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Evaluation of thyroid function at different stages of pregnancy in Iraqi women.

***Alaa Kamal Jabbar Alhamd, *Haethem Qassim Mohammed,**
****Jawad Kadhim Shnayeh Al-dhahiry**
****College of Pharmacy, University of Almustansirya, Baghdad, Iraq***
*****Alkarama Teaching Hospital, Wasatte,Iraq***

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 alterations accompanied this stage of life. Some changes required 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 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) & (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 & 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 µ gm/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 was decreased [1.347±0.0191 vs 1.0583±0.2439 ng/ml, 9.5923±0.31005 vs 7.0466±1.4460 µ gm/dL and 1.6733±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 levels of TT_4 significantly increased 10.3213±0.0914 vs 7.0466±1.4460 µ gm /dL while TSH significantly decreased1.2685±0.0390 vs 3.3466±1.3396 µIU/mL and; P< 0.05]. All alterations, the TT_3 in first trimester was rise significantly, and it was significantly fall in third trimester. TSH was significant fall in third trimester .Conclusion that during pregnancy seemed to be significantly influenced by stress present during pregnancy.

Key word: *Thyroid hormone, Pregnancy, Thyroxin, ELISA,TSH.*

الخلاصة:

ان تقيم وظيفة الغدة الدرقية من ناحية كثرة او قلة افراز هرمون الثايروكسين يعتمد على قياس تركيز ال(ثايرونين ثلاثي اليود) (TT3) أوالثايروكسين(TT4) أوالهرمون المحفز للغدة الدرقية (TSH) في مصل الدم.

خلال فترة الحمل يوجد الكثير من التغيرات الوظائفية حسب متطلبات الحمل، حيث تتأثر وظيفة الغدة الدرقية اثناءالحمل.

درست وظيفة الغدة الدرفية اثناء الحمل عن طريق قياس تركيز ال TT4وTT3وTSH في مصل الدم باستعمال جهاز ال(ELISA) على 35 حامل من النساءالعراقيات.

قورنت النتائج المستحصلة لمجموعة من النساء الحوامل (35) التي تتراوح اعمارهم (27±5) سنة مع مجموعة قياسية من النساء الغير حوامل (30) وبصحة جيدة تتراوح اعمارهم (25±3) سنة بعدان تم اخذ عينات من دم النساء الحوامل خلال فترات مختلفة من الحمل ومقارنتها مع عينات من دم النساء غير الحوامل.

في اشهر الحمل الاولى (الثلث الاول) كان مستوى الTT3وTT4 اعلى من المستوى الطبيعي في المجموعة القياسية (1,2134±0,0445 مقارنة ب1,0539±0,2439ng/ml و8,5266±0,4545 مقارنة ب 1,4465±7,0466 gµ/dl للـ TT3وTT4على التوالي) بينما كان تركيز ال TSH أقل بكثير من المجموعة القياسية (2,3866± 0,3087 مقارنة ب 1,3396 ±3,3466 µIU/ml و ال P<0.05 .

في الثلث الثاني من الحمل كان هنالك زيادة مستمرة بتركيز TT3وTT4 بينما قل تركيز TSH(1,347±0,0191 مقارنة ب 1,0583 ±0,2439ng/ml و9,5923±0,0,31005 مقارنة ب 7,0466 ±1,4460 µg/dl و 1,6733 ± مقارنة ب 1,3396±3,3466 µIU/ml 0,05 >Pعلى التوالي). امافي الثلث الثالث من الحمل ان مستوىTT3 قل بصورة كبيرة (1,2833±0,0447 مقارنة ب 1,0583±0,2439ng/ml)وتركيز TT4 ازداد الى (10,3213±0,0914 مقارنة ب 7,0466 ±1,4460 µg/dl) بينما تركيز ال TSH قل كثيرا (1,268 ± 0,039 مقارنة ب 1,3396±3,3466 µIU/ml P<0,05). ان هذا التغيرفي التركيزمثل ارتفاع الTT3في الثلث الاول من الحمل وانخفاضه في الثلث الثالث من الحمل، كذلك انخفاض مستوىTSH في الثلث الثالث من الحمل نتيجة لتاثير الاجهاد خلال فترة الحمل.

Introduction:

Thyroid hormones Thyroxin (T4) and Triiodothyronine (T3) are one of the major catabolic hormones of our body. In the circulation, whole T4 originates from thyroid secretion but most T3 (80%) is produced extra thyroidally from de-iodination of T4 [1]. The T3 was formed from T4 by the thyroid secretion is the major pathway through which thyroid hormones exerts their effects [2]. Conversion of T4 to T3 may be influenced by various conditions and circulating T3 is a less reliable reflection of thyroid hormone production than T4.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 [3,4,5]. This results in a marginal fall in free T3 (FT3) & free T4 (FT4) 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 FT3 and FT4) despite of increase in total T3 (TT3) & total T4 (TT4) hormones [6,7,8].

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 [9,10,11].

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 abnor malities [12,13, 14].

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 [15,16,].TT3 and TT4 levels are increased due to a rise in the amount of thyroid-binding globulin (TBG).TT4 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 rece ptors on the thyroid gland. TSH levels are significantly lower and FT4 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 supra thyroid 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 (T4) and Triiodo thyronine (T3), in normal pregnancy[17,18.19,]. Thyroglobulin concentration is increased during any thyroid lesion and hyperactivity during pregnancy, which reflects the over-activity of thyroid gland during a normal pregnancy [20, 21]. 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 [22]. Hypothyroidism during pregnancy mainly occur, due to iodine deficiency of maternal regiment and autoimmunity, which is called Hashemite, thyroiditis, low birth weight and mental retardation are part of hypothyroidism side effect.

The measurement of T4, T3 and the determination of auto-antibodies raised against thyroid enzymes and Thyroglobulin are also recommended [23, 24, 25]. The TSH is a single laboratory test which can give a clear outcome of thyroid function test, also the measurement of T4, is critical and it is clearly indicated [26].

The TSH is a hormone which can evaluate the thyroid function and it also recommended by the American thyroid association, as the most important single test of thyroid assessment [27]. In case of high TSH and lowT4 and T3, hypo thyroidism is and when TSH is low accompanied with elevated T4 and T3, the hyperthyroidism are detected respectively. Although, there are cases with normal T4 and T3 but elevated TSH which the subjects on clinical examination are euthyroid [28].

The author in a review of literature found the lipid disorder among subclinical hypothyroid patients. Abnormal elevation of total cholest erol and LDL- Cholesterol are common findings in most reported studies [29,30].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 [31].

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[32,33,34].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 T4 is mainly bound to this protein, which is synthesized within the liver and in early pregnancy its concentration increased. This physiological process, modify the T4 concentration and total thyroxin level increased at early stage of first-trimester of pregnancy [35, 26]. 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 pregnant mothers.

Material and Methods:

The subjects were from South region of Iraq,wasitte(Alkarama Teaching Hospital). The study group (n=30) comprised of young healthy volunteers unpregnants women, aged 20---35 (25±3) year. Thirty-five age matched (27±5) years, normal healthy pregnant women. Serum TT3,TT4 and serum TSH concentrations were assessed in both groups; to do this, 5ml of blood was 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 At onset of first trimester serum TT3 and TT4 levels were significantly higher than those of controls, while serum concentrations levels of TSH were highly significantly lower than those of controls. Immediately, Serum concentrations of TT4 was significantly higher while TSH was significantly lower than those of controls during the period of pregnancy; however serum concentrations levels of TT3 was slightly significantly higher than that of cont rols until it reachs to eighth month where the levels will be decrease.

A comparison of thyroid function, during various trimesters of pregnancy, showed that there was fall in serum TT3 from onset of pregnancy (first trimester and second trimester) to the third trimester of pregnancy. Although a significant variation was observed in serum TT4 during nine months of pregnancy, a highly increase was seen in serum TT4 after four month of pregnancy (second trimester) and slight rise was observed in immediate after seven month (third trimester). Serum TSH concentration level was fall signifycantly through first trimester, and a slightly decrease was observed during third trimester.

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 (-20oC) until use for monoclonal antibody in ELISA Test, which eliminates cross reactivity with other hormones. Quan titative determination of TT3 & TT4 and TSH concentrations was carried out using ELISA which is a solid phase sandwich ELISA method. Results of normal values obtained for healthy adults were follows: TT3: 0.59-1.79 mg/ml; TT4: 4.7-9.7 µg/dl, and serum TSH: 0.9-5.6 µ IU/ml [27].

Statistical Analysis:

The concentrations levels values of TT3, TT4 and 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 and Discussion:

The results in table-1 indicate the concentrations levels of serum T3 and T4values in the control healthy un pregnant women and pregnant women during nine months period of pregnancy. Nine months (1st--- 9th); Serum TT3 and TT4 concentrations levels were slightly increased while TSH was highly decreased through the period of pregnancy. Table -1 compares serum TT3, TT4 &TSH levels among the various groups of pregnant patients during period of pregnancy

Table–1: Serum concentrations of TT3, TT4 &TSH in the pregnant women and pregnant women during nine months from pregnancy.

	Unpregnant women (n=30)		Pregnant women (n=35) \ Month								
			1st	2_{nd}	3_{rd}	4	5th	6th	7th	8th	9
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(µIU/ 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

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

TT3, TT4 & TSH in the un pregnant and pregnant women during three trimesters.

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[18].

There is biochemical evidence of functional stimulation of the thyroid, such as an elevation in serum thyroglobulin levels, preferential T3 secretion, increased T3/T4 ratio and slight increases in basal TSH at delivery[18,19]. A state of physical and mental stress, there is a heavy expenditure of energy, which is provided by metabolism of nutrients

The concentration of TT3, one of the main catabolic hormones, may increase at the onset of first trimester; hence the elevation in levels of serum TT3 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 TT3 at the same condition may be a physiological adaptation enabling energy during high metabolic needs.

Despite TT4 being the main hormone secreted by thyroid gland, it is biologically less active than T3. As already mentioned, there occurs near term a preferential secretion of TT3 by the thyroid.TT4 is converted to TT3 resulting in increased turnover of T4 and a state of relative hypothyroxenemia; hence there is fall in total serum T4 level.

It acts as precursor of T3, the major active form of the thyroid hormone, about 80% of which is produced in the body is derived extrathyroidally from T4 deiodination[1,2]. TT4 level is equilibrated in circulation on a manufacture and expenditure basis. Levels of serum TT3 and TT4 decline immediately after delivery, the

fall being significant only in the case of TT3. Levels of the serum thyroid hormone are determined not only by their synthesis/ secretion but also by their metabolism [13.14]. Fall in thyroid hormone levels (TT3 and TT4) during pregnancy. Variations in TT3 and TT4 seem to be need based.

Serum TT3 level shows a significant decline in which period, all metabolic and hormonal changes begin to revert back to the pre-pregnant state, and serum TT3 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 [19].

In the third trimester there is high concentration of T4 which mainly binds to TBG, results in decline in FT3 and FT4 levels in this trimester [12, 30, 32] 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 [11]. 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[30]. The body responds to stress by releasing 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[11]. 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 hypothy-roidism during pregnancy were evaluated carefully and assessed properly to avoid the irreversible adverse effects on the growing pregnant mothers.

Serum concentration determination of TSH, TT4, and TT3 investigated properly and the concentration levels of thyroglobulin 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 each 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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