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Full Length Research Paper

Clinical evaluation of T_3, T_4 and TSH thyroid function during first, second and third trimester of pregnancy in Iraqi pregnant women

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Abstract

The evaluation of thyroid function of either hyperthyroidism or hypothyroidism should be assessed by determination of serum Triiodothyronine (T_3), Thyroxin (T_4) and Thyroid Stimulating hormone (TSH). Due to specific conditions related to the pregnancy period, There are various alteration accompanied with this stage of life. A variation of changes required to be occurred due to physiological demands of pregnancy. Thyroid function was studied by determination of thyroid hormones using high-sensitive Enzyme Linked Immune sorbent Assay (ELISA) technique in 35 pregnant Iraqi women. The study group comprised of 35 full term pregnant women scheduled follows up the alterations of thyroid hormones, while the control group included 30 healthy women volunteers. Serum concentrations levels of total T_3 (TT_3), total T_4 (TT_4) and (TSH) were estimated using (ELISA) technique. In the study group, blood samples were obtained during various stages of monthly period of pregnancy. Mean age of the study group was (27±5) years, and that of controls were (25±3) years. In first trimester: serum TT_3 and TT_4 levels were significantly higher than that in controls [1.2134±0.0445 vs. 1.0583±0.2439 ng/mL and 8.5266±0.4545 vs 7.0466±1.4460 µg/dL respectively while TSH levels were significantly lower than that of control 2.3866 ±0.3087 vs 3.3466±1.3396 µIU/mL; P< 0.05]. In second trimester, there were continuously increase in concentrations levels of TT_3, and TT_4 than that in control but TSH significantly decreases [1.347±0.0191 vs1.0583±0.2439 ng/ml, 9.5923±0.31005 vs 7.0466±1.4460 µg/dL and .6733±0.1469 vs 3.3466±1.3396 µ IU/mL; P< 0.05]. In third trimester, TT_3 showed significant fall [1.2833±0.0447 vs. 1.0583±0.2439 ng/ml and the concentration levels of TT_4 significantly increased 10.3213±0.0914 vs 7.0466±1.4460 µg/dL while TSH significantly decreased 1.2685 ±0.0390 vs 3.3466±1.3396 µIU/mL and; P< 0.05]. All alterations, the significant rise in TT_3 in first trimester, and the fall in third trimester and the significant fall in TSH in third trimester, seen during pregnancy seemed to be need based and was significantly influenced by stress present during pregnancy.

Keywords: Thyroid function, pregnancy, triiodothyronine, thyroxin, TSH, Elisa.

INTRODUCTION

Thyroid hormones Thyroxin (T_4) and Triiodothyronine (T_3) are one of the major catabolic hormones of our body. In the circulation, whole T_4 originates from thyroid secretion but most T_3 (80%) is produced extra thyroidally from de-iodination of T_4 (Sapin et al., 2003). The T_3 was formed from T_4 by the thyroid secretion is the major pathway through which thyroid hormones exerts their effects (Glinoer D., 1999). Conversion of T_4 to T_3 may be influenced by various conditions and circulating T_3 is a less reliable reflection of thyroid hormone production than T_4.Thyroid binding globulin (TBG) increases beginning early in the first trimester, stabilizing at approximately double baseline value for the remainder of the pregnancy in the third trimester (Robbins, 1981; Guillaume et al., 1985; Vieira et al., 2004).This results in a marginal fall in free T_3 (FT_3) and

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free T_4 (FT_4) levels in the third trimester, in iodine sufficient regions thus resulting in slight rise in serum thyroid stimulating hormone (TSH) levels. Hence in this trimester, there is increased level of TSH (due to fall in FT_3 and FT_4) despite of increase in total T_3 (TT_3) and total T_4 (TT_4) hormones (Lapko et al., 2000; Ardawi et al., 2002; Winkler et al., 1943). The various physiological changes during pregnancy is not only narrowed at thyroid hormonal function tests but due to significant alteration in metabolic processes, many others hormonal change take place during pregnancy to optimize the cellular and molecular demand of maternal and physiological requirements (Osathanondh, 1976; horpa, 1976: Glinoer, 2000; Lemone, 1992: Kuroka andTakahashi, 2005). Although the thyroid should function properly at any time, in males and females but it seems thyroid function tests are more at risk of abnormality among women particularly during pregnancy period. In addition the first trimester of pregnancy should be under specific and particular medical care, due to physiological demand particularly physical mental and brain developments .Therefore, evaluation of thyroid function tests during pregnancy is great importance to prevent the abnormalities (LeBeau and Mandel, 2006; Springer et al., 2009; Hallengren et al., 2009). It should be noted that the proper assessment of thyroid function during pregnancy require the determination of not only the hormone related to the thyroid but also the antibodies raised against the thyroid gland and the iodine requirement of maternal life should be strictly assessed, to prevent the disorder in thyroid hormonal function, tests during maternal life with irreversible side effect particularly to the growing pregnant women, as well (Soldin et al., 2004; LaFranchi et al., 2005). TT_3 and TT_4 levels are increased due to a rise in the amount of thyroid-binding globulin (TBG). TT_4 values are not useful in pregnant women because they rise in response to the estrogen-induced increase in the amount of thyroid-binding globulin. TSH concentrations fall during pregnancy, especially in the first trimester, because hCG cross-reacts with TSH receptors on the thyroid gland. TSH levels are significantly lower and FT_4 levels are significantly higher in the first trimester than levels in the second or third trimesters, TSH levels alone should not be used to diagnose hyperthyroidism in pregnancy. In primary hypothyroidism, TSH levels are elevated. With suprathyroid hypothyroidism, the TSH level may be normal or low, and the TSH level is elevated .Due to the elevated concentration of estrogen during a routine normal pregnancy and its effect on the liver. The serum level of TBG increased, the consequence of increasing amount of TBG, lead to elevated concentration of thyroid hormones of thyroxine (T_4) and Triiodothyronine (T_3), in normal pregnancy (Idris et al., 2005; Kooistra et al., 2006; Chen and Jhon, 2002). Thyroglobulin concentration is increased during any thyroid lesion and hyperactivity during pregnancy, which reflects the over-activity of thyroid gland during a normal pregnancy (Zigman et al., 2003; Glinoer, 2004). During a normal pregnancy, the immune system of pregnant women adapts itself, with the new condition and there is not a serious adverse side effect of immune system against pregnant women (Imaizumi et al, 2001). Hypothyroidism during pregnancy mainly occur, due to iodine deficiency of maternal regiment and autoimmunity, which is called Hashimato, thyroiditis, low birth weight and mental retardation are part of hypothyroidism side effect. The measurement of T_4, T_3 and the determination of auto-antibodies raised against thyroid enzymes and Thyroglobulin are also recommended (Glinoer, 2000; Netto et al., 2004; Dendrinos et al., 2000). The TSH is a single laboratory test which can give a clear outcome of thyroid function test, also the measurement of T_4, is critical and it is clearly indicated (Shahmohammdi et al., 2008) which can evaluate the thyroid function and it also recommended by the American thyroid association, as the most important single test of thyroid assessment (Surks et al., 1990). In case of high TSH and low T_4 and T_3, hypothyroidism is and when TSH is low accompanied with elevated T_4 and T_3, the hyperthyroidism are detected respectively. Although, there are cases with normal T_4 and T_3 but elevated (TSH) which the subjects on clinical examination are euthyroid

(Mansourian et al., 2008). The author in a review of literature found the lipid disorder among subclinical hypothyroid patients. Abnormal elevation of total cholesterol and L DL- Cholesterol are common findings in most reported studies (Mansourian, 2010; Mansourian et al., 2010). The other basic point which can be focused on hypothyroid patients is the level of lipid per- oxidations and free radical productions which can cause tissue injury and other abnormality (Marjani et al., 2008). The Graves disease and Hashimato thyroiditis, the two well known thyroids auto-immune disorder are the stimulator of causing the hyper and hypothyroidism respectively which should also has to be taken into account for pregnant women. ([Rasmussen et al., 1990; Bech et al., 1991; Roti and Emerson, 1992). Hormonal changes during first trimester of pregnancy and steady elevation of Stradiol and other estrogen during the first trimester of pregnancy and their effect on the liver make the few folds increase in the concentration of TBG. It has been shown that the TBG serum level increases at early stage of pregnancy, Thyroxin the main hormone of thyroid gland has a high affinity for the TBG and T_4 is mainly bound to this protein, which is synthesized within the liver and in early pregnancy its concentration increased. This physiological process, modify the T_4 concentration and total thyroxin level increased at early stage of first-trimester of pregnancy (Kumar et al, 2003; Shahmohammdi et al, 2008). The target of this work was to shed light on hyperthyroidism and hypothyroidism during pregnancy and should be evaluated carefully and assessed properly to avoid the irreversible adverse effects on the growing fetus and

Table 1. Serum concentrations levels of TT_3, TT_4 and TSH in the unpregnant women and pregnant women during nine months from pregnancy.

Hormone	Unpregnant women (n=30)		Pregnant women (n=35) \ Month								
			1st	2nd	3rd	4th	5th	6th	7th	8th	9th
TT_3 (ng/ml)	Mean	1.0583	1.171	1.215	1.260	1.325	1.359	1.357	1.317	1.274	1.243
	S.D.	0.2439	0.297	0.293	0.266	0.276	0.301	0.282	0.281	0.296	0.250
TT_4 (µ gm /dl)	Mean	7.0466	8.051	8.571	8.957	9.285	9.585	9.905	10.222	10.34	10.402
	S.D	1.4460	1.516	1.450	1.451	1.417	1.217	1.119	1.178	1.094	1.032
TSH(µ IU/ml)	Mean	3.3466	2.700	2.377	2.082	1.78	1.734	1.505	1.331	1.325	1.148
	S.D	1.3369	1.527	1.467	1.433	1.392	1.475	1.320	1.263	1.423	1.268

Table 2. Serum concentrations levels of TT_3, TT_4 and TSH in the unpregnant and pregnant women during three trimesters.

Hormone	Unpregnant women Controls (n=30)		Pregnant women (n=35) 1st trimester	2nd trimester	3rd trimester
TT_3 (ng/mL)	Mean	1.0583	1.2134	1.347	1.2833
	S.D	0.2439	0.0445	0.0191	0.0447
TT_4 (µgm/dL)	Mean	7.0466	8.5266	9.5923	10.3213
	S.D.	1.4460	0.4545	0.31005	0.0914
TSH (µ IU/mL)	Mean	3.3466	2.3866	1.6733	1.2685
	S.D	1.3369	0.3087	0.1469	1.0390

pregnant mothers.

MATERIAL AND METHODS

The study was conducted between September 2010 to May 2011, College of Pharmacy, University of Almustansirya, Baghdad, Iraq. Subjects were from South region of Iraq, wasitte (Alkarama Teaching Hospital). The study group (n=30) comprised of young healthy volunteers unpregnant women, aged 20---35 (25±3) year. Thirty-five age matched (27±5) years, normal healthy pregnant women. Serum TT_3, TT_4 and serum

TSH concentrations levels were assessed in both groups; to do this, 5ml of Blood was in turn drawn from the antecubital vein. Samples were collected with all aseptic precautions, using sterile needles and syringes in plain sterile bulb. In the controls, samples were obtained from healthy volunteers, while in the study group; samples were taken during nine months of pregnancy period. Samples were kept undisturbed for 30 minutes and centrifuged at 400 rpm for 10 minutes. Serum was separated then stored in deep freezer (-20^{o}C) until for use of monoclonal antibody in ELISA Test, which liminates cross reactivity with other hormones. Quantitative determination of TT_3 and TT_4 and TSH concentrations was carried out using ELISA. This is a solid phase sandwich, Elisa method. Results of normal values obtained for healthy adults were follows: TT_3: 0.59-1.79 ng/ml; TT_4: 4.7-9.7 µg/dl, and serum TSH: 0.9-5.6 µ IU/ml.

Statistical Analysis

The concentrations levels of TT_3 and TT_4 TSH were reported as mean ± standard deviation. Statistical analysis was done by unpaired student's 'T-test' for comparing thyroid function between controls healthy women volunteers and study group pregnant women patients while paired 'T-test' was used for comparing thyroid function in the study group during pregnancy period and three trimesters (first, second and third). Statistical
Significance was taken as $P<0.05$.

RESULTS

The results in table 1 indicate that the concentrations levels of serum TT_3 and TT_4 values in the control healthy unpregnant women and pregnant women during nine months from pregnancy. Nine months (1st- 9th); the serum TT_3 and TT_4 concentrations levels were slightly increased while TSH was highly decreased through the period of pregnancy. Table -1 compares serum TT_3, TT_4 &TSH levels among the various groups and pregnant patients during period of pregnancy. At onset of first trimester serum TT_3 and TT_4 levels were significantly higher than those of controls, while serum concentrations levels of TSH were highly significantly

lower than those of controls. Immediately after delivery to next month then to the last, serum concentrations levels values of TT_4 was significantly higher while TSH was significantly lower than those of controls during the pregnancy period ; however serum concentrations levels of TT_3 was slightly significantly higher than that of controls until reach to eighth month the levels will be decrease. A comparison of thyroid function, during various trimesters of pregnancy, showed that there was fall in serum TT_3 from onset of pregnancy (first trimester and second trimester) to the period immediately after delivery (third trimester). Although there is a significant variation was observed in serum TT_4 during nine months of pregnancy, a highly increasing was seen in serum TT_4 immediately after four month of pregnancy delivery (second trimester) and slight rise was observed in immediate after seven month (third trimester). In case of Serum TSH level, a significant fall was seen immediately after delivery (first trimester), and a slightly decrease which was observed during third trimester.

DISCUSSION

Many changes occur in thyroid function during the transition phase from the non–pregnant to the pregnant state, changes which stabilize by the end of second trimester or the onset of the third trimester (Kooistra et al., 2006). There is biochemical evidence of functional stimulation of the thyroid, such as an elevation in serum thyroglobulin levels, preferential T_3 secretion, increased T_3/T_4 ratio and slight increases in basal TSH at delivery (Kooistra et al., 2006; Chen and Jhon, 2002). A state of physical and mental stress, there is a heavy expenditure of energy, which is provided by metabolism of nutrients. The concentration of TT_3, one of the main catabolic hormones, may increase at the onset of first trimester; hence the elevation in levels of serum TT_3 during pregnancy may be to adjust internal environment of mother to meet the additional requirements imposed pregnancy period by increased metabolic demands, indicating that a significant rise in serum TT_3 at the same condition may be a physiological adaptation enabling energy during high metabolic needs. Despite TT_4 be the main hormone secreted by thyroid gland, it is biologically less active than T_3. As already mentioned, there occur near term a preferential secretion of TT_3 by the thyroid.TT_4 is converted to TT_3 resulting in increased turnover of TT_4 and a state of relative hypothyroxenemia; hence there is fall in total serum T_4 level . It acts as precursor of T_3, the major active form the thyroid hormone, about 80% of which is produced in the body is derived extrathyroidally from T_4 deiodination (Sapin and Schlienger, 2003; Glinoer, 1999). TT_4 level is equilibrated in circulation on a manufacture and expenditure basis. The concentrations Levels of serum TT_3 and TT_4 decline immediately after delivery, the fall being significant only in the case of TT_3. Levels of the serum thyroid hormone are determined not only by their synthesis / secretion but also by their metabolism (Springer et al., 2009; Hallengren et al., 2009). Fall in thyroid hormone levels (TT_3 and TT_4) during pregnancy. Variations in TT_3 and TT_4 seem to be need based. Serum TT_3 level shows a significant decline in which period, all metabolic and hormonal changes begin to revert back to the pre-pregnant state, serum TT_3 levels, which increased during pregnancy, now start to decline in pregnancy, to reach their pre-pregnancy values. Thus normalization of thyroid function begins to start in puerperal period (Chen and Jhon, 2002). In the third trimester there is high concentration of TT_4 which mainly binds to TBG, results in decline in FT_3 and FT_4 levels in this trimester (LeBeau and Mandel, 2006; Mansourian et al., 2010; Rasmussen et al., 1990) and thereby a rise in serum TSH levels near term, (in the last trimester of the gestation period), resembling those of a slight thyroid insufficiency (Kuroka and Takahashi, 2005). This might be the reason behind the significant rise in serum TSH levels during delivery, in all three trimesters when compared to the controls. Immediately after delivery, a fall was seen in serum TSH level, which may be due to stress. Stress has inhibitory effect on thyrotropin releasing hormone (TRH) secretion. Hence a decline in TRH secretion results in a fall in serum TSH level immediately after delivery. Various emotional reactions can also affect the output of TRH and TSH and therefore indirectly affect the secretion of thyroid hormones. Excitement and anxiety-conditions that greatly stimulate the sympathetic nervous system cause an acute decrease in TSH secretion (Mansourian et al., 2010). The body responds to stress by releasing adrenalin and non-adrenalin and glucocorticoid, which also inhibits TSH secretion may be the reason behind the significant decline in serum TSH immediately after delivery, when stress decreases (Kuroka and Takahashi, 2005). Results of thyroid function tests should be cautiously interpreted considering physiological variant-ions during pregnancy.

CONCLUSION

The main conclusions were clinical evaluation of thyroid during various stages of pregnancy and particularly in the first trimester is a great importance due to extra requirement of thyroxine for growing. The hyperthyroidism and hypothyroidism during pregnancy was evaluated carefully and assessed properly to avoid the irreversible adverse effects on the growing pregnant mothers. Serum concentration levels determination of TSH, TT_4, TT_3 investigated properly during pregnancy should be evaluated to assess for any thyroid injury and over activity of thyroid gland. The thyroid function test during the first-trimester of pregnancy should be assessed carefully to prevent the irreversible consequences and damages on pregnancy outcome in the early stage of fetus formation. Finely, the pregnancy is a physiological condition for women with varieties of

new biochemical and metabolically changes. Significant alteration happens in the maternal thyroid gland with eventual effect on the growing fetus. All of the above reference intervals of thyroid hormone for pregnant women in the region should be determined to prevent misdiagnosis of such vital stage of life for growing fetus and pregnant women new physiological demands.

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