

Thyroid Role in Threatened Abortion

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Abstract

Background: Mild impairment of thyroid function may contribute to disturbed reproductive function.

Objective: To evaluate the role of thyroid hormones in maintaining early pregnancy and their association with the outcome of the threatened abortion.

Materials and methods: The study was carried out in Maternity and pediatric Teaching Hospital in Al-Najaf during period between 1st April to 1st September 2008. The study included 80 pregnant women divided into two groups 50 women with threatened abortion and 30 women with normal pregnancy of comparable age, parity, gestational age and body mass index (BMI). Both groups were subjected to clinical examination, obstetric ultrasound examination and were investigated for hemoglobin, total thyroxine (TT4), total tri-iodothyronine (TT3) and thyroid stimulating hormone (TSH). The group of threatened abortion women divided into two groups where 31 women had a positive outcome (continuation of pregnancy to the third trimester) and 19 women had a negative outcome (pregnancy ended with spontaneous abortion).

Results: There was a significant difference in the level of TT3 and TSH between the control group and the women with threatened abortion (lower TT3 and higher TSH in threatened abortion women) with no significant difference in TT4 between the two groups while TT3 and TT4 levels were significantly reduced in the women with negative outcome as compared with the women with a positive outcome while the TSH level was significantly increased in the women with negative outcome.

Conclusion: reduced levels of thyroid hormones in early pregnancy may contribute to some cases of spontaneous abortion.

Key words: thyroid hormones, pregnancy, abortion.

الخلاصة

هدف الدراسة : معرفة دور هرمونات الغدة الدرقية في الحفاظ على الحمل في بدايته وعلاقتها مع نتيجة الحمل المهدد بالإسقاط. المرضى وطريقة العمل : اجري البحث في مستشفى الولادة والأطفال التعليمي في محافظة النجف للفترة من ١/ نيسان ولغاية ١/ تشرين أول. بحثت الدراسة ٨٠ عينة من امرأة حامل ، قسمت العينة الى مجموعتين : تضمنت الأولى ٥٠ امرأة مهدد حملها بالإسقاط و الثانية تضمنت ٣٠ امرأة ذوات حمل طبيعي، مع تسجيل بيانات العمر، عدد الولادات، عمر الحامل الحالي ودالة كتلة الجسم. كلا المجموعتين خضعت للفحوصات السريرية، وفحص الحامل بجهاز الموجات فوق الصوتية ، تم قياس خضاب الدم (الهيموغلوبين) ، و الثايروكسين TT4 الكلي، و الايودوثايرونين الثلاثي الكلي TT3 والهرمون المحفز للغدة الدرقية TSH بالنسبة للنساء المهدد حملهن بالإسقاط أظهرت (٣١) امرأة نتيجة موجبة (استمر الحمل الى الأشهر الثلاثة الأخيرة من الحمل) و أظهرت (١٩) امرأة نتيجة سالبة (انتهى الحمل بإسقاط تلقائي). النتائج: أظهرت الدراسة وجود فرق في مستويات هرمونات الغدة الدرقية بين حالات الإسقاط المهدد وحالات الحمل الطبيعي، وكانت نسبة هرمونات الغدة الدرقية اقل عند الحالات التي انتهت بإسقاط تلقائي. الاستنتاج: تدني مستوى هرمونات الغدة الدرقية في بداية الحمل قد يكون سببا في حصول بعض حالات الإسقاط التلقائي.

Introduction

Abortion is the termination of pregnancy, either spontaneously or intentionally, before the fetus develops sufficiently to survive. It occurs in approximately 15-20% of all pregnancies, as recorded by hospital episode statistics⁽¹⁾.

In most cases of early pregnancy failure, there is an inadequate placentation. In particular, there is a defective transformation of the spiral arteries and a reduced trophoblastic defect of placentation is more pronounced in chromosomal abnormalities⁽²⁾.

Measurements of thyroid stimulating hormone (TSH) and free thyroxin are almost routine in patients with a history of repeated pregnancy losses⁽³⁾. In spite of many studies regarding the physiological changes in the thyroid during pregnancy, it is uncertain if functional disorders of the thyroid play a role in the etiology of spontaneous abortion⁽⁴⁾.

Of all pregnancies in which bleeding occur, more than 50% continue. If bleeding occurs at 10 weeks gestation, more than 90% continue, at 13 weeks, 99% continue. If the menstrual or gestational age is greater than 6 weeks, then ultrasound may show a healthy, ongoing pregnancy. In such cases the likelihood of pregnancy loss is less than 3%. Prognosis can also be determined by serial measurements of placental hormones such as human chorionic gonadotrophin (HCG)⁽⁵⁾.

Regarding Thyroid function during Pregnancy requirements of thyroid hormone and iodine are increased⁽⁶⁾.

It seems that HCG has a thyrotrophic function and there are reports of suppression of thyroid – stimulating hormone (TSH) during the first trimester of pregnancy in association with peak levels of HCG⁽⁷⁾.

It has been suggested that this phenomenon may be associated with increased nausea and vomiting (characteristic of the first trimester) and cases of transient thyroid malfunction have also been reported, these transient thyroid function elevations in early pregnancy do not usually warrant antithyroid treatment⁽⁸⁾.

Current opinion is that normal pregnancy is associated with a marked increase in thyroid binding globulin (perhaps under the influence of estrogen) accompanied by increase in bound thyroxin (T4), T3 (the more active hormone) as well as reverse T3 (a systemically inactive variant) but that circulating concentrations of unbound (free) T4 and T3 differ only slightly from non pregnant norms, if any thing being slightly reduced. Although many of the systemic physiological changes of pregnancy, such as increases in basal metabolic rate and body temperature, tachycardia and increase cardiac output, mimic those associated with thyroid hyperactivity, there is no firm evidence that they result from altered maternal thyroid function⁽²⁾.

The most common complications observed in hyperthyroid patients are abortion, premature delivery, hyperemesis gravidarum, abruption placenta, pre-eclampsia, neonatal thyrotoxicosis, Intrauterine Growth Restriction (IUGR)⁽⁹⁾.

Complications observed in hypothyroid patients are abortion, premature delivery, hypertensive problems, postpartum bleeding, congestive heart failure, congenital anomalies, IUGR, stillbirth, mental retardation⁽¹⁰⁾, locomotor underdevelopment in the child⁽¹¹⁾.

The aim of the study is to assess the role of the thyroid hormones in maintaining early pregnancy and its

association with the outcome of the threatened abortion by comparing the thyroid function test of healthy pregnant women with women with threatened abortion women.

Patients and Methods

This prospective study was conducted at Al-Zahraa Maternity and Pediatric Teaching Hospital in Al-Najaf from 1st April to 1st September 2008.

The study group included 50 patients with clinical diagnosis of threatened abortion –pregnancy less than 24 weeks gestation, have vaginal bleeding or spotting, a closed cervical os, possibly mild uterine cramping and the fetus alive on ultrasound⁽¹²⁾.

The control group consisted of 30 women of normal pregnancy at comparable gestational age.

Informed consent was obtained from all patients for participation in this research.

All patients underwent a thorough physical and thyroid gland examination and obstetric ultrasound assessment.

Fasting morning serum samples were taken for hemoglobin, total tri-iodothyronine (TT3), total thyroxin (TT4) and thyroid stimulating hormone (TSH) for both groups.

Exclusion criteria:

1. History of thyroid disease, metabolic or endocrine disease.
2. Multiple pregnancies.
3. Hypertention.
4. Chronic drug use.

Quantitative determination of T3, T4 and TSH concentrations was done by micro plate enzyme immune assay; in this method the serum is added to a micro plate well.

Enzyme T3 or T4 or TSH conjugate (according to the test

performed) was added and then the reactant were mixed, a competition reaction resulted between the enzyme conjugate and the native T3 or T4 or TSH for a limited number of antibody combining sites immobilized on the well .

After the completion of required incubation period, the antibody bound T3 or T4 or TSH – enzyme conjugate was separated from the unbound one by aspiration or decantation, the activity of the enzyme present on the surface of the well was quantitated by reaction with a suitable substrate to produce color.

Statistical analysis

All analyses were performed using commercially available software (SPSS *version 15*). Continuous variables between groups were compared by the Student's t-test for unpaired observations. A P-value ≤ 0.05 , ≤ 0.01 were considered as statistically significant at level of 5% and 1%.

Significant differences between hormonal assay of age groups of both positive and negative threatened abortion women were assessed by ANOVA. Analysis (*F*-tests ($P \leq 0.05$)).

Results

The demographic characteristics and the thyroid hormone levels of the studied and control groups are summarized in table (1) with no significant differences between the two groups regarding age, parity, number of previous abortions, body mass index and gestational age. The hemoglobin level was less in the threatened abortion group than the control. When comparing the two groups in table (2) regarding the thyroid hormone levels, T3 levels were less in the threatened abortion group while TSH level was significantly higher and the

T4 levels were comparable among the two groups.

Table 1. The descriptive characteristics of threatened abortion and control women

	control(No=30) mean	S.D	Threatened abortion(No=50) mean	S.D
Age	27.26667	5.336493	26.8000	5.37188
Parity	1.80000	1.399507	1.3200	1.49065
Abortion	0.33333	0.479463	0.5600	1.40204
BMI	26.9150	3.71074	24.9254	4.72687
GA	11.0000	2.94782	10.8200	3.51492
Hb	10.3367	0.87158	9.9720	0.59145
T3	1.4800	0.33156	1.1840	0.29162
T4	7.8267	1.10264	7.8400	2.52020
TSH	0.3700	0.15347	0.7140	0.59924

Table 2. Comparison of BMI, Hb, and Thyroid function tests (TFT) in the threatened abortion and control groups.

Variables	Group	Mean	±S.D	t	P
BMI	control	26.915	3.710	1.968	0.053
	threatened abortion	24.925	4.726		
Hb	control	10.336	0.871	2.228	0.029*
	threatened abortion	9.9720	0.591		
T3	control	1.480	0.331	4.174	0.000**
	threatened abortion	1.184	0.291		
T4	control	7.826	1.102	0.027	0.978
	threatened abortion	7.840	2.520		
TSH	control	0.370	0.153	3.077	0.003**
	threatened abortion	0.714	0.599		

* Significant at 5%

** Significant at 1%

Regarding the women with negative outcome they had higher values of T4 and TSH levels with

lower T3 values than the women with a positive outcome as shown in table (3).

Table 3. Comparison of BMI, Hb, and TFT in threatened abortion negative outcome (-ve) and threatened abortion positive outcome (+ve) groups.

	Group	N	Mean	±SD	t	P
BMI	-ve	19	25.952	6.424	1.209	0.233
	+ve	31	24.295	3.263		
Hb	-ve	19	10.047	0.616	0.702	0.486
	+ve	31	9.925	0.580		
T3	-ve	19	0.894	0.1508	8.762	0.000**
	+ve	31	1.361	0.1994		
T4	-ve	19	5.668	2.282	6.451	0.000**
	+ve	31	9.171	1.559		
TSH	-ve	19	1.168	0.728	5.192	0.000**
	+ve	31	0.435	0.238		

* Significant at 5%

** Significant at 1%

Table (4) and (5) records the difference in hormone levels according to the age of the women and according to the gestational age respectively. T3 and T4 showed significant differences within age groups of negative and positive threatened abortion women. T3 assay revealed higher value in positive threatened abortion women than negative threatened abortion women in the first three age groups, whereas positive threatened abortion women showed lower T3 value than negative threatened abortion women in age group of (31-35 years). T4 assay

revealed higher value in positive threatened abortion women than negative threatened abortion women in all age groups. In spite of higher value of TSH in the negative threatened abortion women in comparison with positive threatened abortion women, but no significance differences were recorded between age groups. T3 and T4 showed significant differences within gestational age of negative and positive threatened abortion women, these hormones increased with increasing gestational age.

Table 4. Difference of TFT results according to age groups of the women with threatened abortion

AGE GROUPS	NO	outcome	Hb		T3		T4		TSH	
			Mean	±S.D	Mean	±S.D	Mean	±S.D	Mean	±S.D
15 - 20 YEARS	6	(-)	9.96	0.539	0.883	0.075	6.416	1.592	0.683	0.407
	4	(+)	9.95	0.613	1.200	0.216	7.900	0.942	0.337	0.304
	10	Total	9.96	0.535	1.010	0.213	7.010	1.513	0.545	0.393
21 - 25 YEARS	4	(-)	9.87	0.629	0.975	0.095	6.050	2.209	1.625	1.201
	7	(+)	10.20	0.479	1.343	0.172	9.600	1.543	0.471	0.269
	11	Total	10.08	0.532	1.209	0.234	8.309	2.470	0.891	0.903
26 - 30 YEARS	5	(-)	9.88	0.540	0.900	0.264	5.640	3.343	1.380	0.516
	12	(+)	9.86	0.572	1.383	0.225	9.408	1.985	0.412	0.250
	17	Total	9.87	0.546	1.241	0.322	8.300	2.938	0.697	0.562
31-35 YEARS	4	(-)	10.55	0.759	4.200	1.749	8.250	0.095	1.175	0.538
	8	(+)	9.76	0.678	1.425	0.158	9.075	0.768	0.487	0.181
	12	Total	10.02	0.774	2.350	1.648	6.325	4.108	0.717	0.463
F(df _{3,42})			1.655		27.18		6.470		1.517	
P			0.191		0.000**		0.001**		0.224	

Discussion

Many studies have evaluated a possible role of thyroid hormones or thyroid auto antibodies in maintaining early pregnancy, Maruo, *et al.* proposed that maternal thyroid hormone levels are one of the endocrine factors responsible for the abortus threat⁽¹³⁾, while O'Hara, *et al.* indicated that functional disorders of

the thyroid is not effective in the outcomes of miscarriage.⁽¹⁴⁾

In the studies of thyroid autoantibodies, Pratt *et al.*⁽¹⁵⁾, Bussen *et al.*⁽¹⁶⁾ And Wilson *et al.*⁽¹⁷⁾ found higher thyroid autoantibody levels in women with recurrent first trimester miscarriage than in the normal pregnant women, while in the study of Rushworth, *et al.*⁽¹⁸⁾ and Esplin, *et al.*⁽¹⁹⁾ it was concluded that thyroid antibodies are not associated with

spontaneous abortion. It was seen from these studies that the role played by thyroid hormone or thyroid autoantibody levels in the etiology of spontaneous abortion is not clear.

In this study woman with threatened abortion as compared to normal pregnant women, we evaluated the thyroid function tests according to the outcome (positive and negative).

Table 5. Comparison of Hb, TFT in the negative and positive threatened abortion women groups according to the gestational age.

Group Statistics

G.A				outcom	Hb		T3		T4		TSH	
	N	mean	±S.D		Mean	±S.	Mea	±S.D	Mea	±S.	Mea	±S.
≤11	1	8.643	1.691	Negativ	10.028	0.539	0.857	0.108	5.242	2.018	1.057	0.713
≥ 12	5	15.000	3.461	negativ	10.100	0.871	1.000	0.212	6.860	2.791	1.480	0.756
Tota	19	10.315	3.606	negativ	10.04	0.616	0.894	0.150	5.668	2.282	1.168	0.728
≤11	1	8.842	1.571	positive	9.421	0.598	1.294	0.187	8.726	1.278	0.386	0.195
≥ 12	1	14.750	2.378	positive	9.900	0.576	1.466	0.177	9.875	1.752	0.512	0.286
Tota	31	11.1290	3.481	positive	9.925	0.580	1.361	0.1994	9.171	1.559	0.435	0.238
f-test		88.471			0.006		8.538		5.861		2.238	
P- value		000**			0.940		0.005**		0.019*		0.079	

50 women with threatened abortion and 30 women with normal pregnancy were analyzed, With regard to level of thyroxin (TT4), there were no significant differences (P value 0.978) between the studied (mean 7.84 ± 2.52) and the control groups (mean 7.826 ± 1.10) which was not consistent with other studies^(21, 22), this may be because the T3 is the more active thyroid hormone, while the level of TT3 (abortion group mean 1.184 ± 0.29 , control mean 1.48 ± 0.33) and TSH (abortion group mean 0.714 ± 0.59 , control mean 0.37 ± 0.15) were significantly different (P value < 0.01) between the 2 groups which was consistent with other studies^(20, 21).

The hemoglobin level was significantly different between the studied and the control group with higher hemoglobin level in the control group which was our indicator for iron deficiency, iron deficiency adversely affects thyroid metabolism, which during pregnancy can lead to neuro developmental delays in the child, in the study of Zimmermann *et al* poor maternal iron predicts both higher TSH and lower TT4 concentrations during pregnancy⁽²²⁾. In the study of Hess *et al*⁽²³⁾ on rats iron deficiency sharply reduced thyroid peroxidase activity (thyroid peroxidase is a heme containing enzyme catalyzing the two initial steps in thyroid hormone synthesis).

Of the 50 women with threatened abortion, 31 (62%) of these patients had a positive outcome (continuation of pregnancy to the 3rd trimester) while 19(38%) patients had a negative outcome (pregnancy ended with spontaneous abortion).

No significant difference was noted in the hemoglobin level between the positive outcome and the negative outcome groups of the women with threatened abortion.

Regarding the thyroid hormones, TT3 and TT4 levels were significantly reduced in the women with negative outcome as compared with the women with a positive outcome ($P < 0.01$) while the TSH level was significantly increased in the women with negative outcome which may indicate the presence of a sub clinical hypothyroid situation in this group, this situation may lead to slowing down in the necessary synthesis and oxidation procedures, resulting in termination of pregnancy.

Our findings are consistent with the studies of Donmez *et al* ⁽²⁰⁾, Marca, *et al.* ⁽²¹⁾, while the study of Maruo, *et al.* ⁽¹³⁾ showed higher levels of FT3 and FT4 with no change in the level of TSH in the group with threatened abortion.

The difference in the level of TT4 and TSH between the positive and negative outcome groups was seen in all age groups while the difference in the level of TT3 was seen mostly in the younger age groups so it seems that TT3 concentration was the most sensitive indicator of negative outcome in our study.

With regard to the effect of gestational age on the levels of TT3 and TT4, it was seen that the level of these hormones raised as the gestational age increased which may be due to the reduced level of HCG as pregnancy advances.

Our study highlighted the importance of thyroid hormones in maintaining pregnancy and that thyroid function disorders mainly in the form of sub clinical hypothyroidism play a role in the etiology of some cases of spontaneous abortion.

1. With regard to the importance of thyroid function in maintaining pregnancy and further development of the fetus, specially neurological and locomotor development it is recommended that thyroid hormones and TSH should be measured as a routine test in all early pregnancies with threatened abortion.

2. Further studies to evaluate the effect of iron deficiency anemia (IDA) on thyroid function during early pregnancy as IDA is a common problem in our community.

Further studies to determine the management of sub clinical hypothyroidism and to identify the groups of patients that need treatment with thyroxine

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