (26) e.g. maternal infection notably malaria, sickle cell disease, asthma, malnutrition, anaemias, hypertension, syphilis, smoking habits and alcohol consumption (all of which were excluded from the subjects of the present investigation), a prolonged state of maternal 'compensated hypothyroidism' during pregnancy due to environmental iodine deficiency (EID) is, probably, an additional likely factor associated with the genesis of 'SFD' babies in African population. It is significant in this regard that currently about 1 billion people globally are reported to be at risk of iodine deficiency disorders (IDD); most of them being from developing countries where the incidence of 'SFD' babies is notably high. In Africa over 230 million are reported to be affected with IDD (21).

It is further suggested that in evaluating thyroid status during pregnancy in African countries where the laboratories are relatively less advanced and therefore the measurement of serum free- T_4 is not frequently possible, in addition to measuring serum TSH level, one should measure serum T_4 /TBG ratio in preference to FT_4I (which is virtually useless as thyroid indicator during pregnancy in Africans). Reference ranges for each thyroid parameter should be established at the corresponding stages of pregnancy for more accurate evaluation, as detailed in Table 2. To our knowledge this is the first report of normal reference range values of thyroid parameters at the various stages of pregnancy in healthy Africans. This may eventually serve as an important base-line for effective comparison of 'groups' during pregnancy among Africans. Furthermore, UIE should be measured routinely as a screening procedure for detection of possible iodine deficiency in all the pregnant women attending Antenatal clinic (ANC), especially in developing (tropical) countries since the level of

urinary iodide excretion is easier to measure and involves less expense and cost as compared to the determination of serum T_4 /TBG ratio which is by far more expensive and cumbersome in the IDD affected regions of the third world countries. Women showing UIE level less than 100 $\mu g/l$ should be identified as potential 'iodine deficient group' and the babies born from such women are more prone to develop irreversible brain and physical damage including deaf mutism, spastic diplegia, neurological cretinism, low I.Q with mental and physical growth retardation and congenital hypothyroidism (32). Such women therefore need to be given preventive iodine supplementation during the critical antenatal period in the form of; i) iodized salt, or ii) iodized oral capsule - each capsule containing 200 mg of iodine in the form of poppyseed iodized oil (lipiodol, made by Laboratoire Guerbet, France) capable of protecting from ID for 1 year, and or iii) iodized oil injection (lipiodol injection, France) 1 ml containing 480 mg of iodine and a single injection providing protection for 3 years (21).

ACKNOWLEDGEMENT

We acknowledge with thanks the help provided by Japan International Co-operation Agency (JICA), Tokyo, Japan.

REFERENCES

1. Burrow, G.N. (1977) Thyroid and parathyroid function in pregnancy. In: Fuchs F, Kloppe A (eds) Endocrinology of Pregnancy, ed 2. Haper and Row, New York, p.246.
2. Sterling, K. and Hegedus, A. (1962) Measurement of free thyroxine concentration in human serum. J. Clin. Invest. 41, 1031-1040.
3. Osathanondh, R., Tulchinsky, D. and Chopra, I.J. (1976) Total and free thyroxine and triiodothyronine in normal and complicated pregnancy. J. Clin. Endocrinol. Metab. 42, 98-104.
4. Harada, A., Hershman, J.M., Reed, A.W. et al. (1976) Comparison of thyroid stimulators and thyroid hormone concentration in the sera of pregnant women. J. Clin. Endocrinol. Metab. 48, 493-497.
5. Yamamoto, T., Amino, N., Tanizawa, O. et al. (1979) Longitudinal study of the serum thyroid hormones, chronic gonadotrophin and thyrotrophin during and after normal pregnancy. Clin. Endocrinol. (oxf.) 10, 459-462.
6. Burr, W.A., Ramsden, D.B., Evans, S.E., Hogan, T. and Hoffenberg, R. (1977). Concentration of thyroxine binding globulin: value of direct assay. Brit. Med. J. 1, 485-487.
7. Hopton, M.R., Ashwell, K., Scott, I.V. and Harrop, J.S. (1983) Serum free thyroxine concentration

- and free thyroid indices in normal pregnancy. *Clin. Endocrinol.* 18, 431-436.
8. Whitworth, A.S., Midgley, J.E.M. and Wilkins, T.A. (1982) A comparison of free T4 and the ratio of total to T4 binding globulin in serum through pregnancy. *Clin. Endocrinol.* 17, 307-313.
9. Boss, A.M.B. and Kingatone, D. (1981) Further observation on serum free thyroxine concentration during pregnancy. *Brit. Med. J.* 283, 584-586.
10. Braverman, A.E., Abreau, C.M., Brock, P. *et al.* (1980) Measurement of serum free thyroxine by RIA in various clinical states. *J. Nuc. Med.* 21, 233-236.
11. Hall, R., Anderson, J., Smart, G.A. and Besser, M. (1980) Hormonal changes during pregnancy. In: *Fundamentals of clinical endocrinology*, 3. ed., Pitman Medical, London, Massachusetts. p 371-381.
12. Weeks, J., Dybkjaer, L., Granile, K. *et al.* (1982) A longitudinal study of serum TSH and total and free iodothyronines during normal pregnancy. *Acta. Endocrinol.* 101, 531-537.
13. Guillaume, J., Schussler, G.C. and Goldman, J. (1985). Components of the total serum thyroid hormone concentration during pregnancy. High free thyroxine and blunted thyrotrophin (TSH) response to TSH releasing hormone in the first trimester. *J. Clin. Endocrinol. Metab.* 60, 678-684.
14. Amino, N., Yamada, T., Mitsuma, T. *et al.* (1981) Increase in plasma thyrotrophin releasing hormone in normal human pregnancy. *J. Clin. Endocrinol. Metab.* 53, 1288-1291.
15. Skjoldebrand, I., Brundin, J., Carlstorm, A. and Petterson, T. (1982) Thyroid associated components in serum during normal pregnancy. *Acta. Endocrinol.* 100, 504-511.
16. Rodin, A., Mashiter, C., Quarero, G. *et al.* (1989) Thyroid function in normal pregnancy. *J. Obstet. Gynaecol.* 10, 89-94.
17. Osotimehim, B. and Haffenberg, R. (1980) Serum thyroglobulin measurement in various thyroidal disorders. *African J. Med. Med. Sc.* 9 (3/4), 89-95.
18. Isichei, U.P., Das, S.C. and Egbuta, J.O. (1990) Central cretinism in four successive siblings. *Brit. Postgrad. Med. J.* 66, 751-756.
19. Isichei, U.P., Das, S.C., Banwo, A.I., Morimoto, I. and Nagataki, S. (1987) Endemic goiter in Plateau state, Nigeria. *Abst IDD Newsletter. (ICCIDD/WHO/UNICEF publication) vol. 3, No. 3, p 7.*
20. Isichei, U.P., Morimoto, I., Das, S.C., Egbuta, J.O., Banwo, A.I. and Nagataki, S. (1995) Endemic goiter in the Jos Plateau region of Northern Nigeria. *Endocrine Journal*, 42 (1), 23-29.
21. Hetzel, B.S. (1988) The prevention and control of iodine deficiency disorders. United Nations Administrative committee of coordination Sub-committee on nutrition State-of-the-art series. Nutrition policy discussion paper No. 3 March, 2-25.
22. Das, S.C. and Isichei, U.P. (1993) The fetomaternal thyroid function interrelationships in an iodine deficient region in Africa- the role of T3 in possible fetal defence. *Acta. Endocrinol.* 128, 116-119.
23. Das, S.C., Isichei, U.P., Egbuta, J.C. and Banwo, A.I. (1989) Cations and anions in drinking water as putative contributory factors to endemic goiter in Plateau State, Nigeria. *Trop. Geogr. Med.* 4, 346-352.
24. Morimoto, I., Isichei, U.P., Das, S.C., Banwo, A.I., Egbuta, J.O. and Nagataki, S. (1987) Urinary iodide and thiocyanate concentration among school children in endemic goiter area of Plateau state, Nigeria. *Proc Nigeria/Japan Joint Conf.* G-6, 78-81.
25. Das, S.C., Isichei, U.P. and Egbuta, J.O. (1989) Variations in biochemical indices of coronary risk status in endemic goitre. *Asean J. Clin. Sc.* 9, 85-98.
26. Marc, J.N.C. Keiree. (1984) Epidemiology and aetiology of the growth retarded baby. In: *Clinics in Obstet Gynaecol "Small Baby"*. Howie, P.W. and Patel, N.B. (eds.) W.B. Saunders Company. London. Philadelphia. Toronto. vol III, No. 2, 415-435.
27. *Methodology manuals* (1986). Boehringer Mannheim Immunodiagnostics, Mannheim, Germany.
28. Thilly, C.H., Delange, F., Lagasse, R. *et al.* (1978) Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *J. Clin. Endocrinol. Metab.* 47, 354-360.
29. Chan, B.Y. and Swaminathan, R. (1988) Serum thyrotrophin concentration measured by sensitive assays in normal pregnancy. *Brit. J. Obstet. Gynaecol.* 95, 1332-1336.
30. Smith, S.C.H. and Bold, A.M. (1983) Interpretation of invitro thyroid function tests during pregnancy. *Brit. J. Obstet. Gynaecol.* 90, 532-534.
31. Wright, E.A. (1989) Birth weight of infants in Jos, Nigeria. *West Afri. J. Med.* 8, 166-170.
32. Delong, R. (1987) Neurological involvement in iodine deficiency disorders. In: *Hetzel, B.S., Dunn, J.T. and Stanbury, J.B. (eds). The prevention and control of iodine deficiency disorders.* Amsterdam, Elsevier, Biomedical Division, 49-63.