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RESEARCH ARTICLE

EVALUATION OF THYROID STIMULATING HORMONE AND FREE THYROXINE AND THEIR CORRELATIONS WITH OTHER BIOMARKERS IN SUDANESE PRE-ECLAMPTIC CASES

***[1]Hind M Beheiry, [2]Ibrahim A Ali, [3]Hiba A Awooda, [4]Duria A. M. Rayis, [5]Ibtisam Ahmed Ali and [6]Amal M Saeed**

[1]Department of Physiology, Faculty of Medicine, International University of Africa, Khartoum, Sudan
[2]Department of Physiology, Faculty of Medicine, Hayatt University College
[3]Department of Physiology, Faculty of Medicine, Alneelain University, Khartoum, Sudan
[4]Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum
[5]Department of Medicine, Faculty of Medicine, International University of Africa, Khartoum, Sudan
[6]Department of Physiology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan

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ABSTRACT

Introduction: Pregnancy causes stress on thyroid gland especially in areas of iodine deficiency. Women with pre-eclampsia are more likely to have slightly reduced thyroid function during the last weeks of their pregnancies.
Objectives: This study was to assess changes in serum Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4) in pre-eclamptic cases compared to second-half normal pregnant and non-pregnant Sudanese women and their correlations to other biomarkers.
Methods: This was a case-control study, in Omdurman Maternity Hospital, Sudan. The pre-eclamptic cases (72) were compared to control second-half normal pregnant (96) and non-pregnant (63) Sudanese women. The groups were matched. The clinical and laboratory investigations were undertaken at St Hellier s hospital – London. TSH was measured by two-site sandwich immunoassay and Free T4 by competitive immunoassay using chemiluminescent technology. Liver and renal function tests were performed using atomic absorption spectrophotometer (SiemensAdvia2400 Chemistry System Serial No CA12420098and No a12420083).
Results: There was a highly significant difference in mean of TSH in mU/L between pre-eclamptic (2.52 ± 1.15) and non-pregnant (1.36 ± 0.71) (P-value = 0.000), between pre-eclamptic (2.52 ± 1.15) and pregnant (1.53 ± 0.79) (P-value = 0.000), but no significant difference between non-pregnant (1.36 ± 0.71) and pregnant (1.53 ± 0.79) (P-value = 0.237). There was a highly significant difference in mean of FT4 in pmol/L between non- pregnant (16.11 ± 2.02) and pregnant (13.55 ± 2.09) (P-value = 0.000), between non- pregnant (16.11 ± 2.02) and pre-eclampsia (13.96 ± 2.18) (P-value = 0.000), but no significant difference between pregnant (13.55 ± 2.09) and pre-eclampsia (13.96 ± 2.18) (P-value = 0. 213). TSH, in pre-eclampsia, has significant correlations with serum uric acid (r=0.50, P=0.049), serum albumin (r = 0.28, P = 0.018) , serum Aspartate transferase (AST) (r= 0.24 P= 0.049) and urine protein (r = 0.42, P = 0.000); but had no significant correlations with blood pressure or serum Alanine Transferase (ALT) (r= 0.03, P= 0.792). FT4, in pre-eclamptic cases, had no significant correlations, except with urine creatinine (r=0.3, P=0.003).
Conclusions: This study revealed that TSH was significantly increased in pre-eclamptic when compared to normal pregnant and non-pregnant women, FT4 was significantly decreased in pre-eclamptic cases when compared to non-pregnant women.

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INTRODUCTION

Preeclampsia isdescribed as a new onset of hypertension (SBP >140 mm of Hg or DBP >90mm of Hg) and proteinuria (>0.3g or 300mg protein in a 24 hour urine specimen or 1+ on dipstick) after 20 weeks of gestational age, it's also referred to it as toxemia of Pregnancy (Mashiloane, 2002). Preeclampsia may be associated with other signs and symptoms, such as pitting edema, headache, visual disturbances, and epigastric pain after 20th week gestation in a previously normal pregnant lady with no history of hypertension or proteinuria (American College of Obstetricians and Gynecologists, 2002 and Reports of the National High Blood Pressure Education Program Working Group report on high blood pressure in Pregnancy, 2000). Preeclampsia is a leading cause of maternal and fetal morbidity andmortality in developing countries (Cunningham, 2010 and Sibai & Dekkar, 2005). The most affected organs arekidney, liver and brain; and due to auto-intoxication, functional disorders in theseorgans system are evidential

Corresponding author: Hind M Beheiry
Department of Physiology, Faculty of Medicine, International University of Africa, Khartoum, Sudan

(Duha, 2001). Reduction in utero-placentalperfusion regard as a major cause of fetal compromise in preeclampsia (Bellamy, 2007 and Soloman, 2004). Preeclampsia disorder isunique to human pregnancy in whichnumerousenvironmentaland genetic immunological factorsinteract (Irgens, 2001). Changes in thyroidfunctions are well documented during normal pregnancy. However, information about thyroid functions in preeclampsia is limited in Sudan. During normal conception, thyroid activity undergoes many alterations due to elevated circulating estrogen levels (Kumar, 2005). There is a significant increase in total Thyroxine (TT4), total Tri-iodothyronine (TT3) and thyroglobulin (TGB), It is known that human chorionic gonadotropin (HCG) is stimulating thyroid gland, because alpha subunits of HCG and thyroid stimulating hormone (TSH) is identical. Also, renal iodide clearance increases due to increased glomerular filtration rate (Sardana, 2009 and Fantz, 1999). Although pregnancy is usually associated with mild hypothyroidism, pregnant ladies complicated withpre-eclampsia have high risk of incidence of maternal hypothyroidism that might correlates with these verity of preeclampsia (Lain, 2002). Maternal hypothyroidism is the most common thyroid function abnormalities which occur during pregnancy. It has been associated with fetal effects such as fetal loss, premature birth, increased neonatal respiratory distress, reduced intellectual function in the offspring, low birth weight and adverse maternaloutcomes such as placental abruption, pregnancy inducedhy pertension (PIH) and post partum hemorrhage (Casey, 2005 and Abalovich, 2002).

As the maternal hypothyroidismhas been listed as one of the causes of high blood pressure i.e. the physiological changes in thyroidgland during pregnancy have been suggested asone of the patho-physiological cause ofpre-eclampsia (Endo, 1979). Some investigators reported no change in serum TSH and /or T 3 and T4 in pregnancy; while some found significant increases in TSH and /or T3 and T4 during pregnancy. Nahid *et al*., 2002-2004, in Iran, performed a prospective case-control study to identify the association between the maternal hypothyroidism and pre-eclampsia and they found that themean TSH levels was not significantly higher in pre-eclamptic group as compared to controls ($p>0.05$) (Nahid Mostaghel, 2008). Larijani *et al*., 2004, performed a study in maternal thyroid hormones and pre-eclampsia. They showed that serum levels of free T4 and TSH were increased in women with severe pre-eclampsia when compared with mild pre-eclampsia and normal pregnancy (Larijani, 2005). Kumar *et al*., 2005, as well, performed a study that showed significant elevation in mean serum TSH but FT3 and FT4 were without alterations in pre-eclampsia women (Kumar, 2005). Several studies done by Mostaghel *et al*, Kharb *et al* and Raoofi *et al*., (Mostaghel, 2008; Kharb, 2013; Raoofi, 2014), revealed similar result to Kumar *et al* study as increased level of TSH and decreased levels of T3 and T4 in pre-eclampsia women in compared with normal pregnant women. Ashoor *et al*., 2010, performed a study showed increase serum TSH and decreased in T4 with gestational age (Ashoor, 2010). Khadem *et al*., 2012, in Iran, performed similar study but with different result that showedno changes in FT3, FT4 and TSH levels and stated they do not support the hypothesis of thyroid hormones changes as apossible etiology of pre-eclampsia (Khadem, 2012). Sonali *et al*., 2012 - 2014, performed a case control study. They found that there was a significant association between pre-eclampsia and thyroid hypofunction (Sonali Deshpande, 2015). Hosen *et al*., 2014, in Bangladesh, performed a similar study and found that there was significantly decreased concentration of FT4 were observed in the pre-eclamptic group compared with the normal pregnant group while the TSH level was significantly high (http://creativecommons.org/ licenses/ by/4.0). Satyanarayan *et al*. in 2015, investigated the maternal thyroid profile in pre-eclampsia. The study revealed that there was no significant difference in FT4 and FT3 levels in two groups, but there was a significant increase in TSH levels in pre-eclampsia patients compared to normal pregnancy (Anitha, 2015). Sonal et.al, 2015, in India,studied the difference in T3 and T4 between pre-eclamptic and normotensive pregnant women and they was found no significant differences between the both groups (Sonal Sogani, 2015). Enaam *et al*, In Sudan, performed a case controlstudy and found no significant correlation between TSH and pre-eclampsia, but both FT3 andFT4 were significantly higher in pre-eclamptic women than healthy (Enaam, 2015). Finally, it is reported that women with pre-eclampsia may be at an increased risk factor developing hypothyroidism later in life (Levin, 2009). Despite, the variations in published papers, from different countries, in all over the world;could there be a difference in thyroid profile of pre-eclamptic Sudanese women? This is clearly a valid question. In this study the main objective is to assess changes in serum TSH and FT4 in pre-eclamptic cases compared to normal pregnant Sudanese women and its relations to other pre-eclamptic markers.

MATERIALS AND METHODS

This is a cross-sectional, case-control and hospital-based study performed during a two year period from December 2008 to December 2010; in Omdurman Maternity Hospital, in concomitance with another study. The objectives of the study were to assess changes in serum TSH and FT4 in pre-eclamptic cases compared to second-half normal pregnant and non-pregnant Sudanese women and their correlations to other biomarkers. The samples selection was done by a systematic random selection every other day. It was included three groups, 70 pre-eclamptic newly discovered and/or already diagnosed and followed-up cases in their recent pregnancies, 70 normal pregnant in their second half of pregnancy (20 weeks of pregnancy and onwards) and 70 non- pregnant (control) women; a total of at least 210 subjects. Selected participants were informed about the study; and their written consent was taken prior to admission into the antenatal ward for one day they were assured about the privacy of the data. The inclusion criteria required all the pregnant participants to be in the second half of pregnancy with regular follow–up cardsand all the non-pregnant to have no history of diabetes mellitus, essential hypertension, renal disease or any other chronic disease. The exclusion criteria included subjects with multiple pregnancies and/or have any obstetrical abnormality like placenta praevia, polyhydramnias …etc.

The enrolment of pregnant women for the study was performed by the assigned obstetricians in the antenatal care clinics.Questionnaire Interviews with all participants were done covering information about the age, demographic characteristics and past medical and obstetrical history. Physical examination of the blood pressure - height – weight and calculation of body mass index was done, and then complete medical and obstetrical examination was performed by the assigned Obstetrician followed by confirmatory ultrasonographic measurement of the fetal biparietal diameter of the head and the femur length to confirmthe dates and

viability. Eight ml of venous blood were collected by the standard procedure subject from the anticubital vein under complete aseptic conditions. 5 ml of blood were placed in vacuumed container (Plain Tube) without anti-coagulant; to extract serum for biochemical analysis.

Spearman's test, t□student, Chi□square, Independent sample T-test and Bivariate correlation test. P≤0.05 was considered statistically significant.

Table 1. Descriptive Statistics According to Category of participant

Category of participant	Thyroid stimulating hormone mU/L	Free thyroxine 4 in pmol/L
Non pregnant	1.36 ± 0.71	16.11 ± 2.02
Pregnant	1.53 ± 0.79	13.55 ± 2.09
Pre-eclampsia	2.52 ± 1.15	13.96 ± 2.18
P-value	.000*	.000*

*Normal p-value is <0.05; therefore the statistical difference is highly significant; values are expressed as Mean ± SD.

Table 2. Multiple Comparisons of Thyroid stimulating hormone (mU/L)

Dependent Variable	(I) Category of participant	(J) Category of participant	Mean Difference (I-J)	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Thyroid stimulating hormone mU/L	Non pregnant	Pregnant	-0.173	0.237	-0.460	.1150
		Pre-eclampsia	-1.158	.000*	-1.464	-0.852
	Pregnant	Non pregnant	.1730	.2370	-.115	.4600
		Pre-eclampsia	-0.985	.000*	-1.263	-0.708
	Pre-eclampsia	Non pregnant	1.158	.000*	.8520	1.464
		Pregnant	.985	.000*	.7080	1.263

*Normal p-value is <0.05; therefore the statistical difference is highly significant.

Table 3. Multiple Comparisons of Free thyroxine (pmol/L)

Depentent Variable	(I) Category of participant	(J) Category of participant	Mean Difference (I-J)	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Free thyroxine 4 in pmol/L	Non pregnant	Pregnant	2.554	0.000*	1.883	3.226
		Pre-eclampsia	2.145	0.000*	1.431	2.859
	Pregnant	Non pregnant	-2.554	0.000*	-3.226	-1.883
		Pre-eclampsia	-0.409	0.213	-1.055	0.236
	Pre-eclampsia	Non pregnant	-2.145	0.000*	-2.859	-1.431
		Pregnant	0.409	0.213	-0.236	1.055

*Normal p-value is <0.05; therefore the statistical difference is highly significant.

Table 4. Comparison between TSH and Free thyroxine in Sudanese patients

Correlations		Serum Albumin in g/L	Serum Alanine transferse (Liver enzyme) U/L	Serum Aspartate transferse (Liver enzyme) U/L	Serum Uric Acid in mmol/L	Urine creatinine mmol/L	Serum creatinine umol/L
Thyroid stimulating hormone mU/L	Correlation Coefficient	-0.28	-0.03	0.24	0.50	-0.09	0.21
	P-value	0.018	0.792	0.049	0.000	0.444	0.076
Free thyroxine 4 in pmol/L	Correlation Coefficient	0.08	0.00	0.05	0.02	-0.35	-0.15
	P-value	0.507	0.998	0.670	0.849	0.003	0.203

Other 3 ml of blood were placed in vacuumed container with EDITA (anti-coagulant); for detection of complete blood picture. Total blood count, liver enzymes, serum creatinine and urine creatinine, serum albumin, uric acid and urine protein (using dipstick test) were measured. Creatinine clearance and GFR were calculated.Serum trace elements zinc, copper, selenium and magnesium were measured using atomic absorption spectrophotometer (SiemensAdvia 2400 Chemistry System Serial No CA12420098 and No CA12420083) . All of the biochemical investigations were performed in St Helier Hospital, London. TSH was measured by two-site sandwich immunoassay using direct chemiluminescent technology and free T4was measured by a competitive immunoassay using direct chemiluminescent technology.

Statistical analysis

The data was analyzed by SPSS software R 9.0 (SPSS, Inv., Chicago, IL, USA) program Version 20, with the use of

Ethical consideration

Ethical approval was given by the Research Committee (Faculty of Medicine, U of K). Permission was given from Omdurman Maternal Hospital to conduct the study for cases of pre-eclampsia and normal pregnant subjects. Written consent of all the study subjects was given prior to entry in the study.

RESULTS

Table (1) shows the mean TSH and FT4, for the non-pregnant participants, were 1.36 ± 0.71 mU/L and 16.11 ± 2.02 pmol/L respectively. The mean TSH and FT4, for the normal pregnant participants, were 1.53 ± 0.79 mU/L and 13.55 ± 2.09 pmol/L respectively. The mean TSH and FT4, for the pre-eclamptic cases, were 2.52 ±1.15 mU/L and 13.96 ± 2.18 pmol/L respectively. There was a highly significant difference in mean of TSH in mU/L between Pre-eclamptic (2.52 ± 1.15) and Non pregnant (1.36 ± 0.71) (P-value = 0.000), between Pre-

eclamptic (2.52 ± 1.15) and Pregnant (1.53 ± 0.79) (P-value = 0.000), but no significant difference between Non pregnant (1.36 ± 0.71) and Pregnant (1.53 ± 0.79) (P-value = 0.237).(see Table 2). There was a highly significant difference in mean of Free thyroxine 4 in pmol/L between Non pregnant (16.11 ± 2.02) and Pregnant (13.55 ± 2.09) (P-value = 0.000), there was a highly significant difference in mean of Free thyroxine 4 in pmol/L between Non pregnant (16.11 ± 2.02) and Pre-eclampsia (13.96 ± 2.18) (P-value = 0.000), but there was no significant difference in mean of Free thyroxine 4 in pmol/L between Pregnant (13.55 ± 2.09) and Pre-eclampsia (13.96 ± 2.18) (P-value = 0. 213) (see Table (3). TSH, in pre-eclampsia, has significant correlationswith serum uric acid (r=0.50, P=0.049), serum albumin (r = 0.28, P = 0.018) , serum Aspartate transferase (AST) (r= 0.24 P= 0.049) and urine protein (r = 0.42, P = 0.000); but had no significant correlations with blood pressure or serum Alanine Transferase (ALT) (r= 0.03, P= 0.792). FT4, in pre-eclamptic cases, had no significance correlations, except with urine creatinine (r=0.3, P=0.003). (see Table 4)

DISCUSSION

Pre-eclampsia is a serious disorder of pregnancy with unknown ethological factors that may occur at any stage of second or third trimester of pregnancy (Hasanzadeh, 2008 and Vahid roudsari, 2008). In recent years, the relationship between thyroid dysfunction and complicated pregnancies has been a big matter of concern. However, there is still controversy surrounding this topic and its need further expansions and researches. Some investigators reported no change in serum TSH and / or T 3 and T4 in pregnancy, while some found significant increases or decrease in TSH and / or T3 and T4 during pregnancy. Despite, the variations in published papers, from different countries, in all over the world;could there be a difference in thyroid profile of pre-eclamptic Sudanese women? This is clearly a valid question.

In the present study, TSH was significantly increased in pre-eclamptic women when compared to normal pregnant and non-pregnant women; these findings are in agreement with several studies in literature (Larijani, 2004; Kumar, 2005; Mostaghel, 2008; Kharb,, 2013; Raoofi,, 2014; Ashoor, 2010; Sonali Deshpande,, 2015; http://creativecommons.org/licenses/by/4.0 and Anitha, 2015). In the other hand; Nahid *et al* (Nahid Mostaghel, 2008). Khadem *et al* and Enaam *et al*. studies showed no changes in the level of TSH in both case and control groups. The difference in the results of their studies with the results of the present study could be various geographical areas, different races, and different diets. In this study FT4 was significantly decreased in pre-eclamptic cases when compared to non-pregnant women, this finding is in accordance with severalprevious studies in the literature. This finding is not agree with Larijani *et al* and Enaam *et al*. studies which showed increased in free T4 in women with severe preeclampsia when compared with mild preeclampsia and normal pregnancy.

Contradictory findings was observed by Satyanarayan *et al*. and Sonal et.al showed no difference in the serum level of T4 between preeclamptic and normal women. The difference in the results of their study with the results of the present study could be also due various geographical areas, different races, and different diets. The significant correlations of TSH with serum uric acid, serum albumin and Serum Aspartate transferase (AST) U/L need further elaboration and open a big question about the role of TSH as prognostic or predicted factor to develop hepatic complication of preeclampsia.

Conclusion

This study revealed that TSH was significantly increased in pre-eclamptic when compared to normal pregnant and non-pregnant women; FT4 was significantly decreased in pre-eclamptic cases when compared to non-pregnant women. TSH, in pre-eclamptic cases, had no significant correlations with blood pressure or serum ALT but with urine protein (r = 0.42, P = 0.000), serum uric acid (r=0.50, P=0.049). FT4, in pre-eclamptic cases, had no significance correlations, except with urine creatinine (r=0.3, P=0.003).TSH had significant correlations in pre-eclamptic cases with urine protein, serum uric acid , serum albumin and serum AST,FT4 had significant correlation with urine creatinine. Further researches about the relation between thyroid dysfunction and preeclampsia needed to be done in the future and a question about the use of thryoid profile as a screening program for pregant ladies with obvious risk factors of preeclampsia or pregnancy induced hypertension(PIH) should be answerd.

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