THE TRIAD – IODINE DEFICIENCY, HYPERLIPIDAEMIA, HIGH CORONARY RISK – IN A ‘MATERNAL – NEONATE’ POPULATION OF RURAL AFRICA

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ABSTRACT

In order to see the pattern of changes in differential serum lipid and lipoprotein fractions as a risk marker of coronary complication in paired ‘maternal – neonate’ blood samples in an iodine deficient zone, 26 pregnant women and their corresponding new born infants at term delivery from the iodine deficient Bassa region of Plateau state, Nigeria were assessed and the results were compared with those seen in a similar 44 group of women and their newborns assessed in non iodine deficient region of Jos. The serum thyroid function and lipid and lipoprotein profiles were determined by ‘ELISA’ and ‘enzymatic’ methods respectively. Urinary iodide excretion level was also measured in 14 pregnant women in Bassa, 23 pregnant women in Jos and 16 non pregnant control from Jos. Results indicate that the pregnant women assessed in Bassa were iodine deficient ($P<0.01$) and their thyroid status was strikingly reduced as reflected by a drop in serum level of T4/TBG ratio ($P<0.01$) and a rise in TSH ($P<0.005$) in comparison to that seen in Jos. There was marked hypertriglyceridaemia and total hypercholesterolaemia ($P<0.005$), with differential significant rise in LDL cholesterol fraction ($P<0.005$) in the women assessed in Bassa as compared to Jos. The HDL cholesterol however dropped less significantly in the group ($P<0.05$) with a concurrent marked rise ($P<0.001$) in the serum ratio of LDL cholesterol/ HDL cholesterol, total cholesterol/ HDL cholesterol and triglycerides/ HDL cholesterol in the iodine deficient group. A similar pattern of changes were seen in the corresponding neonates in the Bassa group as compared to Jos group. It is concluded that the pregnant women and their newborn offsprings living in a longstanding environmental iodine deficiency run a higher risk of developing coronary complications than those living in non endemic region. It is striking that such newborns surrounded by a continued state of iodine deficient may at a later adult- period of life develop marked risk of coronary complication and other features of hyperlipidaemias associated with varying thyroid insufficiency and accompanied iodine deficiency disorders. Prophylaxis measures as intervention has been highlighted.

KEY WORDS

Iodine Deficiency, Serum lipid, Lipoproteins, Coronary markers, Maternal-neonates.

INTRODUCTION

Iodine deficiency disorders (IDD) in which a visible goitre, cretinism, low intelligence quotient (IQ) among children and varying forms of reproductive failure in women are the major

clinical features, currently occupies a prominent place in the spectrum of international health hazards and its global ramifications. Long standing environmental iodine deficiency (EID) can lead to the onset of various forms and degrees of thyroid dysfunctions ranging from subclinical (compensated) hypothyroidism to the clear, overt and established cretinism, juvenile hypothyroidism or adult myxoedema (1-4). The prevalence of neonatal congenital hypothyroidism is remarkably high in babies born in such environment associated with EID (5-7). A sustained subnormal level of thyroid function in mother may, in turn, cause substantial changes in various serum lipid and lipoprotein fractions in both mothers and their offsprings. Hyperlipidaemias and hyperlipoproteinaemias are

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frequent findings in such subjects with different form and grades of hypothyroidism (8). Present work is directed to examine the possible changes in lipid and lipoprotein profiles occurring in the blood of mothers and their corresponding neonates in an iodine deficient (ID) regions of tropical Nigeria. Currently, about 1/5th of the world population (nearly 1.3 billion) is reported to be at risk of iodine deficiency and its consequences and majority of which lies in the tropical developing countries including a significant proportion of Africa (9,10).

MATERIALS AND METHODS

The Bassa district and surrounding hilly rugged terrains of Plateau State, Nigeria is located about 4000 ft above sea level and is an established iodine deficient zone [goiter prevalence (GP) in school children 25% and adult 42%] with widespread dietary goitrogens, increased hardness of water with low iodine in drinking water, soil and local staple crops (11-14). In contrast, the Jos metropolis – the state capital (50km away from Bassa) is a relatively iodine sufficient zone (GP in school children 0.4% and adult 3.8%) with adequate bioavailability of iodine (11-14). The former has been used as an iodine deficient test zone and the later as non ID control region in the comparative assessment of present investigation.

Forty four pregnant African women (age range 16-36 years) at term delivery (40 weeks of gestation) and their corresponding newborn babies from Jos metropolis (seen at University of Jos Teaching Hospital) and 26 mothers (age range 15-44 years) and corresponding neonates (born at term delivery) from Bassa region (at 7- Day Adventist Hospital) were assessed randomly without any nutritional, socio-economic or population selection-bias and their unhaemolysed sera obtained by centrifugation (at 5000 xg) of the respective 'paired' maternal-cord blood samples were subjected to the

determination of various lipid and lipoprotein fractions using commercial test-kits (Boehringer, Germany) based on spectrophotometric enzymatic principle (15). All the women assessed were normotensive, nondiabetic, nonsmokers and their regular diets included normal African foods low in saturated fats e.g yam, cassava, rice, corn, millet, guinea corn, fish, chicken, groundnut oil and vegetables. Parameters measured were serum total cholesterol, triglycerides, beta-lipoprotein and its cholesterol fraction, HDL cholesterol (28 paired samples from Jos and 18 from Bassa) and LDL Cholesterol (by derivation using Friedwald's formula: LDL cholesterol = Total cholesterol – Triglycerides/2.2 – HDL cholesterol mmol/l) (16). (28 paired sample from Jos and 18 from Bassa). The samples were run in batches and accuracy checked by inclusion of quality control sample 'Precipath U' supplied by Boehringer Mannheim, Germany and inter and intra-batch variations (precision) determined as co-efficient of variation (C.V) was less than 10% in each bath of analysis. Jaundiced and haemolysed sera were excluded. The thyroid function status of these women and their newborn babies were determined by measuring serum Thyroxine (T4), Thyroxine binding globulin (TBG), T4/TBG ratio and Thyroid Stimulating Hormone (TSH) level by 'ELISA' (Boehringer) technique (13). The use of this technique is widespread in Nigeria including the clinical laboratory of our hospital where the technique is routinely used for diagnostic hormonal analysis in patients

Urinary iodide excretion (UIE) was determined at term delivery in 23 women in Jos and 14 in Bassa by conventional 'ceric ion – arsenous 'ion' method to detect the degree of iodine deficiency. The results were further matched with that determined in 16 non pregnant control subjects selected from Jos. The student 't' test was used to determine the level of significance between the paired parametric data.

TABLE 1: The major serum thyroid parameters determined in the paired 'maternal-neonate' blood samples in the Bassa (Test zone) and Jos region (Contol Zone) and a comparison of the results with that in non pregnant control

SerumThyroid Parameters	Jos Non Pregnant Control			Jos (Non ID Control Zone) Pregnancy						Bassa (Test ID Zone)					
				Maternal		(at delivery)		Cord blood (BW 3.14±44Kg)		Maternal		(at delivery)		Cord blood (BW 2.9 ± 46 Kg)	
	n	Mean ± SD	Range	n	Mean ± SD	Range	Mean ± SD	Range	n	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
T4 (nmol/l)	44	94.6±17.1	60.4-126.3	46	125.5±17.8	90-161	72±14.3	44-101	26	106±27.7**	51-162	61.8±16.2 ^b	29.4-94.2		
TBG (nmol/l)	44	274±47	172-371	38	387±64.4	258-526	417±69	280-554	26	494±79	336-653	601±101 ^d	399-803		
T4/TBGX10	44	3.23±0.32	2.59-3.85	38	3.26±0.27	2.72-3.8	1.81±0.18	1.45-2.2	26	2.24±0.41**	1.52-3.16	1.17±0.21 ^a	0.7-1.59		
TSH (mU/l)	44	1.68±0.76	0.47-4.03	43	3.2±1.16	1.94-5.6	24.9±7.1	11-39	26	7.58±4.1***	3.1-11.7	34.5±10.6 ^c	13.3-55.7		

P values vs Jos: Between mothers, * <0.05, ** <0.01, *** <0.005; Between babies, ^a <0.05, ^b <0.01, ^c <0.005, ^d <0.001

RESULTS AND DISCUSSION

Table 1 shows the results of the prominent thyroid parameters (T4, T4/TBG ratio and TSH) determined in the maternal-neonate paired serum samples in both Jos and Bassa regions. The level of serum T4 in both the mothers and neonates from Bassa were significantly lower ($P<0.01$) than those recorded in corresponding groups in Jos. Similarly, the level of serum T4/TBG ratio in Bassa group of mothers and newborns were significantly reduced as compared to the values seen in Jos groups. In contrast, mean serum TSH values in Bassa group of mothers and in neonates were found to be markedly elevated ($P<0.005$) in comparison to the corresponding values observed in Jos group.

Table 2 shows that among the various serum lipid and lipoprotein fractions determined in the women of Bassa region, the mean serum total cholesterol, triglycerides, beta lipoprotein, beta lipoprotein cholesterol and LDL cholesterol were all found to be significantly elevated ($P<0.005$) as compared to the corresponding mean serum values seen in Jos groups. The level of maternal HDL cholesterol in Bassa group was, however, significantly reduced ($P<0.05$) in

comparison to Jos. Consequently the serum value of LDL cholesterol/ HDL cholesterol, total cholesterol/ HDL cholesterol and triglycerides/ HDL cholesterol were all significantly increased ($P<0.001$) in the Bassa group compared to Jos. Neonates from Bassa registered significant rise in serum total cholesterol ($P<0.05$), triglycerides ($P<0.001$) and in LDL cholesterol level ($P<0.05$) as against their counterparts in Jos. The serum level of LDL cholesterol/ HDL cholesterol ($P<0.05$), total cholesterol/ HDL cholesterol ($P<0.005$) and triglycerides/ HDL cholesterol ($P<0.001$) were found to be significantly elevated in the cord blood of Bassa group compared to those in Jos. The UIE levels in Bassa group of mothers were significantly reduced ($P<0.01$) as compared to that seen in Jos group of pregnant women as well as non pregnant control.

Iodine deficiency and its attendant complication popularly known as IDD (17) is indeed a depressing global reality and poses distinct major health hazards to a vast majority of developing third world countries. The scourge of this micronutrient deficiency is, in fact, presently causing a massive loss of human manpower resources, low gross national product and reduced generation of national revenues at a significant rate among the impoverished developing nations (18).

TABLE 2: Major serum lipid and lipoprotein fractions in paired 'maternal – cord blood' samples in the Bassa (ID zone) and Jos (non ID) groups. (Results are in mean $\pm$ SD).

SerumThyroid Parameters	Jos Non Pregnant Control			Jos (Non ID Control Zone) Pregnancy					Bassa (Test ID Zone)				
				Maternal	(at delivery)	Cord blood (BW 3.14±0.44Kg)			Maternal	(at delivery)	Cord blood (BW 2.9 ± 0.46 Kg)		
	n	Mean ± SD	Range	n	Mean ± SD	Range	Mean ± SD	Range	n	Mean ± SD	Range	Mean ± SD	Range
Total Chloesterol (mmol/l)	32	3.64±1.08	1.46-5.82	44	4.78±0.49	3.8-5.8	1.78±0.31	1.18-2.44	26	5.59±0.84 ^b	3.9-7.3	2.12±0.33 [†]	1.46-2.78
Triglycerides (mmol/l)	32	0.53±0.2	0.14-.98	44	1.93±0.25	1.4-2.4	0.35.08	0.19-0.5	26	2.32±0.23 ^b	1.9-3.0	0.6±0.1 ^{***}	0.41-0.79
Betalipoprotein (g/l)	32	2.73±0.23	2.3-3.2	44	3.86±0.17	3.5-4.2	1.12±0.17	0.77-1.47	26	4.22±0.41 ^b	3.4-5.1	1.12±0.27	0.58-1.66
Betalipoprotein Cholesterol (mmol/l)	32	2.49±0.23	2.1-2.9	44	3.5±0.15	3.2-3.8	1.0±0.16	0.69-1.32	26	3.8±0.37 ^b	3.1-4.5	1.06±0.19	0.68-1.44
HDL Cholesterol (mmol/l)	9	1.85±0.31	1.2-2.5	28	2.5±0.29	1.9-3.1	0.53±0.11	0.31-.75	18	1.8±0.6 ^a	1.0-2.6	0.45±0.2	0.05-0.85
LDL Cholesterol (mmol/1)	9	1.55±0.28	1.0-2.1	28	1.5±0.29	0.9-2.1	1.06±0.2	0.82-1.62	18	2.2±0.37 ^b	1.4-2.9	1.22±0.22 [†]	0.62-1.5
LDL cholesterol/ HDL cholesterol	9	0.81± 0.3	0.21-1.41	28	0.6±0.27	0.06-1.14	2± 0.15	1.7-2.3	18	1.22±0.47 ^c	.28-2.16	2.71±0.21 [†]	2.29-3.13
Total cholesterol/ HDL cholesterol	9	1.97±0.69	0.59-3.35	28	1.91±0.39	1.13-2.69	3.35±0.22	2.8-3.8	18	3.1±7.2 ^c	1.66-4.54	4.7±0.26 ^{††}	4.2-5.2
Triglycerides/ HDL cholesterol	9	0.28±0.26	0.02-0.54	28	0.77±0.28	0.21-1.33	0.66±0.1	0.46-0.86	18	1.29±0.42 ^c	0.35-2.13	1.3±0.15 ^{†††}	1-1.6
UIE (ug/dl)	16	15.2±3.1	9-21.4	23	17.8±2.6	12.6-23	—	—	14	3.75±1.8 ^c	.15-7.35	—	—

P values: Bassa Vs Jos (mothers) ^a <0.05, ^b<0.005, ^c < 0.001; Bassa Vs Jos (neonates) [†] <0.05, ^{††} <0.005, ^{†††} <0.001

From the result of the present investigation it is evident that the pregnant women assessed at Bassa region of Plateau State, Nigeria were, in fact, significantly iodine deficient ($P<0.01$) and their thyroid function status was strikingly reduced ($P<0.01$) to a low 'subclinical hypothyroid' state as compared to the women assessed in Jos. In one of our earlier studies we have demonstrated that the serum T4/TBG ratio together with serum TSH levels are considered preferable indicator of thyroid function during pregnancy, particularly in the absence of measurement of serum free – T4 concentraton (19).

This state of chronic subnormal function of thyroid seen in this group of women assessed in the ID region of Bassa in turn appeared to have exerted hyperlipaemic effect on their sera leading to a relative but significant hypercholesterolaemia ($P<0.005$), hypertriglyceridaemia, ($P<0.005$) and hyperbetalipoproteinaemia ($P<0.01$) when compared to non ID region of Jos (Table 2). Serum HDL Cholesterol level however dropped significantly ($P<0.05$) in this group while LDL cholesterol showed a comparatively greater rise ($P<0.005$), with a concomitant significant rise in serum LDL cholesterol/ HDL cholesterol ratio – a potential coronary risk marker – in Bassa groups (both in mother ($p<0.001$) and cord blood ($P<0.05$) as compared to that in Jos. Similarly the serum quotients of total cholesterol/HDL cholesterol and triglycerides/ HDL cholesterol also registered a significant higher value ($p<0.001$) in the former groups compared to the later (see Table 2). Since a high serum LDL cholesterol and a low HDL cholesterol (therefore a significantly higher value in serum LDL cholesterol/HDL cholesterol ratio together with an elevated level of total cholesterol/ HDL cholesterol and triglycerides/ HDL cholesterol quotients) in association with existing total hypercholesterolaemia and hypertriglyceridaemia are indicative of potential atherogenic coronary risk in a subject (20-22), it is likely that the pregnant women investigated at Bassa ran a greater risk of developing coronary complications compared to their counterparts in the non-endemic region of Jos. The co-existence of the triad – hypercholesterolaemia, hypertriglyceridaemia, and a low urinary I excretion is particularly striking amongst the women population during pregnancy in the ID region of Bassa. This contrasts sharply with the picture of a relatively low cholesterol, low triglycerides and adequate urinary I levels seen during pregnancy in the non ID region of Jos. It is however important to emphasize that serum lipid and lipoprotein levels in Nigerian are generally lower than in Caucasians (23, 24) and so a substantial rise in serum fractions in Nigerians should be considered significant.

Analysis of cord serum lipid and lipoprotein fractions further

indicates that the level of total cholesterol, triglycerides and LDL cholesterol fraction together with serum value of LDL cholesterol /HDL cholesterol ($P<0.05$), total cholesterol/HDL cholesterol ($P<0.005$) and triglycerides/ HDL cholesterol ($P<0.001$) ratios were significantly higher in newborn infants assessed in Bassa compared to those assessed in Jos (Table 2). This finding is probably related to the higher level of lipid and lipoproteins seen in the sera of the corresponding mothers. Or does it reflect that the neonates born in a sustained environment of iodine deficiency run a higher risk of developing coronary complication in association with relative thyroid insufficiency and accompanied IDDS, at a later period of adult life particularly if the ID is not corrected in such regions? Infants and children in such environment may even develop other syndromes of hyperlipidaemias at a higher proportion. We believe this is an additional pressing factor (apart from the development of neurological cretinism, low I.Q and mental retardation etc in infants and children of ID regions) (4,25) which calls for immediate intervention to prevent such long term effect of ID. The intervention may be carried out in the form of (26); a) iodization of salt and water, b) intake of iodized oral capsules (lipiodol, made by Laboratoire Guerbet, France) – one capsule (containing 200mg of iodine) is sufficient for one year protection, or iodized oil injection Lipiodol (made by Laboratoire Guerbet, France), one injection (1ml) containing 480mg of iodine) capable of providing projection for 3 years to the pregnant women. In addition, iodized oil oral spray (once in a year) can be given to the newborn infants in such areas. Many have tried iodized bread in the communities affected with significant ID with great success. (26,27).

REFERENCES

1. Hetzel BS. Iodine deficiency disorders (IDD) and their eradication. *Lancet* ii 1983;1126-9.
2. Delong R. Neurological involvement in iodine deficiency disorders. In: Hetzel B.S, Dunn J.T, Stanbury J.B eds. *The prevention and control of Iodine Deficiency Disorders*. Amsterdam: Elsevier, Bio-medical Division 1987: pp 49-63.
3. Medeiros-Neto G. Iodine deficiency disorders. *Thyroid* Mary Ann Liebert Inc 1990; 1:73-82.
4. Vanderpas J, Boardoux P, Lagasse R. et al. Endemic infantile hypothyroidism in a severe endemic goiter area of central Africa *Clin Endocrinol* 1984; 20: 327-32.
5. Das SC, Isichei UP, Otokwula AA, Emokpae MA, Mohammed AZ. Neonatal chemical hypothyroidism in Nigeria. *Ann Trop Paed* 2004;24: 237-40.

6. Kochupillai N. Incidence of neonatal chemical hypothyroidism (NCH) in areas of severe environmental iodine deficiency and endemic cretinism. In: Therell BL Jr, ed. *Advances in Neonatal screening*. Amsterdam: Elsevier, Bio-medical Division 1987: pp 53-5.
7. Kochupillai N, Pandav CS, Godbole MM, Mehta M, Ahuja MMS. Iodine deficiency and neonatal hypothyroidism. *Bull. WHO* 1986; 64: 551-67.
8. Das SC, Isichei UP. Hypothyroidism and its effect on thyroid tissue and plasma lipids. *Ind J Expt Biol* 1988; 26:92-4.
9. Hetzel BS. An overview of the prevention and control of iodine deficiency disorders. In: Hetzel BS, Dunn J.T, Stanbury JB, eds. *The Prevention and control of Iodine Deficiency Disorders*. Amsterdam Elsevier, Bio-medical Division 1987:pp 7-31.
10. Scriba PC, Beckers C, Burgi H et al. Report of the subcommittee for study of Endemic Goitre and iodine deficiency of the European Thyroid Association. *Lancet I* 1985:1289-93.
11. Das SC, Isichei UP, Egbuta JO, Banwo AI. Cations and anions in drinking water as putative contributory factor to endemic goitre in Plateau State, Nigeria. *Trop Geogr Med* 1989; 41: 352-66.
12. Das SC, Isichei UP. Feto-maternal thyroid function inter-relationships in an iodine deficient region in Africa-the role of T3 as possible fetal defense. *Acta Endocrinol* 1993;128:116-9.
13. Isichei UP, Das SC, Egbuta JO. Central cretinism in four successive siblings. *British Postgrad Med J* 1989; 66: 751-6.
14. Isichei UP, Morimoto I, Das SC, Egbuta JO, Banwo AI, Nagataki S. Endemic goiter in the Jos Plateau region of Northern Nigeria. *Endocr J* 1995; 42:23-9.
15. Laboratory Manual,. Serum lipids and lipoproteins. Laboratory Manual series. Boehringer Mannheim GmbH, Mannheim, Germany 1986.
16. Friedwald WT. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. *Clin Chem* 1972; 13(6): 499-502.
17. Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramidul L, Berguist H. Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *J Clin Endocrinol Metab* 1978; 47:354-360.
18. Levin HM. Economic dimension of iodine deficiency disorders. In Hetzel B.S, Dunn J.T, Stanbury J.B, eds. *The Prevention and control of Iodine Deficiency Disorders*. Amsterdam: Elsevier, Bio-medical Division 1987: pp 195-208.
19. Das SC, Isichei UP, Mohammed AZ, Otokwula AA, Emokpae A. Impact of iodine deficiency on thyroid function in pregnant African women – a possible factor in the genesis of 'small for dates' babies. *Ind J Clin Biochem* 2005; 20(2):35-42.
20. Kannel WB. Serum lipid precursors of coronary heart disease. *Human Pathol* 1973;2:109-13.
21. Castelli WB Cholesterol and other lipids in coronary heart disease: The cooperative lipoprotein phenotyping study. *Circulation* 1977;55:76-9.
22. Keys A. Coronary artery disease in seven countries. *Circulation* 1970; 42(suppl. 2): 211-4.
23. Das SC, Isichei UP. Beta lipoprotein cholesterol, Beta lipoprotein and associated major serum lipids in healthy Nigerians. *Nigerian. Postgrad Med J* 1997; 4: 88-92.
24. Taylor GO. Studies on serum lipids in Nigerians. *Trop Geogr Med* 1971; 23:158-66.
25. Delong GR, Stanbury JB, Fierro-Benitez R. Neurological signs in congenital iodine-deficiency disorders (endemic cretinism). *Dev Med Child Neurol* 1985; 27:317-20.
26. Dunn JT, Thilly C, Pretell E. Iodized oil and other alternatives to iodized salt for the prophylaxis of endemic goiter and cretinism. In: Dunn J.T, Pretell E.A, Daza C.H, Viteri P.E, eds. *Towards the eradication of Endemic Goitre, Cretinism, and Iodine Deficiency*. Pan American Health Organization, Washington 1986: pp 170-77.
27. Dunn JT. Alternatives to salt and oil for iodine supplementation. In: Hetzel B.S, Dunn J.T, Stanbury J.B, eds. *The Prevention and Control of Iodine Deficiency Disorders*. Amsterdam; Elsevier, Bio-medical Division 1987: pp 135-8.