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Assessment of some biomarkers (angiopoietin2, kisspeptin1) In Recurrent Aborted Women and its relationship with hypothyroidism

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ABSTRACT

This study aims to determine the relationship between hypothyroidism and kisspeptin-1 in recurrent aborted women (RAW) during the first trimester of pregnancy in Wasit Governorate, by measuring thyroid hormones T3, T4 and TSH, evaluating the level of thyroid antibodies to determine thyroid disease , and measuring the level of kisspeptin-1 and angiopoietin 2 in the serum. Blood samples were taken from pregnant women with recurrent abortion and control groups that included normal pregnant women (NPW). Thyroid hormones, Tg-Ab and kisspeptin-1 were tested by the using of ELISA. The results of the current study indicate the level of the kisspeptin-1 significantly increases P≤ 0.05 in miscareide women RAW, and its rates reached in RAW and control 352.84 ±103.55 , 129.48 ±26.19 respectively. And there are significant increase in angiopoietin 2 P≤ 0.05 20.24 ±2.60 , 13.17 ±2.09 in RAW and NPW respectively. And the thyroid function parameters show statistically significant differences, where there is a highly statistically significant decrease P≤ 0.05 in both T3 and T4 hormones, as well as thyroid-stimulating hormone TSH in RAW when compared with control group NPW. There rates were 1.509 ±1.36, 3.864 ±1.08, 1.098 ±0.18 for T3,T4,TSH respectively in RAW, While their rates reached 9.573 ±2.13 , 9.541 ±2.53, 4.090 ±0.83 respectively in control group (NPW). Also, the level of antithyroglobulin (Tg-Ab) significantly increase P≤ 0.05 in RAW comparing to control and the rates reach (144.06 ± 47.42), (82.77 ± 7.84) in RAW and NPW respectively.

Key words: Kisspeptin-1 , Hypothyroidism , Recurrent Abortion , Anti Thyroglobulin, angiopoietin 2..

Keyword: *angiopoietin2, kisspeptin1, hypothyroidism*

1. INTRODUCTION

Of all recognized gestations, 15–20% finish in spontaneous loss. Three or more consecutive abortions are called recurrent and warrant investigation for etiologic factors, either genetic, hormonal, immunological or others [1, 2]. spontaneous abortions so common in human due to Some factors such as chromosomal, hormonal, infectious and anatomical abnormalities are implicated. An important factor gaining space in the etiology of abortions is autoimmunity. Antiphospholipid antibodies and anticardiolipin antibodies are present in more or less 10% of aborted one or more times women. previous studies indicate There are significant association between thyroid autoimmunity and risk of abortion has been shown and studies indicate that there are some biomarkers serve as a factors of abortion such as kisspeptin1 and angiopoietin 2 [3, 4].

Thyroid disease as a factor of abortion:

thyroid disease refers to problems in thyroid gland itself this could (primary thyroid disease). In contrast, (the secondary thyroid disease) refers to central problems arising from the anterior pituitary that affects thyroid function "indirectly". A thyroid problem can exist in tow form as hyperthyroidism or hypothyroidism. Hyperthyroidism refers to an excessive thyroid hormone synthesis or release. Hypothyroidism, on the other hand, happens due to inadequate thyroid hormone secretion [5]. Hypothyroidism is the one of the abortion factors and it's prevalence is higher in recurrent pregnancy loss women. Although these studies have examined the relationship between antithyroid antibody and abortion covering different types of childbearing women, including healthy pregnancies, and women using assisted reproductive technology [6].

- **Kisspeptin**

Kisspeptin-1 is a peptide hormone encoded by the gene KISS1 it plays an essential role in reproductive function, including:

placental development and pregnancy maintenance [7]. Kisspeptin-1 influences the maternal metabolism during pregnancy and its serum levels increase almost 10,000 times in the final third of pregnancy, rapidly returning to base level after birth, suggesting that the placenta is one of the main sources of kisspeptin1. So, evaluation of its plasma profile has been suggested as a predictive factor of pregnancy success [8]. Since alterations of circulating and placental levels of kisspeptin1 have already been observed in "preeclampsia, abortion, gestational diabetes, and obesity". Furthermore, these gestational diseases may be associated with failures in intrauterine trophoblast migration , a key process for pregnancy success and which is influenced by the expression of kissepeptin1 [9].

- **Angiopoietin**

There are two angiogenic proteins: (Angiopoietin-1 and angiopoietin-2) Angio-1 play role in new blood vessels maturation and stabilization, the inhibition of endothelial apoptosis and reduction of vascular permeability in stable environment. Angio-2 is an antagonist of Angio-1 and it known to enhance the plasticity, destabilization and permeability of blood vessels and vascular remodeling site. Angio-2 is a secreted glycoprotein that plays a very complex role in angiogenesis and inflammation. Angio-2 is widely expressed during development, but is restricted to highly vascularized tissues after birth such as the placenta, ovaries, and uterus [10]. Angiopoietin-2 (Angio-2) is a key regulator of angiogenesis and vascular permeability its elevation during abortion, whether recurrent abortion or induced, may be attributed to many physiological mechanisms[11]. So, despite the fact that maternal hypothyroidism is one of the main pregnancy metabolic disease affecting fetoplacental development, intrauterine trophoblastic migration and associated with abortion and preeclampsia , there are still no studies about the relationship between maternal hypothyroidism and serum level of kisspeptin-1 and angiopoietin-2 in human [9]. Thus, the aim of this study was to evaluate the serum level of Kiss1 and angiopoietin 2 in maternal hypothyroidism.

2. MATERIAL AND METHODS

- **Collection of samples:**

The Peripheral blood samples of 57 of repeated aborted women RAW group and 34 of the normal pregnant women NPW as control groups were collected. The collected samples were 5 ml of blood withdrawn from all subjects stood for about 30 minutes at room temperature, then, was put in a gel tube to separate serum in centrifuged (at 3000 r.p.m for 5 minutes) then freeze at -20º, used to Serological tests, evaluate the level of T3,T4,TSH and Tg-Ab. And evaluate the serum kisspeptin-1 and angiopoietin 2 By the using of ELISA technique**.**

- **Diagnosis of thyroid diseases and abortion biomarkers (kisspeptin-1, and angiopoietin 2) serum level:**

All tests (T4 ,T3, TSH , anti-Tg-Ab , kisspeptin-1 and angiopoietin 2) are done by using ELISA method, and this methods was used depending on the manufacturer's information,

- **Statistical analysis:**

The SPSS version 20 was used to perform a t. test to compare patients with controls and compare age groups of patients with each other. with a probability level ($P \leq 0.05$).

3. RESULTS

The results in table 1 of this study show that there are significant statistical differences in thyroid functions parameters, T3 and T4 are significantly decrease ($P \leq 0.01$) as well as thyroid-stimulating hormone TSH highly decrease ($P \leq 0.01$) but, the Tg-Ab level is highly increase in women with recurrent abortions comparing with control group NPW. There rates were 1.509 ±1.36, 3.864 ±1.08, 1.098 ±0.18, 144.06±47.42 for T3,T4,TSH, and Tg-Ab, respectively in RAW, While their rates reached 9.573 ±2.13 , 9.541 ±2.53, 4.090 ±0.83, 82.77 ±7.84, respectively in (NPW). this study agree with [12], [13] ,[14] and agree with [15]. This study is consistent with [16] and [17] and consistent with [18]**.**

When comparing the level of the kisspeptin-1 hormone in recurrent aborted women with the control group, as can be seen in Table (2), the level of the kisspeptin-1 significantly increases ($P \leq 0.01$) in aborted women, and its rates reached in patients and control 352.84 ±103.55, 129.48 ±26.19 respectively. This study agree with [19] ,[20] , [21] and agree with [22]. But our study Disagree with [23] and disagree with [24]. The large discrepancy between the results of the studies may be due to the difference in the protocols for measuring kisspeptin-1 concentrations and the period in which the sample was taken from the patient because kisspeptin-1 concentrations vary during the months of pregnancy and increase with the progression of pregnancy in the case of normal pregnancy in addition to the volume of sample [25]. The same table reveals the statistical results of the level of angiopoietin-2 protein was significantly increased in recurrent aborted women compared to the control group, and its rates ranged 20.24 ±2.60, 13.17 ±2.09 respectively. And the table also shows significant negative correlation ($P \leq 0.01$) between kiss-1 level and angiopoietin 2 ,the rate is -0.43 .

4. DISCUSSION

The study found low TSH and T4 and T3 levels in aborted women during the first trimester of pregnancy, indicating hypothyroidism due to pituitary gland issues [12]. Thyroid hormones are crucial for fetal growt and brain development, and

are identified in the fetal brain as early as 8 weeks of fetal age. Untreated maternal hypothyroidism increases the risk of adverse pregnancy outcomes and child outcomes [26] TSH remains the primary test for detecting thyroid dysfunction during pregnancy, with recent studies showing impaired stimulation of thyroid hormones by hCG. TSH test results can change during pregnancy due to hCG stimulation, which is impaired in women with thyroid dysfunction. Autoimmune hypothyroidism can lead to first-trimester abortion, abortion, and poor blood supply. Women with autoimmune hypothyroidism are at higher risk of blood clots, pregnancy loss, and abortion, with thyroid autoimmunity being closely linked [27]. The results of this study showed high level of kiss-1 in RAW comparing to NPW, Kiss-1 levels can be elevated during abortion due to two potential causes: placental disintegration, where trophoblast cells break down, and inflammatory and stress responses, which may influence kisspeptin-1 secretion into circulation, leading to a temporary increase in plasma levels [28]. Kisspeptin-1 plays a crucial role in pregnancy maintenance and hormonal dysregulation, potentially leading to pregnancy loss due to disruptions in placental signaling and impaired implantation, as well as abortion [29]. Kisspeptin-1 levels increase during abortion, but its exact role is unknown. Some studies suggest it could be a biomarker for pregnancy viability and early abortion detection. Maternal hypothyroidism affects reproductive function by altering the secretion of GnRH, LH, and FSH. Thyroid hormones (T3,T4) influence the expression of KISS-1, and hypothyroidism may cause compensatory upregulation of kisspeptin-1 to counteract imbalances. Hypothyroidism may also increase KISS-1 expression during abortion due to placental dysfunction, hormonal disturbance, and oxidative stress and inflammation. The molecular mechanisms remain unclear, but some studies suggest that thyroid dysfunction affects GnRH, placental function, and inflammatory pathways, leading to increased KISS-1 expression [30]. Correlation between kiss-1 and angio-2 in Recurrent abortion may be Potential Correlation Angiopoietins and KISS-1 are linked through their roles in trophoblast function and placental vascularization. They regulate blood vessel formation and trophoblast invasion, which are crucial for successful pregnancy. Imbalances can lead to recurrent abortion and indirectly affect maternal immune tolerance [31]. Angiopoietin-2, a regulator of angiogenesis and vascular permeability, is elevated during abortion due to physiological mechanisms, promoting vascular remodeling and destabilization, potentially leading to trophoblast detachment and placental dysfunction. Pregnancy loss often leads to an inflammatory response, characterized by increased cytokines and hypoxia factors. This can upregulate Angio-2 expression, promoting vascular leakage and apoptosis in placental tissue. Hypoxia can induce Angio-2 expression, causing vascular endothelial disorders [11, 32]. Angio-2 levels increase in pregnancy loss cases associated with pre-eclampsia or hypertensive disorders, indicating increased trophoblast apoptosis and decidua damage, and endothelial damage and increased vascular permeability [33, 34]. Elevated Angio-2 during abortion is linked to vascular instability, inflammation, and hypoxia, contributing to placental dysfunction and fetal death [31, 35].

The table (2): reveals a negative correlation between increased kisspeptin concentration and decreased angiopoietin-2, potentially causing abortion. Regulation of neovascularization and angiogenesis is crucial for placenta formation, and disorders can lead to pregnancy complications like preeclampsia and abortion [36-38]. Kisspeptin controls fetal angiogenesis and new vessel growth by inhibiting angiogenic factors and angiopoietin expression. Plasma concentrations of angiopoietin are lower in physiological pregnancy compared to placental abruption, a condition causing decreased blood flow [39]. Angiopoietins and KISS-1 expression may contribute to recurrent pregnancy loss, affecting placental development, angiogenesis, and trophoblast function, potentially providing biomarkers and therapeutic targets [40].

Table (1): Comparison between RAW and control NPW in T3, T4,TSH,and Tg-Ab level.

Groups	No.	Mean ±SD			
		T3 pg/ml	T4 ng/ml	TSH mlU/L	Tg-Ab pg/ml
RAW	57	1.509 ±1.36	3.864±1.08	1.098 ±0.18	144.06±47.42
NPW	33	9.573 ±2.13	9.541±2.53	4.090 ±0.83	82.77 ±7.84
T-test	---	0.732 **	0.761 **	0.227 **	16.572 **
P-value	---	0.0001	0.0001	0.0001	0.0001
** (P≤0.01).					

Table (2): Comparison between RAW and control NPW in kiss-1 and Angio2,and the Correlation coefficient-r between them.

Parameters	No.	Mean ±SD		P-value
		Kiss-1	Angio1	

RAW	57	352.84±103.55	20.24±2.60	**(P≤0.01).
NPW	33	129.48 ±26.19	13.17±2.09	
T-test	---	36.559 **	1.058 **	
P-value	---	0.0001	0.0001	
Correlation coefficient-r	-0.43 **			**(P≤0.01).

5. CONCLUSION

This study concludes that there are significant relationship between thyroid autoimmune diseases and abortion biomarkers angiopoietin 2 and kisspeptin-1 in recurrent aborted women, The final conclusion is that it can be suggested that the complex interaction between central hypothyroidism and autoimmune disorders may be a central mechanism responsible for recurrent miscarriage, through its multiple effects on the hormonal, immune, and placental systems.

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