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RESEARCH ARTICLE OPEN ACCESS

The effect of Tetraiodothyronine hormone levels on miscarriage rate and pregnancy complications among women in Thi-Qar City, Iraq

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Abstract

Objective: Although previous studies have demonstrated an association between tetraiodothyronine (T4) levels and miscarriage risk, regional data from Thi-Qar City remain limited. This study investigates the relationship between T4 levels and miscarriage rates among pregnant women in Thi-Qar, thereby providing novel insights into the local influence of thyroid function on pregnancy outcomes.

Methods: This study included singleton pregnant women aged 18–40 attending antenatal clinics. Exclusion criteria were pre-existing thyroid disorders, multiple pregnancies, chromosomal abnormalities, or medical conditions affecting pregnancy outcomes. Clinical assessments covered maternal demographics, medical and obstetric history, and anthropometric measurements. Serum T4 levels were measured in the first trimester. Participants were followed throughout pregnancy, and miscarriage rates were compared between women with normal and abnormal T4 levels. Statistical significance was set at $P < 0.05$.

Results: Among 110 pregnant women, those who miscarried (n=23) had significantly lower T4 levels ($P < 0.001$) than those who did not have miscarriages (n=87). No significant differences in demographic data were found between the groups. However, nausea and vomiting were significantly higher in the miscarriage group ($P = 0.008$, 0.01). Miscarriage rates (43.3%) and vaginal bleeding (63.3%) were significantly higher ($P < 0.001$) in the group with lower T4 levels.

Conclusion: This study highlights a possible link between low T4 levels and increased miscarriage risk. Understanding thyroid hormones' role in pregnancy may guide clinical strategies to reduce miscarriage rates and enhance maternal-foetal health. Further research is essential to improve obstetric care and pregnancy outcomes.

Keywords: Tetra-iodothyronine, Thyroid hormones, Miscarriage, Pregnancy, Obstetrics

Plain English Summary

Miscarriage is the unexpected loss of a pregnancy before 5 months and affects many women around the world. While many factors can increase the risk of miscarriage, the effect of a hormone called thyroxine (T4), which is made by the thyroid gland and helps support the baby's growth and development, is not fully understood. This study looked at whether T4 levels are related to miscarriage. This was a comparative study with 110 pregnant women—some who had a miscarriage and others who did not- to explore this link. We found that women who had miscarriages had significantly lower levels of T4. These findings suggest that low T4 levels during pregnancy may increase the risk of miscarriage.

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Background

The occurrence of miscarriage, characterised by spontaneous pregnancy loss before the completion of the 20th week of gestation, represents a profound and distressing occurrence affecting a significant proportion of pregnancies worldwide. Despite considerable strides in obstetric care, miscarriage remains a formidable challenge in maternal-foetal medicine, imposing substantial emotional, physical, and psychological burdens on women and their families. Numerous factors contribute to miscarriage risk, ranging from maternal age to genetic and environmental influences. Current research and debate focus on the potential role of thyroid function, particularly tetraiodothyronine (T4), in influencing miscarriage susceptibility (1).

Thyroid hormones, such as T4, have a role in supporting pregnancy and the growth of the baby. The mother's thyroid function varies during pregnancy to accommodate the increasing baby and the mother's metabolic needs. The thyroid gland secretes the T4, essential for regulating metabolism, energy production, cellular division, and growth. Moreover, T4 plays a part in the development of foetal brains and in sustaining pregnancy (2). Problems with thyroid functioning indicated by changes in T4 levels have been associated with adverse results during pregnancy, such as miscarriages. When the thyroid is underactive (hypothyroidism), indicated by T4 levels, it has been connected to an increased likelihood of miscarriages, premature births, low birth weights, and developmental issues in children. On the other hand, if the thyroid is overactive (hyperthyroidism), as shown by T4 levels, it has also been tied to unfavourable pregnancy outcomes like premature births and growth restrictions and can even lead to miscarriages. It is the second most common disorder of endocrine disorder, after diabetes, that affects females during pregnancy.

Pregnancy is linked with complex consequences depending on the state of the thyroid in a female. Thyroid dysfunctions like thyroid nodules, hypothyroidism, and thyrotoxicosis might grow during pregnancy, leading to complications such as placental abruptions, pre-term delivery, pre-eclampsia, reduced intellectual functioning in the baby, and abortion. Hence, maintaining the state of euthyroid is significant for foetal and maternal health during and after pregnancy (3). Even though there is evidence suggesting a relationship between thyroid disorder and miscarriage risks, the suitable correlation between miscarriage and T4 levels seems to be relatively underexplored. It needs further investigation as the previous research investigating this association has not made headway, with some studies showing that miscarriage is highly associated with abnormal T4 stages. In contrast, others have concluded no significant affiliation. Furthermore, most present studies were restricted by diverse study populations, small pattern lengths, and methodological inconsistencies, highlighting the need for additional research in this area (4).

Given the superiority and the impact of miscarriage on maternal and foetal health, there may be a pressing need to elucidate on the role of thyroid function in the incidence of miscarriage risk. Understanding the association between T4 levels and miscarriage may pose a significant breakthrough in the management of pregnancy, which includes the identification of women at risk of miscarriage and the implementation of targeted therapies to enhance thyroid function and lower the incidence of miscarriages (5). This study seeks to close this knowledge gap by examining the association between pregnant women's T4 levels and miscarriage rates. Using a potential cohort layout and method, this research aims to provide valuable insights into the potential effect of thyroid function on pregnancy (6). The results of this study may also include medical practice recommendations and public health regulations aimed at reducing miscarriage and improving maternal and foetal health outcomes.

Methods

Study Design

prospective observational cohort study was conducted at Bint Al-Huda Educational Hospital from January 2023 to January 2024 to examine the association between T4 hormone levels and miscarriage rates in pregnant women.

Study Population

Pregnant women attending antenatal clinics at Bint Al-Huda educational hospital were eligible for inclusion in the study. Participants' ages ranged between 18 and 40 years. Informed consent was obtained from all participants before enrolment. Women with singleton pregnancies confirmed by way of ultrasound examination were enrolled. Women with preexisting thyroid disorders, more than one pregnancy, known chromosomal abnormalities, or clinical conditions negatively impacting pregnancy were excluded from the study.

Data Collection
Participants had comprehensive clinical assessments at enrolment, including maternal demographics, medical records, obstetric history, and anthropometric measurements. Five millilitres of blood were taken from each woman in the first trimester to assess T4 levels using standard procedures. Serum T4 degrees were measured using radioimmunoassay and expressed in ng/dl.

Follow-up and Outcome Assessment
Participants were followed up throughout pregnancy. Miscarriage was defined as the spontaneous loss of pregnancy before 20 weeks of gestation. Miscarriages were confirmed by obstetricians using ultrasound examination. Participants' antenatal clinic records, including miscarriages, were recorded for each woman.

Radioimmunoassay (RIA) principles
It is an analytical technique that has been effectively used on various chemicals. The basis of immunoassays is using specific antibodies selected as reagents that can measure chemicals in complicated matrices without needing pre-treatment. Numerous types of immunoassays exist, including RIA and ELISA. Antigen-antibody competitive reaction or RIA is the competition for restricted binding sites of antibodies that form antigen-antibody complexes between radiolabelled antigens and analytes present in standard solutions or blood samples undergoing tests. A separation system is used to improve the bound complexes' fine separation. A lithium iodide crystal gamma countermeasures the bound complex's radioactivity. The amount of analyte in the sample is inversely correlated with the antigen bound to the antibody. One can interpolate the analyte concentration in the unknown samples by calculating the percentage of the labelled antigen bound in reference standards with different known analyte concentrations. These assays use a labelled analogue of T4, and they work on the basis that the labelled analogue of T4 only binds to the anti-T4 antibody reagent and not to serum T4 binding proteins, which allows them to assess the free fraction rather than the total fraction (7).

Radioimmunoassay (RIA) reagents
The reagent kit includes standards, radiolabelled antigens, antibodies (Abs), nonspecific binding reagents, and separating agents. Human sera are stripped of standards with concentrations, such as thyroxine(T4) at 0,20, 40, 80, 160, and 240 ng/dl. Radiolabelled antigen (tracer) solutions are made in baritone buffer using analino-1-naphthalene sulfonic acid ANS and bovine serum albumin. Tracers consist of 1251 with a T4 label. Antibodies, including T4 antibodies, are manufactured as solutions containing cellulose, an antimicrobial agent (sodium azide), and magnetic particles. A typical human's normal range of T4RIA is 5.6 to 13.1 ng/dl (8).

T4 Protocol
The serum samples and all the reagents were kept at room temperature. Each standard bottle was filled with one millilitre of distilled water. Tubes were numbered in duplicates for total and standard solutions, and serum samples and quality control were arranged neatly on magnetic tube racks. Each tube with a corresponding label was filled with 50 microliters of standard solutions, control samples, and blood samples. Then, 500µl of 125I labelled T4 was added, and finally, 500µl antibody suspensions. Except for the total tubes, all the mixture's tubes were well mixed using a multi-shaker before being incubated for 45 minutes at 37 ºC. Following the incubation period, the tubes were all placed on a magnetic base at room temperature for ten minutes. The supernatant was poured and placed on sorbet pads for five minutes. A gamma counter was used to read the residue for a minute.

Statistical Analysis
Descriptive statistics were used to summarise participant characteristics, including mean, median, standard deviation, and frequency distribution. T4 levels were categorised as normal or abnormal based on predefined reference ranges. Miscarriage rates were compared between women with normal and utilizing the proper statistical methods, such as Fisher's exact test or chi-square test, to identify aberrant T4 levels. Although iodine status is recognized as an important covariate, it was not measured in this study; we recommend that future investigations incorporate iodine status as a confounding variable. A statistically significant p-value was defined as one that was less than 0.05.

Results
Comparison of Demographic Characteristics, Miscarriage Rates, and Pregnancy Complications Based on T4 Hormone Levels
As shown in Table 1, there were no statistically significant differences between the two groups concerning age (p=0.15), place of residence (p=0.96), and occupation (p=0.87). Figure 1 visually compares these demographic characteristics across T4 level groups. However, the miscarriage rate was significantly higher in

women with low T4 levels (43.3%) compared to women with normal levels (12.5%) (p<0.001). A significant increase in nausea (66.7% vs. 43.7%, p=0.008) and vomiting (56.7% vs. 31.3%, p=0.01) was also observed in the low T4 group. Additionally, vaginal bleeding was significantly more common among women with low T4 levels (63.3%) compared to the group with normal levels (12.5%) (p<0.001), suggesting a strong association between low T4 levels and an increased risk of pregnancy complications.

Table 1: Distribution of Age, Residence, Occupation, Miscarriage Rate, and Pregnancy Complications among Women with Normal and Low T4 Levels

	The normal level of T4 (N=80)	Low level of T4 (N=30)	Test	p-value
Age				
Mean ± SD	28.9±3.7	26.8±3.15	t = 1.443	0.15
Residence				
Urban	35 (43.7%)	13(43.3%)	X^2=0.002	0.96
Rural	45 (56.3%)	17 (56.7%)		
Occupation				
Working	44(55%)	17 (56.7%)	X^2=0.025	0.87
Housewife	36 (45%)	13(43.3%)		
Miscarriage rate	10(12.5%)	13(43.3%)	X^2=12.543	< 0.001
Complications				
Nausea	35 (43.7%)	20(66.7%)	X^2= 6.993	0.008
Vomiting	25(31.3%)	17 (56.7%)	X^2=5.971	0.01
Vaginal bleeding	10(12.5%)	19(63.3%)	X^2=29.041	< 0.001

**T4 levels in ng/dl*

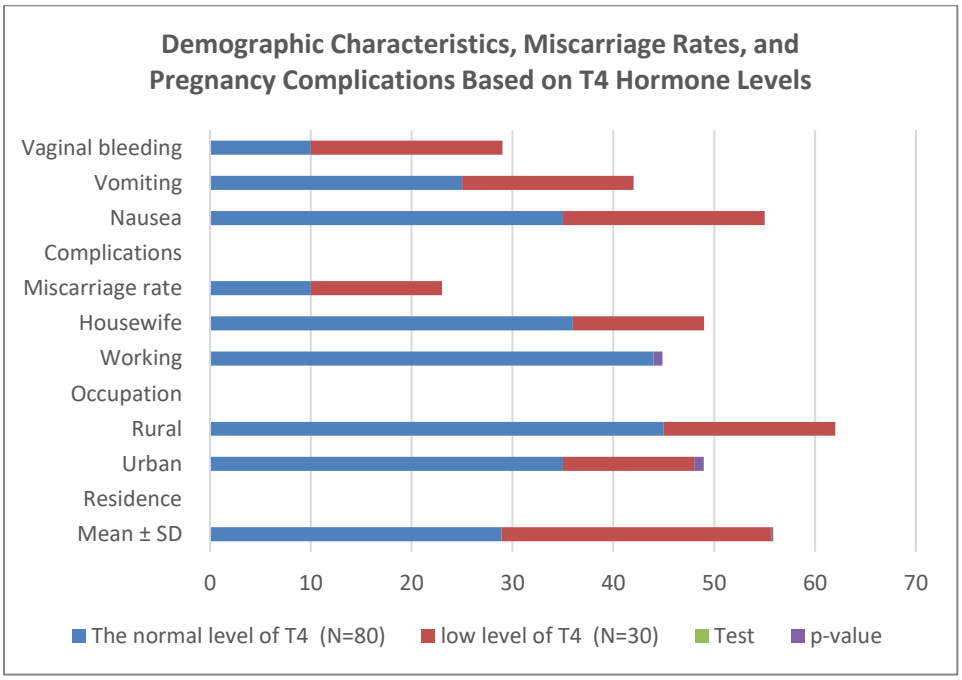

Figure 1: Comparison of Demographic Characteristics of the study population

Comparison of Demographic Characteristics between Miscarriage and Ongoing Pregnancy Groups

As detailed in Table 2, no statistically significant differences between the miscarriage group and the ongoing pregnancy group with regard to age (p=0.18), place of residence (p=0.85), or occupation (p=0.49). Figure 2 illustrates these comparisons graphically, showing the relatively even distribution across both groups. The mean age was similar between the two groups, and there was no clear difference in the distribution of women

between urban and rural areas. Furthermore, there was no significant difference in the proportion of working women and housewives between the two groups, indicating that these factors were not directly related to the incidence of miscarriage in the studied sample.

Table 2: Association between Age, Residence, and Occupation and Pregnancy Outcomes

	Miscarriage Group (N=23)	Ongoing group (N=87)	Test	p-value
Age				
Mean ± SD	28.6±3.12	27.8±3.15	t = 1.3382	0.18
Residence				
Urban	10 (43.5%)	41 (47.1%)	X^2= 0.033	0.85
Rural	13 (56.5%)	58 (52.8%)		
Occupation				
Working	14 (61%)	46 (52.8%)	X^2= 0.469	0.49
Housewife	9 (39%)	41(47.2%)		

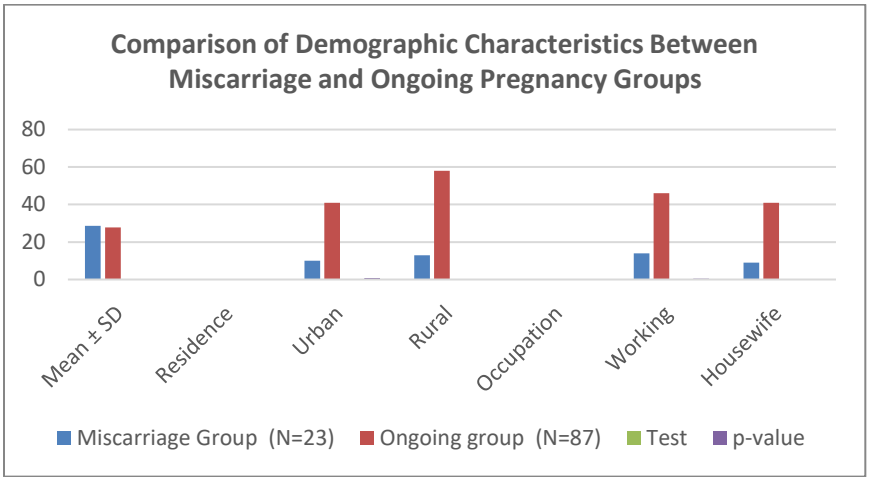

Figure 2: Age, Residence, and Occupation in Pregnancy Outcomes

Comparison of First-Trimester Serum Tetraiodothyronine (T4) Levels between Miscarriage and Ongoing Pregnancy Groups

The results showed a significant decrease in mean tetraiodothyronine (T4) levels in the miscarriage group (4.93±0.92) compared to the ongoing pregnancy group (11.1±2.6), and this difference was highly statistically significant (p<0.001), as shown in Table 3. The difference is further visualised in Figure 3, emphasising the marked contrast in T4 levels between the groups. This suggests a strong association between low T4 levels in the first trimester of pregnancy and an increased risk of miscarriage, reinforcing the importance of monitoring thyroid function during pregnancy to ensure stable levels and reduce the risk of pregnancy loss.

Table 3: Association between First-Trimester Serum Total Tetraiodothyronine (T4) Levels and Pregnancy Outcomes

	Miscarriage Group (N=23)	Ongoing group (N=87)	Test	p-value
1st-trimester serum total tetra- iodothyronine T4 (ng/dl) Mean ± SD	.93±0.92	11.1± 2.6	t = 2.48	<0.001

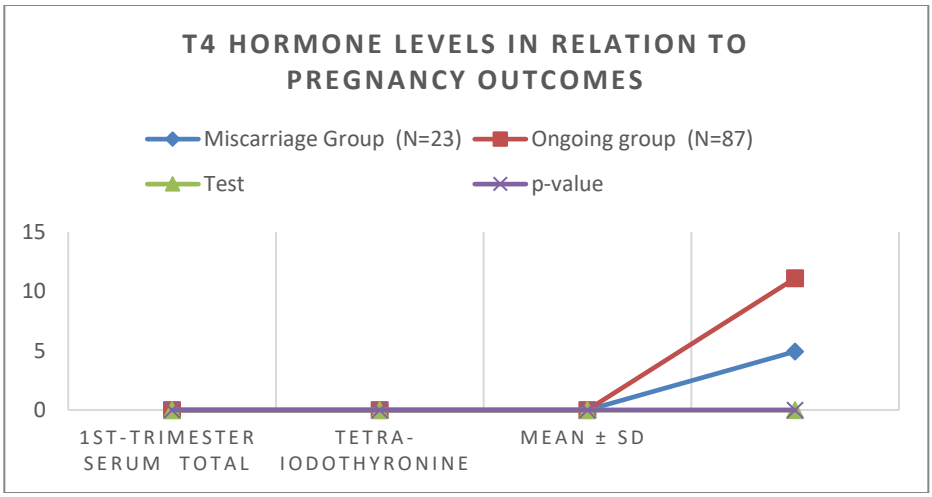

Figure 3: Comparison of First-Trimester Serum Tetraiodothyronine (T4) Levels

Comparison of Second-Trimester Serum Tetraiodothyronine (T4) Levels between Miscarriage and Ongoing Pregnancy Groups

The results showed a significant decrease in mean tetraiodothyronine (T4) levels during the second trimester in the miscarriage group (4.36±0.9) compared to the ongoing pregnancy group (11.92±2.4), and this difference was highly statistically significant (p<0.001), as presented in Table 4. Figure 4 illustrates this drop in T4 levels during the second trimester in the miscarriage group compared to ongoing pregnancies. This sharp decrease in T4 levels in women who had miscarried indicates the importance of hormonal balance during this critical stage of pregnancy, which may help improve pregnancy outcomes and reduce the risk of miscarriage.

Table 4: Association between Second-Trimester Serum Total Tetraiodothyronine (T4) Levels and Pregnancy Outcomes

	Miscarriage Group (N=23)	Ongoing group (N=87)	Test	p-value
2nd-trimester serum total tetra- iodothyronine T4 (ng/dl) Mean ± SD	4.36±0.9	11.92± 2.4	t =8.01	<0.001

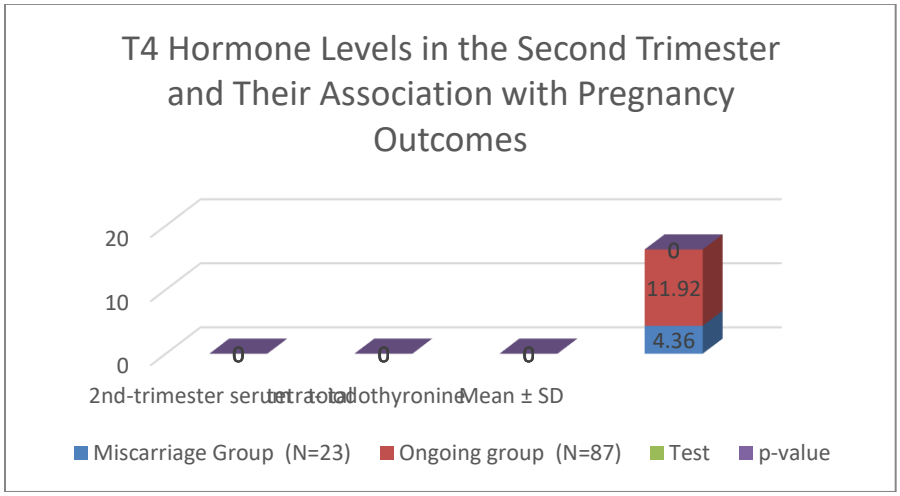

Figure 4: Second-Trimester Serum Tetraiodothyronine (T4) Levels Between Miscarriage and Ongoing Pregnancy Groups

Discussion

Hypothyroidism is a universal endocrinal condition that is easy to diagnose and manage, but if left untreated, it can be fatal in severe cases (9). According to Allan et al., women are up to 8 times more likely than men to have primary hypothyroidism. The risk of miscarriage, early birth, hypertension, and placental abruption have been linked to significant hypothyroidism (10). In one study, non-pregnant women with repeated pregnancy loss at the gestational age of 12 weeks, confirmed by a quantitative HCG-pregnancy test or ultrasound, were chosen as controls, along with women who had at least one successful pregnancy and no history of miscarriages. Thyroid hormone levels, including levels in non-pregnant women with repeated pregnancy loss and controls, were estimated. One control subject and seven women who had experienced repeated miscarriages had hypothyroidism.

Serum thyroid hormone levels in women with repeated and frequent pregnancy loss in the first trimester differed significantly between thyroid and hypothyroid women (11). Rao and his colleagues concluded that there is a solid association between hypothyroidism and repeated pregnancy loss in the first trimester. Therefore, diagnosing hypothyroidism may increase the chance of subsequent pregnancies for women who experience recurrent miscarriage. Changes during pregnancy should include an up to 100% rise in thyroid hormones to satisfy the requirements of the mother and the baby throughout pregnancy. This is based on the thyroid gland's heightened requirement for healthy development and metabolic haemostasis throughout the pregnancy and the foetal periods (12).

The critical correlation between thyroid antibodies and miscarriage has attracted the attention of numerous investigations. The relationship between thyroid autoimmunity and miscarriage has been the subject of numerous published studies involving healthy women, women with multiple miscarriages, and women using assisted reproductive technologies. Although it is difficult to compare all these studies since different selection criteria were used for different study objectives, most of them have demonstrated a strong positive relation between the incidence of miscarriages and thyroid autoantibodies (13,14). Although thyroid function during pregnancy is the subject of numerous studies, it is unclear if thyroid dysfunction contributes to the aetiology of spontaneous miscarriages (15). However, this study attempted to evaluate thyroid hormones as potential causes of miscarriage. The development of a foetus depends on thyroid hormones. Therefore, pregnant women need more thyroxine than non-pregnant women to provide T4 for themselves and their developing foetuses.

Thyroid gland function in the foetus is not fully developed until the twelfth week of pregnancy. The chance of miscarriage may rise if the mother's thyroid hormone levels are low (16). Most women do not know if they are pregnant even one to two months after their last menstrual cycle. Hence, they wait until the first trimester, which is more than half over, to visit their doctors and have their thyroid function tested. After being aware that they are pregnant, women with a history of miscarriages are advised to get a thyroid test immediately. Because pregnancy alters thyroid function and maternal thyroid disease can impact both the pregnancy and the foetus, treating thyroid problems during pregnancy requires specific consideration. Coordination between several healthcare providers is necessary for care. Due to the possibility of harm to foetal brain development.

With the increased risk of miscarriage and premature birth, preventing thyroid dysfunction in both mother and foetus is essential (17). The current study's statistic results (Table 1) showed a highly significant variation in the rate of miscarriages and vaginal bleeding among the groups under study. Table 3 demonstrated a highly statistically significant difference in the first-trimester serum total tetra-iodothyronine between the studied groups. Additionally, Table 4 demonstrated a statistically significant difference in the total tetra-iodothyronine in the second-trimester serum between the groups under study. These results confirm the association between the incidence of miscarriage and low serum total tetraiodothyronine (T4) level. This link may be explained by several biological mechanisms. Low T4 levels can impair placental development and vascularisation, leading to placental insufficiency, which is a known risk factor for early pregnancy loss. Inadequate T4 also affects foetal neurodevelopment, particularly during the first trimester when the foetus depends entirely on maternal thyroid hormones. Disruption in these processes may contribute to pregnancy complications such as miscarriage (18).

This study has several limitations. First, the sample size was relatively small (N = 110), which may affect the generalizability of the findings. Second, it was conducted in a single centre in Thi-Qar City, which limits external applicability to other regions or healthcare settings. Future studies with larger, multi-centre cohorts are recommended to validate these results and explore additional confounding

variables such as iodine intake or autoimmune markers.

Anecdotal data in literature suggests that certain women with low thyroid hormone levels need larger doses of T4 throughout their pregnancy than they do when they are not pregnant (19). It is clinically significant since, among other issues, hypothyroidism during pregnancy is linked to an increased risk of spontaneous miscarriage (20). More than 30 years ago, Mandel et al. (1990) showed that women with low thyroid hormone levels should raise their dose of T4 hormone during pregnancy (21). Verga et al. showed how crucial T4 modulation is for women with subclinical hypothyroidism, especially during the first trimester of pregnancy. Furthermore, there is some placental transfer of maternal T4 and a unique allocation of thyroid hormones in the foetal/placental unit (22). For these reasons, we recommend beginning treatment as soon as the pregnancy is confirmed and closely monitoring the patients every month until term (23, 24).

Conclusion:

This study explores the relationship between T4 levels and pregnancy complications, including miscarriage, vaginal bleeding, nausea, and vomiting. Our results found that low T4 levels (hypothyroidism) were associated with an increased risk of miscarriage, vaginal bleeding, nausea, and vomiting. Investigating women with a history of miscarriage revealed lower T4 serum levels as a contributing factor. Continuous monitoring during pregnancy highlighted fluctuations in T4 levels. These findings emphasise that maintaining adequate T4 levels is important for reducing miscarriage risk and improving pregnancy outcomes.

These findings underline the value of including routine thyroid function screenings, especially for T4 levels, in the care of pregnant women, even when they are asymptomatic. Given the link between thyroid disorders and miscarriage, early detection is critical to avoid complications. For resource-limited settings like Thi-Qar, including thyroid tests is efficient and affordable for maternal health services. Also, these results emphasise the importance of establishing national guidelines for thyroid health during pregnancy. Further extensive, multicentre studies to confirm these links and explore the long-term benefits of focused intervention strategies are required.

List of abbreviations

T4: tetra-iodothyronine
RIA: Radioimmunoassay

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Bint Al-Huda Educational Hospital (Approval Number: 4162), and all participants provided informed consent before enrolment. The research protocol was designed and conducted following the ethical principles outlined in the Declaration of Helsinki.

Consent for publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests

The author affirms that she has no potential conflicts of interest related to writing or publishing it.

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Author contributions

The entire project was created by the author, who also gathered data and performed statistical studies on it. The author endorsed the final draft of the paper.

Acknowledgement

Not applicable.

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