American Journal of Biology and Natural Sciences
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Evaluation of T3, T4, TSH and Detection of Antithyroglobulin Antibodies Tg-Ab in Recurrent Miscarriage Women, Iraq

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Received: 2024, 15, Mar
Accepted: 2025, 21, Apr
Published: 2025, 16, May

Annotation: There are many studies on the effect of thyroid diseases on the female reproductive system, but there is a lack of data that clarify the relationship between hypothyroidism and recurrent miscarriage, especially in the first three months of pregnancy. Therefore, this study aims to verify the existence of a definite relationship between recurrent miscarriage and maternal hypothyroidism. Thyroid function was evaluated by measuring the levels of thyroid hormones T3, T4, and TSH. The presence of thyroid autoimmune diseases was verified by searching for the presence of antibodies to thyroglobulin A-b. Blood samples were taken from recurrent miscarriage women (RMW) during the first trimester and from control (normal pregnant women). Thyroid hormones and Tg-Ab were tested by the ELISA technique. Results of the current study show a highly significant increase in Tg-Ab ($P \leq 0.05$) in recurrent miscarriage compared to control, and percentages reach 144.06 ± 47.42 and 82.77 ± 7.84, respectively. But thyroid hormones T3, T4, and TSH were highly

significant decreases ($P \leq 0.05$) in recurrent miscarriage; the percentages reached 1.509 ± 1.36, 3.864 ± 1.08, and 1.098 ± 0.18 and reached 9.573 ± 2.13, 9.541 ± 2.53, and 4.090 ± 0.83, respectively, in RMW and control groups, respectively. This study concluded a relationship between changes in the levels of thyroid hormones T3 and T4 and thyroid-stimulating hormone, that they decreased significantly in women with recurrent miscarriages and the thyroglobulin antibodies increased clearly in the serum of women with recurrent miscarriages comparing to control.

Keywords: soils of the Almalyk Mining and Metallurgical Plant, heavy metals, recurrent miscarriage, hypothyroid women, antithyroglobulin Tg-Ab antibodies.

Introduction

There are several unique changes in maternal thyroid hormone metabolism during pregnancy. For example, as a consequence of increasing maternal glomerular filtration rate, there is an increase in the clearance of iodine and a subsequent decline in serum iodine. In areas of iodine sufficiency, the change in iodide clearance is of little consequence. In iodine-replete regions, there is no increased incidence of clinically detectable goiter during pregnancy. Ultrasound studies in this patient population revealed either a small increase in thyroid volume during pregnancy, which was not a clinically detectable change, or no increase in volume. In areas of iodine deficiency, parts of Europe, Asia, and Africa, pregnancy may induce a relative iodine-deficient state, which can result in maternal hypothyroidism and goiter [1]. Pregnancy-related changes in thyroid hormone metabolism include an estrogen-induced increase in thyroid-binding globulin synthesis, a subsequent increase in total T4 and T3 levels, and a slight increase in first-trimester free T4 levels. This increase in free T4 levels results from placental production of human chorionic gonadotropin (hCG) during the first trimester. hCG in large quantities, has been shown to have thyrotropin-like bioactivity. Rising hCG levels in the first trimester are mirrored by falling TSH levels. Free T4 levels subsequently decrease after hCG levels fall in the second trimester. In most women, these changes in free T4 are small, such that free T4 concentrations remain within the normal range for nonpregnant women. Finally, the negative-feedback control mechanism of the hypothalamic-pituitary-thyroid axis functions normally in pregnant women, as evidenced by second-trimester and third-trimester TSH concentrations similar to those in nonpregnant women, as shown in the table[2,3].

Table (1): changes in maternal thyroid hormone physiology during pregnancy.

High	Renal clearance of iodide	Secondary to high glomerular filtration rate
High	Thyroid-binding globulin	Secondary to high hCG
High	Total T4 and T3 levels	Secondary to high hCG
High	Free T4/ low TSH* in first trimester only	Secondary to high hCG

*Changes are small and occur at normal range of non-pregnant women.

The role of the placenta in thyroid hormone transportation is that TRH, iodine, and thyroid-stimulating immunoglobulins can readily transfer across the placenta, whereas TSH does not. The extent of placental transfer of T4 or T3 is controversial. Investigations have suggested that the placental transfer of maternal thyroid hormone was insignificant and that normal fetal growth and development were independent of maternal thyroid hormone. Scientific evidence indicates that maternal thyroid hormones play a critical role in fetal development, especially during the early stages of pregnancy, before the fetal thyroid gland matures. Studies indicate Clinical measurements of serum thyroxine[4]. levels in newborns with an intrathyroidal iodine organization defect, a disorder that prevents T4 synthesis, have shown that birth levels of this hormone range from 20% to 50% of normal levels in healthy newborns. This clearly indicates a partial transfer of T4 from the mother to the fetus across the placenta. Furthermore, studies have confirmed the presence of nuclear receptors for triiodothyronine (T3) in fetal brain tissue in early stages of embryonic development, before the fetal thyroid gland begins to function effectively [5]. These data support the hypothesis that maternal thyroid hormones, particularly T4, contribute to the fetal brain's adequate supply of T3, which may mitigate the adverse effects of fetal thyroid hormone deficiency, particularly in cases of congenital hypothyroidism resulting from dysgenesis or absence of the gland (thyroid agenesis) [6]. This hypothesis is reinforced by the clinical observation that most children born with congenital hypothyroidism do not exhibit obvious symptoms at birth, but rather classic symptoms develop gradually over the first weeks or months of life. This indirectly reflects the temporary compensation role played by maternal thyroid hormones. TSH, T3, T4, and anti-thyroglobulin (Tg-Ab) as a biomarker for thyroid disease. Thyroid disorders are divided into two types: hypothyroidism, resulting from impaired thyroid function that prevents it from producing sufficient thyroid hormones, and primary hyperthyroidism, resulting from excessive thyroid hormone secretion above normal levels. Excessive thyroid hormone secretion inhibits the secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary gland via negative feedback. Primary hypothyroidism results from a deficiency in T3 and T4 secretion, leading to an increase in TSH secretion due to decreased inhibition of negative feedback. Secondary hyperthyroidism typically results from excessive secretion of TSH from the anterior pituitary gland, which further increases T3 and T4. Secondary hypothyroidism, on the other hand, occurs when there is insufficient secretion of TSH from the pituitary gland, resulting in insufficient stimulation of the thyroid gland to synthesize T3 and T4 [7]. The hypothalamus-pituitary-thyroid axis is made up of the traditional pituitary-thyroid feedback loop and the hypothalamus-thyroid feedback loop. These loops affect thyroid function and hormone levels [8]. There are more feedback loops and other processes that help keep thyroid homeostasis and control thyroid hormones. TSH levels, free thyroxine (FT4) levels, and free triiodothyronine (FT3) levels are all part of thyroid function tests. Therefore, measuring TSH levels is used as the first step in evaluating thyroid dysfunction. Its results can usually be interpreted in conjunction with T3 and T4 levels, and TSH may be used to differentiate between primary, secondary disorders. Thyroid autoimmunity refers to the presence of thyroid autoantibodies, including thyroperoxidase or thyroglobulin, thyroid-stimulating hormone receptor antibodies, or a combination thereof. Studies has been suggested that thyroid autoantibodies may serve as a marker of thyroid risk in pregnancy[10].

Material and methods:

From October 2023 to July 2024, across-sectional study was carried out at the Al-Batool Maternity Hospital, and outpatient clinics for obstetrics, gynecology, and infertility in Wasit province, Iraq. The Study subject were divided in to tow groups according to the age (18-29 years) and (30-42 years) for patients and control. Blood samples are collected from 57 aborted women in the experimental group and 34 normal pregnant women in the control group. The blood samples, which were 5 ml each from all participants, were left at room temperature for about 30 minutes, then placed in a gel tube to separate the serum by spinning them in a centrifuge at 3000 r.p.m. for 5 minutes, and finally frozen at -20º for serological tests to check the levels of T3, T4, TSH, and Tg-Ab . The ELISA method, for thyroid hormone T4, T3, and TSH tested by Cloud-Clone Corp (USA). And anti-Tg-Ab, was tested by SunLong Biotech(China) depending on the manufacturer's information. 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 ($P \leq 0.05$).

Results:

The results of this study showed there are significant statistical differences between recurrently miscarrying women, whose number was 57, and the number of normal pregnant women were 34 as a control group, in thyroid function parameters and in thyroid autoimmunity. The results show that there is a significant statistical decrease ($P \leq 0.01$) in thyroid T3 of recurrent miscarriage women compared to the control; the percentages are 1.509 and 9.573, respectively as it showed in (Figure 1).

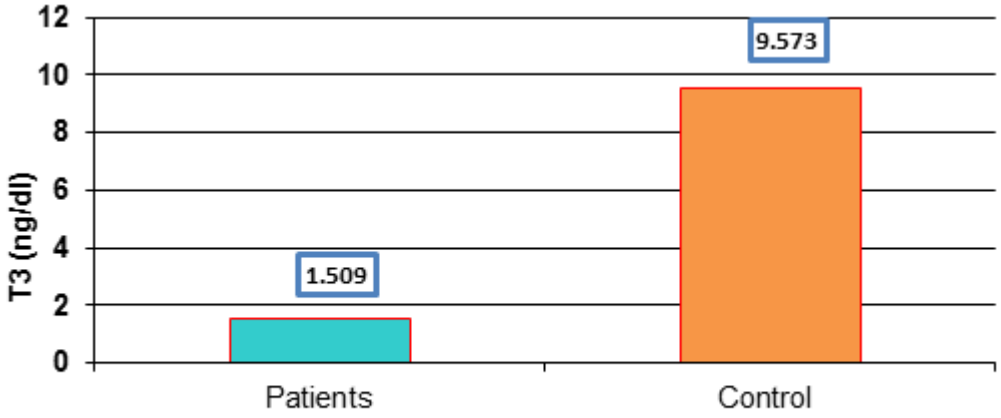

Figure1: Comparison between RMW and contol groups inT3

And Figure 2: shows a significant statistical decrease ($P \leq 0.01$) in T4; the percentages were 3.864 and 9.541 in recurrent miscarriage women and controls, respectively.

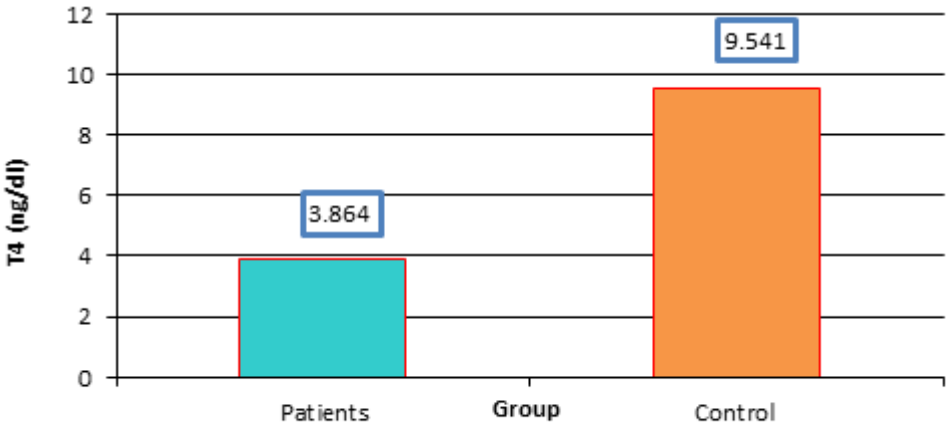

Figure2: Comparison between RMW and control groups in T4

As well as thyroid-stimulating hormone (TSH), it highly decreased (P≤0.01) in recurrent miscarriage women compared with the control group, as shown in figure 3: The percentages were 1.098 and 4.09, respectively.

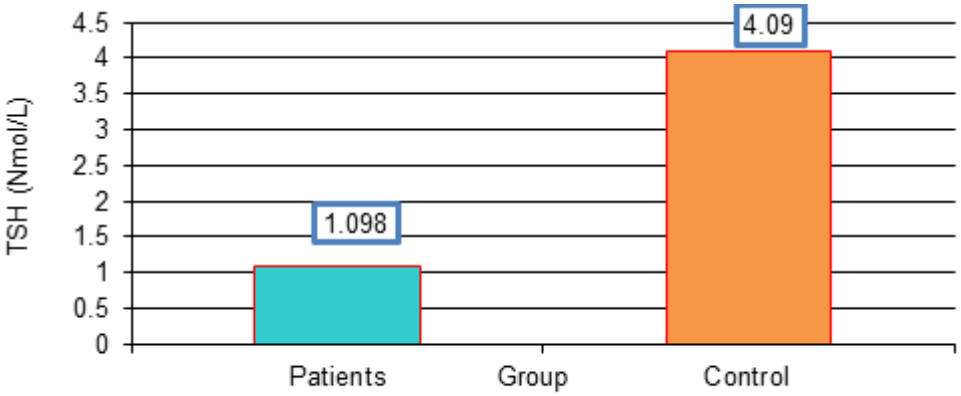

Figure 3: Comparison between RMW and control groups in TSH

In figure 4, the data shows there is a highly significant increase (P≤0.01) in the level of Tg-Ab; the percentages were 144.06 and 82.77 in recurrent miscarriage women and controls, respectively.

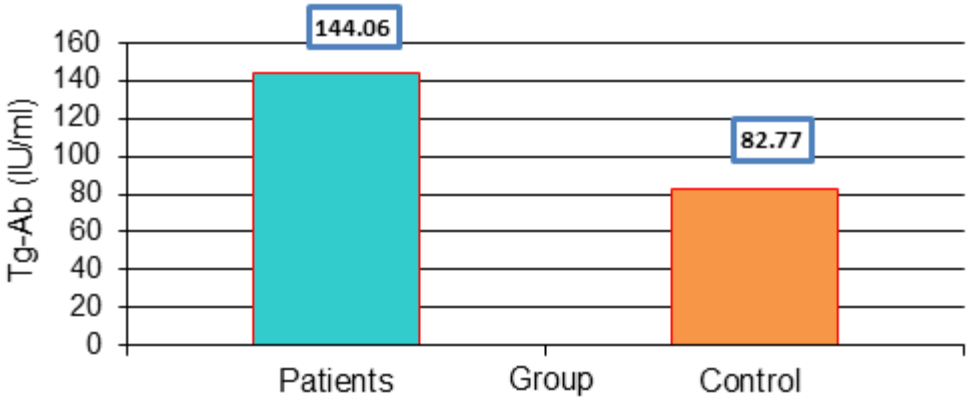

Figure 4: Comparison between RMW and control groups in Tg-Ab

Discussions:

Based on the results of this study, we conclude that a decrease in both thyroid hormones and thyroid-stimulating hormone is evidence of central hypothyroidism resulting from a dysfunction of the pituitary gland These results agree with [11], [12], [13], and [14] and agree with [15]. T3 affects metabolism and energy processes in the body, with low levels potentially due to hypothyroidism, malabsorption, or certain diseases. Low T3 levels may be due to hypothyroidism, autoimmune diseases, non-thyroidal illness syndrome (NTIS), iodine deficiency in the diet, severe stress or starvation, liver disease, or selenium deficiency. Studies indicate that low T3 alone is not the main factor, but low T4 and high TSH are more dangerous. Miscarriage in the first trimester of pregnancy in women with autoimmune hypothyroidism can occur due to several interrelated factors, including thyroid hormone disorders, abnormal immune responses, and the presence of thyroid antibodies. Recurrent miscarriage can result from several conditions, such as placental and blood flow disorders, increased risk of blood clots, and subclinical hypothyroidism and overt hypothyroidism with thyroid autoimmunity [16]. Thyroid hormones have a significant effect on female reproductive organs and embryos during implantation, and abnormal TSH levels may have a detrimental effect on ovarian function. In addition, TSH levels can be a factor affecting ovarian reserves. Hypothyroidism and subclinical hypothyroidism are common diseases in endocrinology, obstetrics, and gynecology. In mothers with hypothyroidism, insufficient amounts of thyroid hormones are transferred to the fetus, leading to abnormal pregnancy outcomes and fetal neuropsychological development. Thyroid autoimmunity is the most prevalent autoimmune

condition in women of reproductive age, with an increase in anti-Tg levels indicating an autoimmune thyroid disorder like Hashimoto's thyroiditis or Graves' disease. These conditions may cause thyroid dysfunction, which may be related to recurrent miscarriage. Hypothyroidism may lead to hormonal imbalance that affects the lining of the uterus and fetal growth [17]. Autoantibodies directed towards the endometrium play a crucial role in regulating metabolism and reproductive hormones, such as estrogen and progesterone. An imbalance in these hormones can disrupt ovulation, implantation, and pregnancy maintenance failure or early pregnancy loss. Insufficient thyroid hormone secretion caused by autoimmune thyroiditis can cause growth restriction, neurodevelopmental impairments, and increased risk of miscarriage and preterm birth [18]. The mother's immune system is essential for the success and continuation of pregnancy. However, in some cases, an abnormal immune response occurs, leading to an imbalance in the immune balance necessary for the continuation of pregnancy. These abnormal immune responses include increased activity of hostile immune cells, imbalance of cytokines, production of autoantibodies, and failure of the immune system to adapt to fetal tissues. The presence of Tg-Ab increases the risk of blood clots, which may lead to poor placental blood flow. Studies indicate the increased risk of blood clotting disorders due to factors such as autoimmune thyroid diseases, chronic inflammatory disorders, and antiphospholipid syndrome[19]. Patients with autoimmune hypothyroidism, associated with elevated Tg-Ab, suffer from changes in fibrinogen levels and clotting factors that increase the risk of clotting. Hypothyroidism slows blood flow, increasing the risk of clots, which may lead to blockage of blood vessels in the placenta, development of placental insufficiency, and increased likelihood of premature placental abruption, which may lead to miscarriage or premature birth. Several main theories explain the presence of anti-thyroid antibodies, including the possibility of a broader spectrum of active autoimmunity leading to reproductive failure, abnormal levels of thyroid-stimulating hormone, and decreased fertility in older women [20]. Hashimoto's disease is an immune disease and the most common cause of hypothyroidism in women, with increased demand for thyroid hormone during pregnancy. Several mechanisms suggest the apparent decrease in fertility, including increased numbers of T cells within the endometrium, polyclonal B cells that interact with placental tissue, vitamin D deficiency, hyperactivity and migration of natural killer cells into the uterus, and cross-reactivity with placental antibodies and the zona pellucida. Autoimmune thyroid disease may also occur in conjunction with other autoimmune conditions known to affect fertility or coexist with other conditions associated with impaired fertility. In summary, hypothyroidism and subclinical hypothyroidism are significant diseases that significantly impact pregnancy outcomes and fetal neuropsychological development. It is crucial to maintain a delicate balance in the immune response to ensure the successful continuation of pregnancy [21].

Conclusion: The current study concluded that there is a close relationship between autoimmune thyroid disorders, especially central autoimmune hypothyroidism, and recurrent miscarriage in the first trimester of pregnancy.

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