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MATERNAL IODINE DISORDER, OXIDATIVE STRESS STATUS AND THYROID FUNCTION AMONG PREGNANT SAUDI WOMEN

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ABSTRACT:

Pregnancy is associated with physiological changes in thyroid function. We aimed to assess iodine status and thyroid dysfunction among pregnant women. 150 pregnant women were analyzed for serum and urinary iodine levels, free tri-iodothyronine hormone (FT3), free thyroxine hormone (FT4), thyroid stimulating hormone (TSH), thyroperoxidase antibodies (TPO-Abs), thyroglobulin antibodies (TG-Abs), total antioxidant status (TAS) and antioxidant enzymes as superoxide dismutase (SOD) and glutathione peroxidase (GPx) were measured. The3rd trimester pregnant women declined urinary and serum iodine by -37.5% and -36.6%, respectively. Mild serum iodine deficiency was detected during 1st trimester, 4% (2/50) and more deficiency was detected during 2nd and 3rd trimester 18% (9/50) and 24% (12/50), respectively. The FT3 and FT4 levels of 3rd trimester were declined by -14.7% and -30.6%, respectively, and accompanied with increment in TSH by +80.4%. TPO-Abs was elevated among 2nd and 3rd trimester by +216.7% and +244%, respectively. TG-Abs was elevated among 2nd and 3rd trimester by +47.4% and 87.1% respectively. 3rd trimester decreased SOD, GPx and TAS by -28.6%, -36.1% and -30%, respectively. 1st and 2nd trimester declined GP_X by -16.7% and -26.6%, respectively. Positive correlation between urinary and serum iodine, negative correlation between TSH and each of FT3 and FT4, positive correlation between TPO-Abs and urinary iodine and negative correlation between TPO-Abs and serum iodine were detected. We conclude that mild thyroid hormones, iodine levels and oxidative stress abnormalities were detected among pregnant women. These findings lead us to recommend the measuring of iodine and thyroid hormones levels as a routine check-up to avoid adverse effects on maternal thyroid function.

Keywords: Pregnancy, Iodine, Thyroid function, Oxidative stress, Thyroperoxidase antibodies (TPO-Abs), Thyroglobulin antibodies (TG-Abs).

[I] INTRODUCTION

Pregnancy is associated with physiological changes in thyroid function resulting from a combination of several factors specific for the pregnancy state. These changes may result in a state of hypothyroidism [1,2]. The symptoms of hypothyroidism in pregnancy include extreme fatigue, cold intolerance, muscle cramps, constipation and problems with memory or concentration. High levels of thyroid stimulating hormone (TSH) and low levels of free thyroxine (FT4) generally indicate hypothyroidism. Because of normal pregnancy-related changes in thyroid function, test results must be interpreted with caution. The TSH test can also identify sub-clinical hypothyroidism (mild form of hypothyroidism that has no apparent symptoms) that occurs in 2-3 of every 100 pregnancies

showing high levels of TSH and normal FT4. If sub-clinical hypothyroidism is discovered during pregnancy, treatment is recommended to help ensure a healthy pregnancy [3].

The trace elements iodine plays an essential role in the thyroid gland under normal physiological conditions and in disease of pregnant and non-pregnant women [4,5]. A sufficient level of iodine is required for the proper functioning of the body's thyroid stimulating hormones (TSH), T4 and tri-iodothyronine (T3) that stimulate growth and other metabolic activities [6]. A low level of iodine can lead to fall in the level of T4. This can result in the simultaneous release of TSH and increased in T3 production which is 100 times more biologically active than T4 in iodine utilization and conservation for biosynthesis. Similarly, thyroid hormones are de-iodinated in the liver thereby releasing iodine back into the blood circulation for reuptake and reuse by the thyroid gland. Even under these circumstances, iodine is passively lost in the urine [6].

It was extensively investigated that deficiency of iodine remain a major health problems affecting greater than or equal to 30% of the global population [7]. Saudi Arabia is between the moderate iodine-deficient countries [7]. Diminished iodine intake is rampant in developing countries due to inadequate consumption of iodine and in developed countries where there is decline in iodine consumption or where consumed vegetables are grown in iodine-deficient soils. If there is insufficient iodine in the body, the thyroid gland responds to iodine deficiency by developing goiter in order to capture more iodine which supports normal growth development [8]. Eradication of iodine deficiency disorders (IDD) is a global public health priority [9,10]. The addition of iodine to table salt has largely eliminated IDD in the several nations. However, iodine deficiency still remains a serious public health problem in some areas of the world. Iodine supplements during pregnancy together with proper salt iodization relieve the stress of iodine deficiency of both maternal and fetal thyroid function, together with the prevention of fetal brain damage that results from maternal iodine deficiency [11].

This study was undertaken to assess the maternal iodine status among pregnant women in Almadina Almunawarah *via* the assessment of iodine levels in the blood and urine samples as one of the major strategies in knowing the iodine levels in pregnant women. Besides, the biochemical serum analysis of the total antioxidant status (TAS), antioxidant enzymes levels such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) and serum thyroid profile such as free tri-iodothyronine hormone (FT3), free thyroxine hormone (FT4), thyroid stimulating hormone (TSH), thyroperoxidase antibodies (TPO-Abs) and thyroglobulin antibodies (TG-Abs) will be carried out.

[II] MATERIALS AND METHODS

2.1. Chemicals and Kits

The serum FT3 and FT4 ELISA kits were purchased from Atlas Medical Co., UK. The serum TSH ELISA kits was purchased from ANOGEN Co., Canada. The serum TPO-Abs ELISA kit was purchased from EIAab Co., China. The serum TG-Abs ELISA kit was purchased from Hölzel Diagnostic Co., Germany. The TAS, SOD and GPx spectrophotometric kits were purchased from Randox Laboratories Ltd., UK. All other chemicals used were of the highest available grades.

2.2. Subjects and Samples Collection

150 pregnant women were selected for this study. All subjects were normotensive healthy pregnant women free from diabetes mellitus, renal diseases, liver diseases and anemia. A total of 300 samples comprising of 150 blood and 150 urine samples were collected during the 1st, 2nd and 3rd trimester of pregnancy from the pregnant women who attended the maternity clinics in Ohud Hospital, Madina Maternity Children Hospital and two other primary health care

centers in Almadinah Almunawarah. A 100 non pregnant women samples (50 urine and 50 blood) were studied as controls.

A 10 ml blood was collected in vaccutainer tube and allowed for few minutes to clot to obtain the serum. Preservation of the blood samples began at the site of the collection using ice packs blocks and transported immediately to the laboratory. A 10ml urine samples were collected, preserved by adding 2 drops of 20% formalin and kept in the refrigerator to minimize volatilization of iodide and analyzed within 24 hrs. Both the urinary and serum iodine were estimated. Serum samples were stored at -20°C until further analysis to assess the thyroid status through the measurement of serum FT3, FT4, TSH, TG-Abs and TPO-Abs. Besides, serum SOD, GPx and TAS activities were assessed.

2.3. Biochemical Parameters Estimation

The laboratory analysis of the iodine in blood and urine samples was done by the titrimetric methods for determining salt iodate content in fluids according to the WHO guidelines on iodine testing [7,12]. 1 ml of each blood and urine sample was diluted with 20 ml of water and the pH was adjusted to 2.8 by the addition of 0.6% HCl dropwise, after which 2 ml of the 30% KI was added to convert all the iodate to elemental iodine. The liberated iodine was titrated with freshly prepared sodium sulphate solution using 1% starch solution as the end or equivalence point indicator. The titre value obtained at this point was multiplied by 1.058×10^{-4} to obtain the concentration of serum or urinary iodine in (μg%).

Serum FT3, FT4 and TSH were assessed quantitively using ELISA kits. The FT3 and FT4 were expressed as pmol/L, however the TSH was expressed as mIU/L. The serum TPO-Abs and TG-Abs were measured spectrophotometric kits and expressed as IU/ml. The Normal levels for were adjusted to each trimester according to laboratory standards.

The SOD and GPx were determined using spectrophotometric kits. SOD activity was measured by the degree of inhibition of formazan dye formation at 550nm and expressed as U/mg protein. While, GPx activity based on the measuring the disappearance of NADPH at 340 nm and was expressed as U/mg protein.

TAS was measured in serum spectrophotometrically using kit that based on the incubation of 20μl serum in a cuvette with 1ml of chromogen reagent composed of 610μmol/L ABTS [2,2`-Azino-di-(ethylbenzthiazoline sulphonate)] and 6.1μmol/L metmyoglobin. The reaction mixed well and the initial absorbance (A_1) was recorded. Then, the substrate was added (200μl of 250μmol/L H_2O_2). The contents were mixed well and the absorbance was recorded after 3 min (A_2). The ΔA was calculated for each of the sample, standard and blank.

The total antioxidant status (mmol/L) was calculated from the following equation:-

TAS (mmol/L)=factor×($\Delta A_{blank} - \Delta A_{sample}$);

Factor =standard conc. / ($\Delta A_{blank} - \Delta A_{standard}$)

2.4. Data Analysis

Results were reported as mean±standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA). If the overall P-value was found statistically significant, further comparisons among groups were made according to post hoc Tukey's test. Criteria for significance was chosen to be at $p<0.05$. Pearson's correlation coefficient was used to compare the correlation between different parameters. The statistical analysis was performed using GraphPad InStat 3 software while the figures were sketched using GraphPad Prism version 4 software (GraphPad software, Inc. La Jolla, CA, USA).

[III] RESULTS

The pregnant women in their 3rd trimester elicited significant decline in both urinary iodine and serum iodine by -37.5% and -36.6%, respectively compared to normal non-pregnant mothers.

However, the 1st and 2nd trimester pregnant mothers showed non-significant decline in serum and urinary iodine [Table-1]. Among pregnant mothers, mild serum iodine deficiency was detected during the 1st trimester 4% (2/50) and elevated during the 2nd trimester and 3rd trimester to be 18% (9/50) and 24% (12/50), respectively [Table-2]. These findings were concomitant with the urinary iodine loss.

Concomitantly, the serum FT3 and FT4 levels of the 3rd trimester pregnant mothers were significantly declined by -14.7% and -30.6%, respectively compared to the non-pregnant mothers. These findings were accompanied with a huge significant increment in serum TSH level by +80.4% compared to the non-pregnant mothers [Table-3]. In contrary, the 1st trimester and 2nd trimester pregnant women showed non-significant changes in serum FT3, FT4 and TSH levels.

The serum TPO-Abs level was significantly elevated among 2nd and 3rd trimester pregnant mothers by +216.7% and +244%, respectively compared to the non-pregnant mothers [Table-4]. Similarly, the TG-Abs level was significantly elevated among 2nd and 3rd trimester pregnant mothers by +47.4% and +87.1% respectively compared to the non-pregnant mothers [Table-4].

The antioxidant profile of the pregnant women involved in this study showed significant decrease in SOD, GPx and TAS activities by -28.6%, -36.1% and -30%, respectively compared to the non-pregnant mothers. However, the 1st and 2nd trimester pregnant women elicited significant decline in GP_X activity only by -16.7% and -26.6%, respectively compared to the non-pregnant mothers [Table-5].

The linear regression analysis was conducted to evaluate the strength of associations between urinary iodine (µg%) and the serum iodine (µg%) [Figure-1A]. Also, between the serum TSH and each of the serum FT3 (pmol/L), serum FT4 (pmol/L) and serum TAS (mIU/L) of the 3rd trimester pregnant women involved in this study [Figure-1B, C and D, respectively]. There was a positive significant correlation noticed between urinary iodine and serum iodine (r^2=+0.1452, $p<0.05$). On the other hand, a significant negative correlation was observed between serum TSH and each of the serum FT3 and serum FT4 (r^2= -0.01, $p<0.1$ and r^2=-0.76, $p<0.0001$, respectively). However, the linear regression analysis showed no association between serum TSH and serum TAS activity.

The linear regression analysis between serum TPO-Abs levels (IU/ml) and its association with each of the urinary and serum iodine (µg%) levels of the 3rd trimester pregnant women were conducted [Figure-2A and B]. Similarly, the linear regression analysis between serum TG-Abs levels (IU/ml) and its association with each of the urinary and serum iodine levels of the 3rd trimester pregnant women was investigated [Figure-2C and D]. There was a positive significant correlation noticed between serum TPO-Abs and urinary iodine (r^2=+0.676, $p<0.05$). In contrary, a significant negative correlation was detected between serum TPO-Abs and serum iodine (r^2= -0.1267, $p<0.05$). However, the linear regression analysis showed no association between serum TG-Abs levels each of the urinary and serum iodine levels.

Table 1: Mean serum and urinary iodine of pregnant women.

Group		Parameter	Urinary iodine (µg%)	Serum iodine (µg%)
Group I:	Normal non-pregnant women			
		Range	4.5 – 33.6	5.5 – 36.3
		Mean ± SEM	18.4±1.8	19.1±1.7
Group II:	1st Trimester pregnant women			
		Range	5.6 – 31.1	6.1 – 29.6
		Mean ± SEM	15.1±1.7	15.7±1.6
		% Change from group I	-18%	-17.8%

Group III:	2nd Trimester pregnant women		
	Range	4.6 – 31.2	3.8 – 30.2
	Mean ± SEM	14.1±0.8	14.5±1.3
	% Change from group I	-23.4%	-24.1%
Group IV:	3rd Trimester pregnant women		
	Range	6.7- 15.1	1.9 – 16.2
	Mean ± SEM	11.5±1.4*	12.1±1.1*
	% Change from group I	-37.5%	-36.6%

Data represent the means±SEM (n = 50).
*Significant change difference compared to normal non-pregnant women, $p < 0.05$.

Table 2: Number of iodine deficient pregnant women (serum iodine <10□g%) involved in this study.

	1st Trimester n=50	2nd Trimester n=50	3rd Trimester n=50
No. of iodine deficient pregnant women	2 (4%)	9 (18.0%)	12 (24.0%)

Table 3: Mean serum FT3, FT4 and TSH of pregnant women.

Group	Parameter	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mIU/L)
Group I:	Normal non-pregnant women			
	Range	1.9 – 6.1	5.8 – 28.1	6.2 – 33.0
	Mean ± SEM	3.4±0.1	14.4±0.5	4.6±0.04
Group II:	1st Trimester pregnant women			
	Range	1.8 – 5.4	7.4 – 24.2	2.1 – 6.8
	Mean ± SEM	3.8±0.3	14.0±1.10	4.2 ±0.06
	% Change from group I	+11.8%	-2.8%	-8.7%
Group III:	2nd Trimester pregnant women			
	Range	1.3 – 6.2	5.4 – 29.2	3.3 – 18.2
	Mean ± SEM	3.7±0.2	12.1±1.23	5.6 ±0.03
	% Change from group I	+8.8%	-16%	+21.7%
Group IV:	3rd Trimester pregnant women			
	Range	1.1 – 6.5	3.5 – 22.0	3.8 – 12.1
	Mean ± SEM	3.9 ±0.18*	10.0±0.6*	8.3 ±0.04*
	% Change from group I	-14.7%	-30.6%	+80.4%

Data represent the means±SEM (n = 50).
*Significant change difference compared to normal non-pregnant women, $p < 0.05$.
TSH: thyroid stimulating hormone; FT3: free T3 hormone; FT4: free T4 hormone.

Table 4: Mean serum TPO-Abs and TG-Abs of pregnant women.

Group	Parameter	TPO-Abs (IU/ml)	TG-Abs (IU/ml)
Group I:	Normal non-pregnant women		
	Range	0.08- 3.1	23.6 – 89.9
	Mean ± SEM	1.8 ± 0.03	60.5 ± 3.7
Group II:	1st Trimester pregnant women		
	Range	0.923- 4.56	20.3 – 92.2
	Mean ± SEM	2.1 ± 0.6	66.1 ± 3.8
	% Change from group I	+16.7%	9.3%+
Group III:	2nd Trimester pregnant women		
	Range	2.3 – 14.3	33.1 – 100.5
	Mean ± SEM	5.7±0.91*	89.2 ± 7.8*
	% Change from group I	+216.7%	+47.4%
Group IV:	3rd Trimester pregnant women		
	Range	3.1 – 16.3	42.3 – 149.6
	Mean ± SEM	6.2± 1.6*	113.2± 9.92*
	% Change from group I	+244%	+87.1

Data represent the means±SEM (n = 50).
*Significant change difference compared to normal non-pregnant women, $p < 0.05$.
TPO-Abs: thyroid peroxidase antibodies, TG-Abs: thyroglobulin antibodies.

Table 5: Mean serum SOD, GPx and TAS of pregnant women.

Group	Parameter	SOD (% inhibition rate)	GPx (pmol/L)	TAS (mIU/L)
Group I:	Normal non-pregnant women			
	Range	45.6 – 82.4	13.4 – 35.0	3.2 – 9.5
	Mean ± SEM	70.2 ±8.1	25.2 ±1.6	6 ±0.2
Group II:	1st Trimester pregnant women			
	Range	41.1 – 85.6	12.3 – 29.1	1.9 – 10.7
	Mean ± SEM	61.4±6.2	21.0±1.1*	7.0 ±1.31
	% Change from group I	-12.5%	-16.7%	+16.7%
Group III:	2nd Trimester pregnant women			
	Range	40.6 – 71.3	13.4 – 32.0	2.0 – 8.8
	Mean ± SEM	57.1±3.7	18.5±1.3*	5.2 ±0.26
	% Change from group I	-18.7%	-26.6%	-13.3%
Group IV:	3rd Trimester pregnant women			
	Range	36.1 – 66.0	12.0 – 28.2	1.9 – 7.8
	Mean ± SEM	50.1 ±2.1*	16.1±1.4*	4.2 ±0.6*
	% Change from group I	-28.6%	-36.1%	-30%

Data represent the means±SEM (n = 50).
*Significant change difference compared to normal non-pregnant women, $p < 0.05$.
SOD: superoxide dismutase enzyme; GPx: glutathione peroxidase enzyme; TAS: total antioxidant status.

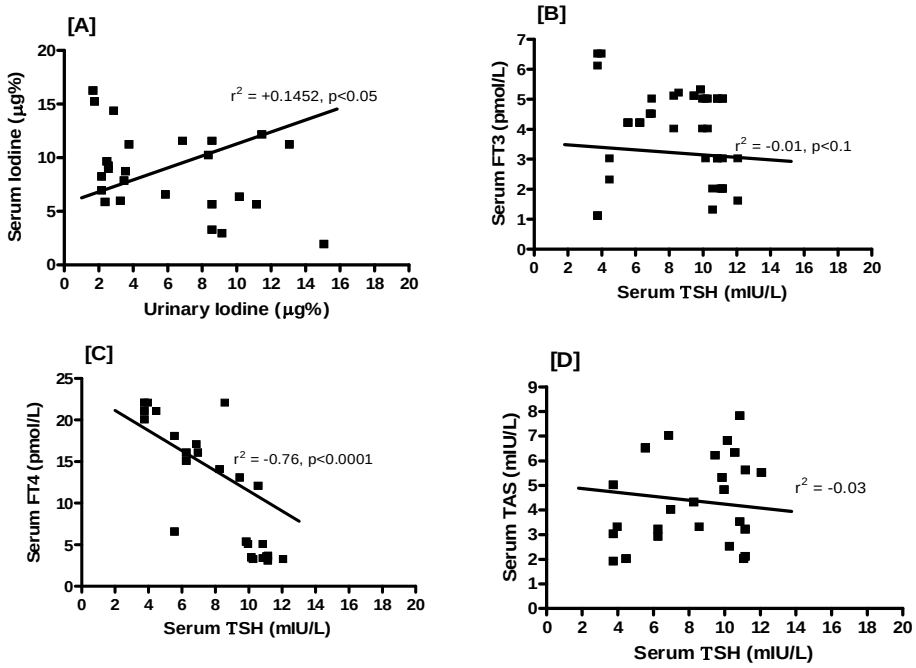

Figure 1. Linear regression analysis of some significant data of the 3rd trimester pregnant women involved in this study. Linear regression analysis**[A]** between urinary iodine levels (µg%) and serum iodine levels (µg%), r^2=+0.1452; P<0.05. The linear regression analysis between serum TSH (mIU/ml) and each of **[B]** serum FT3 (pmol/L), r^2= -0.01; P<0.1, **[C]** serum FT4 (pmol/L), r^2= -0.76; P<0.0001 and **[D]** serum TAS (mIU/L), r^2= -0.03,NS. Values were expressed as raw data. TSH: thyroid stimulating hormone; FT3: free T3 hormone; FT4: free T4 hormone, TAS: total antioxidant status; NS: non-significant.

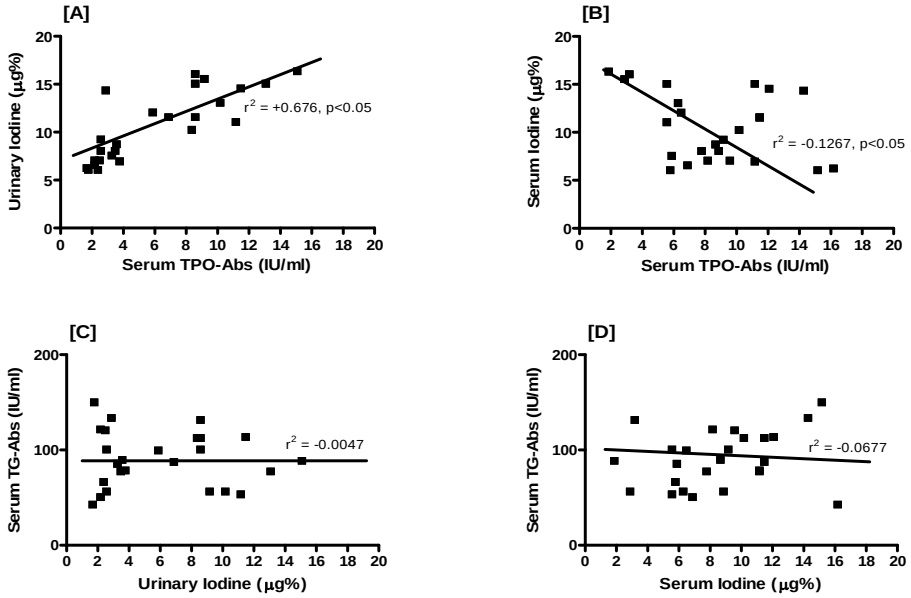

Figure 2. Linear regression analysis of some significant data of the 3rd trimester pregnant women involved in this study. Linear regression analysis **[A]** between serum TPO-Abs (IU/ml) and urinary iodine levels (µg%), r^2=+0.676; P<0.05, **[B]** between serum TPO-Abs (IU/ml) levels and serum iodine levels(µg%), r^2=-0.1267; P<0.05, **[C]**between urinary iodine levels (µg%) and serum TG-Abs levels (IU/ml), r^2=-0.0047, NS and **[D]** between serum iodine levels(µg%) and serum TG-Abs levels (IU/ml), r^2=-0.1267, NS. Values were expressed as raw data. TPO-Abs: thyroid peroxidase antibodies, TG-Abs: thyroglobulin antibodies; NS: non-significant.

[IV] DISCUSSION

Iodine is a important micronutrient for the human nutrition, being especially necessary for the thyroid metabolism and biosynthesis that regulate the metabolic rate in all body cells [13]. A marginal hypothyroidism was found during pregnancy even in iodine sufficient area that is amplified when there is iodine restriction or overt iodine deficiency and the maternal iodine deficient status leads to goiter formation associated with neuropsycho-intellectual impairment that is preventable by iodine supplementation during pregnancy [14,15,16]. Peoples living in areas affected by severe iodine deficiency may have mental deficiency that has an immediate effects on child learning capacity, women's health, quality of the life of communities and economic productivity [17].

Iodine necessity should be enhanced (200–300µg/day) during the pregnancy to maintain the increased need of maternal FT4 and fetal thyroid function to compensate the enhanced urinary iodine excretion [13,18]. In our study, the 3rd trimester pregnant women who attended the maternity clinics in some hospitals and two primary healthcare centers in Almadinah Almunawarah, Saudi Arabia exhibited significant rise in both urinary excretion and serum iodine level [Table-1]. The number of iodine deficient pregnant women (serum iodine <10mg%) was increased during the 3rd trimester compared to the 1st and the 2nd trimester pregnant women [Table-2]. This results were consistent with other studies reported that pregnant women developed iodine deficiency which adversely affects the thyroid function [19,20]. It was reported that the iodine deficiency reduces the level of circulating FT4 and elevates the level of TSH, thus populations with deficiency of iodine usually have elevated TSH levels than iodine sufficient population [21]. The occurrence of high levels of serum TSH and low levels of both serum FT3 and FT4 in 3rd trimester pregnant women [Table-3] is an important biomarker in a population with severe iodine deficiency. Besides, the TPO-Abs and TG-Abs were significantly increased in the 2nd and 3rd

trimester pregnant women compared to normal control non-pregnant women [Table-4].

In this study, pregnant women found to be iodine deficient progressively because of the failure of adequate dietary iodine intake particularly in advanced pregnancy. This could be due the non-appetizing and anorexic problems incident to the pathophysiological changes during pregnancy [20]. These results are consistent with many other reports done abroad [20,21]. However our results contrasted with some other reports that showed urinary iodine concentration either increased [22] or unchanged [23] during pregnancy as compared to non pregnant values. These differences could be explained by the existence of urinary iodine threshold called iodostat; the level of which is set by the dietary iodine practice of community concern. In pregnancy, the iodostat may not change to conserve iodine despite the enhanced urinary iodine excretion. The latter may result in depletion of thyroidal iodine be increased significantly in 3rd trimester of pregnancy compared to 1st or 2nd trimester. Our study clearly documented the changes in urinary iodine excretion, serum iodine level and in thyroid hormones during the course of pregnancy. Some studies on the changes of FT4 and FT3 level during pregnancy have shown conflicting picture with some showing an increase and in others no change at all [24]. These discordant results can be partly related to the methodologies employed and the studied population [25]. Few sporadic studies on the changes of serum TSH concentration during the course of pregnancy found conflicting with respect of ours. These reported unchanged [15,26] or slightly increased TSH level [27]. These contradictory results are also party explained by the methodologies employed and probably by the baseline iodine status of the population studied [25].

Oxidative stress has emerged as a likely promoter of several pregnancy-related disorders. Nutritional and environmental factors may contribute to adverse pregnancy outcomes and increase the susceptibility of offspring to disease. The links between oxidative stress, the female reproductive system and development of adverse pregnancy outcomes, constitute important issues in human reproductive medicine [28]. Our results elaborated significant decline in each of the SOD, GPx and TAS activities in the 3rd trimester pregnant women compared to the normal non-pregnant women [Table-5]. These findings may be attributed to the impairment of the antioxidant defense systems and enhancement of reactive oxygen species generation among pregnant women which alters cellular signaling and/or damage cellular macromolecules [28].

The linear regression analysis of the data obtained from the pregnant women revealed significant positive correlation between urinary iodine excretion and serum iodine level, however a significant negative correlations were observed between serum TSH and each of the serum FT3 and serum FT3 [Figure-1]. In studies conducted in Hong Kong [29] and Saudi Arabia [30], maternal free thyroxine and urinary iodine excretion values respectively, have been found to be negatively correlated with neonatal TSH values. On the other hand, significant positive correlation between serum TPO-Abs and urinary iodine excretion was noticed, however significant negative correlation was observed between serum TPO-Abs and serum iodine level [Figure-2].

[V] CONCLUSION

This study recommended the merit measurement of serum thyroid hormones and serum and urinary iodine in all pregnant women as a part of routine antenatal check-up to avoid adverse effects on fetal development and maternal thyroid function.

FINANCIAL DISCLOSURE

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