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Maternal overt and Subclincal hypothyroidism, and the risk of miscarriage in Iraq

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Abstract

Background: Overt hypothyroidism complicating pregnancy is associated with an increased rate of miscarriage; recent studies have associated pregnancy loss with subclinical hypothyroidism and an adverse pregnancy outcome. In Iraq, there are limited data on the association of these conditions with early pregnancy complications and subsequent miscarriage.

Aim of study: To measure the prevalence of undiagnosed overt hypothyroidism and subclinical hypothyroidism among a group of Iraqi pregnant women early in pregnancy and looking to the potential relationship with early pregnancy loss whether recurrent or sporadic.

Design: A cross sectional study.

Patients and Methods: This study was conducted at Al-Elwiya Maternity Teaching Hospital, from Jan.,1st ,2015 to Jan., 1st 2016. Recruitment of 240 apparently healthy pregnant women at their early pregnancy up to 23 weeks+6 days, whom they had a singleton pregnancy that complicated by any type of spontaneous miscarriage (admitted to emergency unit) or still pregnant(came to consulting clininc). Their Thyroid stimulating hormone & free thyroxin were measured. Overt and subclinical hypothyroidism were defined as an elevated trimester specific Thyroid stimulating hormone concentration in both with a decrease in the free thyroxin concentration in the former but not in the later.

Results: In our study, laboratory evidence of low thyroid status (Any low thyroid status) was observed in 18.8% of the study sample (95% confidence interval 14.1% to 24.3%). The most frequently observed hypothyroidism status was "isolated low free thyroxin" documented in 10% of pregnant females (with an anticipated 95% confident interval in the reference population ranging between 6.5% to 14.5%). Ranked second was subclinical hypothyroidism observed in 7.1% of women (95% confidence interval 4.2% to 11.1%), while undiagnosed overt hypothyroidism was observed in only 1.7% of cases (95% confidence interval 0.5% to 4.3%).

The rate of any low thyroid status, isolated low thyroxine and overt hypothyrodism were slightly higher in those with recurrent miscarriages (24.1%, 16.7% & 1.9% respectively), though the difference was not significant statistically.

In addition, the rate of any low thyroid status was significantly higher among women tested in the first trimester of pregnancy (30.5%) compared to those tested in the 2nd trimester (12.7%).

Conclusion: There is a high prevalence of abnormal low thyroid status, in the form of isolated low free thyroxine, subclinical hypothyroidism and undiagnosed overt hypothyroidism tested in early pregnancy in the sample that had been studied, though no significant association had been found between such low thyroid status and early pregnancy loss whether recurrent or sporadic.

Keywords: hypothyroidism, rate of miscarriage, pregnancy.

Introduction

Miscarriage

Spontaneous miscarriage is defined as the loss of a pregnancy prior to viability, taken legally in the UK as a gestation date of 23 weeks plus 6 days, and where the same definition had been adopted by the Iraqi Ministry of Health. The majority of first-trimester miscarriage occurs below 12 weeks' gestation. The overall rate is 20%, while second trimester miscarriage account for 1-4% of all miscarriage [1]. While some second-trimester miscarriages can be explained as first-trimester losses where the diagnosis is made in the second-trimester, nevertheless it seems likely that the causes are different [2].

Types of miscarriage [3]:

1. Threatened miscarriage: vaginal bleeding in the presence of a viable pregnancy.
2. Inevitable miscarriage: vaginal bleeding in the presence of an open cervical os and pregnancy associated tissue still present.
3. Incomplete miscarriage: vaginal bleeding that on going where pregnancy tissue has already been passed but ultrasound suggests the presence of further products within uterine cavity.
4. Complete miscarriage: cessation of bleeding and a closed cervix following miscarriage and ultrasound showing an empty uterus.
5. Missed miscarriage: miscarriage occurring in the absence of symptoms or minimal symptoms, where the pregnancy is still visible within the uterus by U/S.
6. Recurrent miscarriage: three or more consecutive early pregnancy loss.

Etiology:

Causes of miscarriage in the first and second trimester appear different.

* First trimester miscarriage causes are [4]:

- Trisomy: 68%, mainly trisomy 16, 21 and 22.
- Maternal disease: antiphospholipid syndrome, diabetes and thyroid disease.
- Drugs: methotrexate and some antiepileptic drugs.
- Uterine abnormality like fibroid.
- Uterine infection like varicella, rubella and other viral illnesses.

* Second trimester miscarriage causes are [4]:

- Cervical surgery.
- Infection may be local to the genital tract or systemic.
- Uterine anomalies.
- Thrombophilia.

Thyroid gland

It is a butterfly shaped structure that lies on the windpipe below the Adam's apple. The thyroid lobes can be imagined as wings, while the body lies in front of the windpipe and is called the thyroid isthmus. The isthmus usually lies over the second and third tracheal rings opposite the fifth, sixth and seventh cervical vertebrae. The lobes of the thyroid are almost always asymmetrical with the right lobe larger than the left. The thyroid is usually larger in women than men. The total weight of it is approximately 20-25 grams but is smaller in parts of the world where supplies of iodine are abundant.

It is a very vascular organ and is surrounded by a sheath. This sheath attaches the thyroid to the larynx and the trachea [5].

Function:

Hormones that secreted by this gland; thyroxin (T4), and 3,5,3'-triiodothyronine (T3), are critical determinants of brain and somatic development in infants and of metabolic activity in adults. They also affect the function of virtually every organ system. Thyroid hormone biosynthesis and secretion are maintained within narrow limits by a regulatory mechanism that is sensitive to small changes in circulating hormone concentrations [6].

Classification of thyroid disease :

Hyperthyroidism:

Overactive thyroid, is defined as an overproduction of the thyroid hormones T_3 and T_4. This condition is most commonly caused by the development of Graves' disease, an autoimmune disease in which anomalous antibodies stimulate the thyroid to secrete excessive quantities of thyroid hormone [7].

Hypothyroidism:

Is the underproduction of the thyroid hormones T_3 and T_4. Hypothyroid disorders may occur as a result of:

- Congenital thyroid abnormalities (Thyroid deficiency at birth).
- Autoimmune disorders such as Hashimoto's thyroiditis.
- Iodine deficiency (more likely in poorer countries).
- Removal of the thyroid gland following surgery to treat severe hyperthyroidism and/or thyroid cancer.

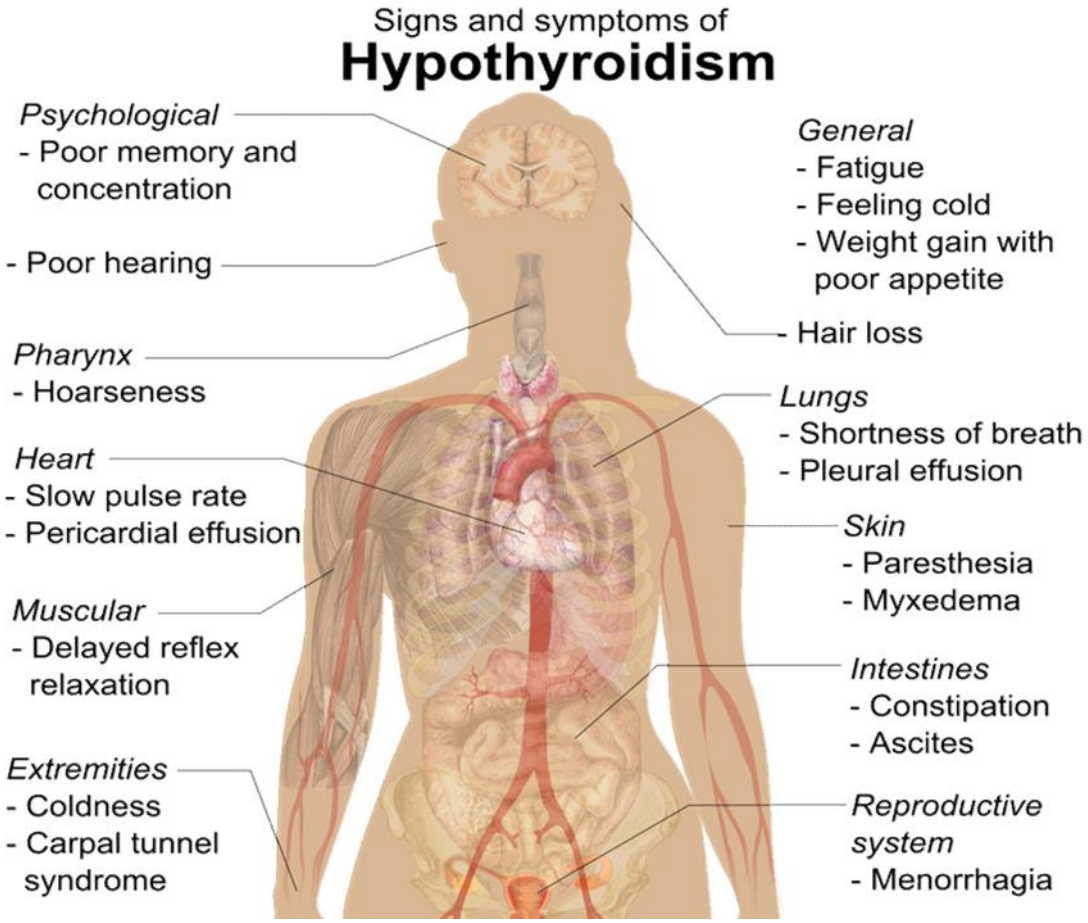

Figure 1: Clinical features of hypothyroidism [8]

Typical symptoms of hypothyroidism are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as levothyroxine, which is typically required for the rest of the patient's life. Thyroid hormone treatment is given under the care of a physician and may take a few weeks to become effective [9].

Hypothyroidism can be overt or subclinical; overt hypothyroidism (OH) is characterized by an elevated serum level of thyroid stimulating hormone (TSH >10 mIU/L) and a subnormal free thyroxin (fT4) level, whereas subclinical hypothyroidism (SCH) is characterized by an enhanced TSH level, usually beyond the upper reference limit, and a normal fT4 level 0[8].

Thyroid disorder and pregnancy:

Thyroid dysfunction is the second most frequent endocrine disease among reproductive-aged women[10]**.** Fecundity followed by pregnancy is the fundamental process to sustain life and requires a close interplay between normally functioning and adapting endocrine and immune systems. Besides estrogens and progesterone, which are necessary for uterine receptivity, the maturation of oocytes demands normal levels of thyroid hormone. Infertility and reproductive impairment can, therefore, be related to abnormalities in the endocrine or immune system, or both.

These systems are also directly linked to the thyroid gland since thyroid autoimmunity (TAI) is the most frequent cause of hypothyroidism in women of reproductive age [11].

Interaction of the thyroid and gonadal axes in pregnancy:

Such interaction can be demonstrated in the following orders:

- Many women with thyroid dysfunction experience menstrual irregularities, infertility and untreated hypothyroidism is associated with pregnancy morbidity[12].

- Thyroid stimulating hormone receptor (TRα1, TRβ1) and TSHR are expressed in human endometrium, the highest level is seen in the receptive endometrium[13]. Several paracrine factors are of importance for successful embryo implantation, leukemia inhibitory factor (LIF), and Leptin being among the most studied[14]. TSH increases LIF and LIF receptor expression in endometrial epithelial cells and in thyroid cells[15]. TSH releases leptin in human adipose tissue culture, and it is possible that this effect is present also in the human endometrium, thereby playing a role for successful implantation. Possible interaction between the embryo and endometrium is shown in figure (2). The thyroid system is involved in the regulation of LIF and interleukins key factors for successful implantation[16]. 0nce conception has occurred, thyroid hormone remains important not only for the development of the fetus but for the viability of the pregnancy itself and increased incidence of fetal loss is observed in both hypothyroid and hyperthyroid pregnancies[17].

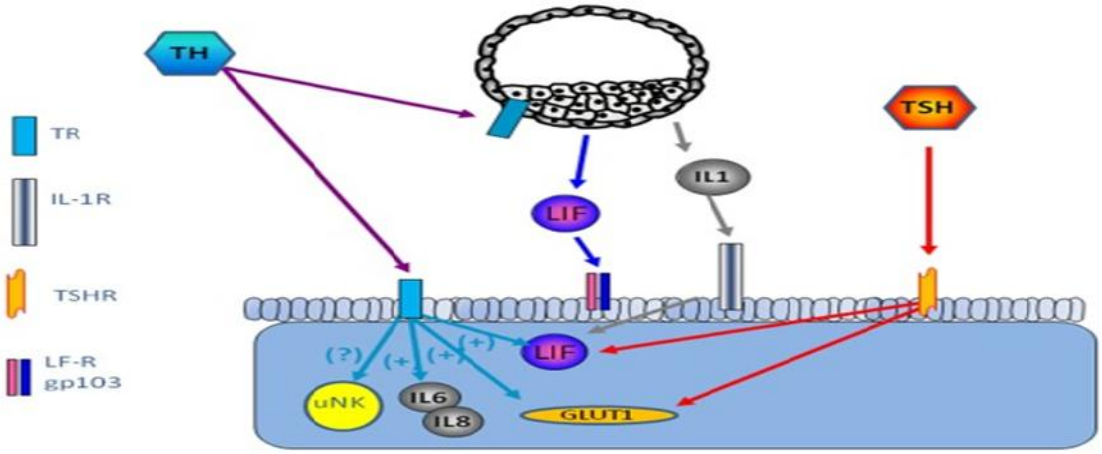

Figure (2): Possible interaction between the embryo and endometrium is shown. The thyroid system is involved in the regulation of LIF and interleukins, key factors for successful implantation [16].

- During preparation for ART, when ovarian hyper stimulation is used to obtain multiple cumulus–oocyte complexes, estradiol concentrations are much higher than normal and are comparable to those found in the second trimester of pregnancy (1,470–2,203 pmol/l [400–600 pg/ml]). The marked rise in estrogen concentrations induces an additional strain on the hypothalamic–pituitary–thyroid axis and could, therefore, considerably impair thyroid hormone distribution and kinetics, especially in women who have TAI[18].

- Two studies identified the need for a rapid increase in T4 concentrations in weeks 4–6 of pregnancy among women who had been treated previously for hypothyroidism. The timing of this need was earlier (and more pronounced) when conception was achieved by assisted reproductive technologies (ART) [19].

- Other indirect effects might occur through hyperprolactinemia, due to increased thyrotropin-releasing-hormone production and altered pulsatile secretion of gonadotropin releasing hormone, leading to a delay in the luteinizing hormone response and inadequate formation of the corpus luteum. A direct effect of thyroid hormones on the gonads occurs through modulation by T3 of the actions of follicle-stimulating hormone and luteinizing hormone on steroid biosynthesis [20].

- The majority of circulating endogenous T4 and T3 is transported in serum bound to thyroxin-binding globulin, transthyretin and albumin. Thyroxin-binding globulin has the highest affinity constant for T4, 50-fold greater than transthyretin and 7,000-fold greater than albumin. Thyroxin-binding globulin binds around 75% of circulating T4, transthyretin around 20%, and albumin around 5%. During pregnancy, levels of thyroxin-binding globulin is doubled and that is contribute to the mark increases the in number of T4 binding sites [21].

- Pregnancy is also associated with an increase in renal blood flow and glomerular filtration (with an increase in iodine clearance), changes in maternal thyroid hormones (low T3 and high reverse T3 hormones) under the influence of placental type 3 iodothyronine deiodinase, and thyrotropic stimulation of peak serum human chorionic gonadotropin levels near the end of the first trimester.

- In pregnant women with a low iodine intake or a history of TAI (or thyroidectomy), if the required increase in the thyroid hormone production cannot be adequately met, potentially this will lead to development of hypothyroidism [22].

Hyperthyroidism:

* **Overt hyperthyroidism**: occurs in approximately 0.1–0.4% of pregnancies and is defined as a serum TSH level below the trimester-specific reference range with elevated levels of free T3, free T4 or both. The most common cause of overt hyperthyroidism in pregnancy is Graves' disease. Other causes include gestational transient thyrotoxicosis, toxic adenoma or multinodular goiter, thyroiditis, or excessive hormone intake[23].

However, correlation with signs and symptoms may help elucidate the diagnosis. A diffuse goiter, ophthalmopathy, hyperthyroid symptoms prior to pregnancy, and serum thyroid hormone receptor antibody (TRAb) positivity favor the diagnosis of Graves' disease. Transient gestational thyrotoxicosis is more common in women with morning sickness, especially those with the most severe form; hyperemesis gravidarum [24].

Pregnant women with untreated overt hyperthyroidism are at increased risk for spontaneous miscarriage, congestive heart failure, thyroid storm, preterm birth, pre-eclampsia, fetal growth restriction, and increased perinatal morbidity and mortality [25]. Treatment of overt Graves' hyperthyroidism in pregnancy to achieve adequate metabolic control has been associated with improved pregnancy outcomes [23].

* **Subclinical hyperthyroidism:** is defined as a serum TSH level below the trimester-specific reference range with normal levels of free T3 and T4[26]. Although various TSH cut-off values have been used in studies to define subclinical hyperthyroidism, in general, subclinical maternal hyperthyroidism has not been found to be associated with adverse maternal or fetal outcomes, and recommendations are for monitoring in pregnancy, but not therapy [26].

Hypothyroidism:

*** Overt hypothyroidism (OH):** Around 0.5% of all pregnant women have OH, defined as an elevated TSH level with a decreased level of free T4 [26, 27]. Two factors contribute for being unusual problem in pregnancy; as some hypothyroid women are anovulatory, and hypothyroidism (new or inadequately treated) complicating pregnancy is associated with an increased rate of first trimester spontaneous abortion [28]. The most common etiology of OH in pregnant women is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Other causes of OH include endemic iodine deficiency (ID), and prior radioactive iodine therapy or thyroidectomy. While severe endemic ID can lead to OH, mild to moderate ID is more frequently associated with isolated hypothyroxinemia rather than OH. Currently, 30 countries worldwide are considered iodine deficient (middle east area are included) [29]. Although median urinary iodine concentrations and other measures can be used to determine the iodine status of populations, there are no biomarkers to diagnose ID in individuals [30].

Untreated OH in pregnancy has consistently been shown to be associated with an increased risk for adverse pregnancy complications, as well as detrimental effects on fetal neurocognitive development, as shown below [23]:

- Fetal / Neonatal complications: Because fetal thyroid hormones originate almost exclusively from the maternal system before 12–14 weeks of gestation, maternal thyroid disorders in early pregnancy are closely related to fetal development. Neurological deficits in infants and juveniles, including low intelligence

quotient scores, cognitive delay, and psychomotor development impairment, are the main complications induced by maternal hypothyroidism during early pregnancy [31]. Thyroid hormone deficiency beyond the first trimester also cannot be ignored, although fetal thyroid hormones are functional at this time, while triiodothyronine activates enzymes are important for neurological development in late pregnancy [32].

- Obstetrical complications: include increased risks for premature birth, low birth weight, fetal death and miscarriage [23]. Allan et al. and Abalovich et al. demonstrated an increased risk of fetal loss in patients with OH [27]. Leung et al. demonstrated a 22% risk of gestational hypertension in pregnant women with OH, higher than for euthyroid women or those with SCH [25]. Other obstetrical complications include; placentae abruption, non reassuring fetal heart rate tracing, preterm delivery, increase rate of CS, perinatal morbidity and mortality and postpartum hemorrhage [33].
- Because of the clear associations between OH and risk to the mother and fetus, treatment of overt hypothyroidism during pregnancy is mandatory. The goal of levothyroxine (LT4) treatment is to normalize maternal serum TSH values to within the trimester-specific pregnancy reference range [34].

*** Subclinical hypothyroidism (SCH) in pregnancy:**

Subclinical hypothyroidism is defined as an elevated TSH level with a normal level of circulating free T4. The prevalence of SCH during pregnancy in the European is estimated to be 2- 2.5 % and in the US is estimated to be 0.25–2.5% [27]. Symptoms of SCH, if present, are typically subtle, and might be attributed to pregnancy. This condition has been associated with:

- Neurodevelopmental disorders in fetuses and infants.
- Several adverse maternal outcomes, including gestational diabetes mellitus (GDM) [34].
- Women who have been previously diagnosed with SCH are at increased risk of stillbirth and GDM in subsequent pregnancies[35].
- It is also associated with gestational hypertension and pre-eclampsia. A study of 68 hypothyroid women found that gestational hypertension was significantly more common in both overt hypothyroidism and SCH patients than in the general population, with rates of 22, 15 and 7.6%, respectively [36]. A retrospective study of pregnancy outcomes in 24,883 women found hypertension in pregnancy in 10.9% of SCH and 8.5% in euthyroid patients, with a significant association between SCH and severe pre-eclampsia [37]. Though a meta-analysis had found a significantly increased risk of pre-eclampsia in patients with SCH (OR = 1.7, 95% CI = 1.1–2.6) but no association between SCH and pregnancy-induced hypertension (OR = 1.00, 95% CI = 0.79–1.29) [38, 39].

- Confirmation of an increased risk of pre-eclampsia, superimposed pre-eclampsia and preterm birth in primary hypothyroidism has recently been obtained [38]. Although positive thyroid antibodies seem to be significantly associated with the risk of preterm delivery (OR = 1.9, 95% CI = 1.1–3.5), this was not the case with SCH (OR = 1.0, 95% CI = 0.59–1.8) [26]. A report of 404 women with SCH showed a doubled rate of preterm birth with respect to controls, and a 3-fold increased rate of preterm deliveries in SCH women was shown in a Chinese study of 1,000 women [39]. A study involving 5,971 pregnant women showed that those with a TSH >97.5th percentile had an increased risk of premature and very premature delivery. However, a TSH >97.5th centile was not associated with premature delivery or very premature delivery after the exclusion of TPOAb+ women or comorbidities [40].
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- Other complications confirmed by some and denied by others are placental abruption, perinatal mortality, admission to the neonatal intensive care unit, low Apgar score and low birth weight [41] and no increased risk was found for high birth weight, congenital malformations and respiratory distress syndrome [30].

- In a study of 3315 Chinese women at low risk for thyroid dysfunction, the rate of pregnancy loss was significantly higher among women with SCH (TSH between 5.2 and 10 mU/L) than those with normal thyroid function (7.1 versus 2.2 %). Women with SCH and positive anti-thyroid peroxidase (TPO) antibodies had the highest risk of pregnancy loss (15.2 %) [42].

***Isolated maternal hypothyroxinemia (low free T4)**

Defined as a maternal free T4 concentration in the lower 5th or 10th percentile of the reference range, in conjunction with a normal TSH. The effect of isolated maternal hypothyroxinemia on perinatal and neonatal outcome is unclear [42, 43].

- In one study, maternal serum free T4 concentrations below the 2.5th percentile (with normal TSH) were not associated with adverse pregnancy outcomes [44]. However, in the FASTER consortium, among the women with hypothyroxinemia and normal TSH (232 and 247 women in the first and second trimesters, respectively), there was an increased odds ratio for preterm labor (1.62, 95% CI 1.00-2.62), macrosomia (1.97, 95% CI 1.37-2.83), and gestational diabetes (1.70, 95% CI 1.02-2.84) [45]. In the Generation R study, maternal hypothyroxinemia was associated with a 2.5-fold increased risk of premature delivery[45].
- In some studies, infants and toddlers whose mothers had reduced serum free T4 concentrations (with normal TSH) during gestation (12 to 20 weeks) had lower mean intelligence, psychomotor, or behavioral scores compared with children born to women with normal thyroid function during gestation [42, 43, 46]. As an example, in one study of 3727 mother-child pairs, the children of mothers whose free T4 was in the lowest 5 % during the first trimester had an IQ scores at six years that were 4.3 points lower than the children of mothers with higher free T4 concentrations[47]. However, in the randomized trial described above, there was no difference in the IQ of children of mothers with low free T4 who did or did not receive T4 treatment before 20 weeks gestation. Similar findings were noted in a case control study that examined children at age two years born to mothers who had second trimester free T4 levels <3rd centile versus those with free T4 levels between the 10th and 90th centile[48].

Pregnancy loss and hypothyroidism:

Overt hypothyroidism is associated with an increase in miscarriage rate[49]. There is an established association between poorly controlled hypothyroidism and variety of adverse outcome[2]. However, data about whether or not SCH is associated with an increase in the incidence of miscarriages are conflicting; evidence for that:

- One study found TSH values were elevated at 11–13 weeks in 202 women with singleton pregnancies that subsequently miscarried compared with 4,318 singleton pregnancies with no history of thyroid disease that resulted in live birth after 34 weeks [50].
- Several studies have found that elevated TSH levels in pregnancy are associated with an increased risk of miscarriage in patients without a diagnosis of hypothyroidism [51.]
- Allan et al. showed that fetal death is significantly more frequent when TSH is higher than 6.0 mU/l (3.8 vs. 0.9%) [27].
- Benhadi et al. reported a significantly higher mean TSH in women who experienced child loss compared with successful pregnancies (1.48 vs. 1.11 mU/l), and that the incidence of child loss increased by 60% for every doubling in TSH concentration[52].
- A comparison of the TSH at 11–13 weeks in women who suffered fetal death versus those who did not found an increase in TSH multiple of the median (MoM; 1.133 vs. 1.007 MoM), and a decrease in fT4 MoM (0.958 vs. 0.992 MoM) [53].
- Negro et al observed a significant increase in miscarriage rate in TPOAb– women with first trimester TSH 2.5–5.0 mU/l versus <2.5 mU/l (6.1 vs. 3.6%); SCH and thyroid autoimmunity were independently associated with very early embryo loss in 216 women[30].

- An increased risk for miscarriage in women with untreated hypothyroidism compared with euthyroid controls (OR = 5.78, 95% CI = 2.4–14) was confirmed in a prospective study but not in a retrospective study where 240 SCH patients showed no difference in miscarriage rate when compared with 10,518 controls (OR = 0.69, 95% CI = 0.10–5.0) [53].

Thyroid Function Testing in Pregnancy:

Normal pregnancy is associated with significant changes in maternal thyroid physiology.

1. Serum thyroid-stimulating hormone (TSH) concentration is the initial and most reliable test for assessing thyroid function in pregnancy [54]. Serum TSH testing is relatively inexpensive, readily available, and is a reliable test in pregnancy, assuming that trimester-specific reference ranges are applied. A decline in TSH levels in the first trimester is seen due to elevation of human chorionic gonadotropin (hCG), which functions as a weak stimulator of the TSH receptor. Due to these dynamic changes during pregnancy, use of trimester specific and assay-specific TSH normal ranges is recommended.

Where such reference ranges are not available, the following cutoffs may be used:

- First trimester, <2.5 mIU/L.
- Second trimester, <3 mIU/L.
- Third trimester, <3 mIU/L [55].

Thyroid function tests during pregnancy are also affected by estrogen-mediated increases in the level of thyroxin- binding globulins (TBG).

2. Total T3 and T4 levels are increased starting in early pregnancy, due to the increased TBG levels, so that the upper limit of normal for total T3 and T4 in pregnancy is approximately 1.5-fold the upper limit of the non-pregnancy reference range. Free T4 assays may be unreliable in pregnancy due to interference by the high TBG levels [56]. Method-specific and trimester-specific reference ranges for direct immunoassays of free T4 are not currently widely available. The free T4 index may be more reliable than free T4 assays during pregnancy, and its use is advocated by the 2012 Endocrine Society guidelines [55, 56].

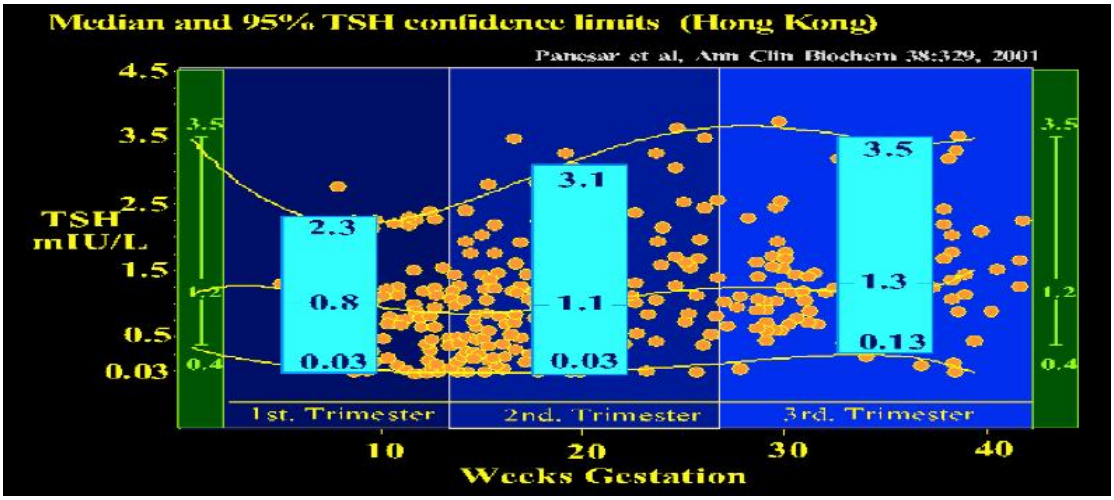

Figure 3: Gestation-related reference intervals for serum TSH in a Chinese population (343 healthy pregnant women & 63 non-pregnant controls) [39].

3. Antithyroid Antibody Positivity in Pregnancy: TPO Ab and thyroglobulin (TG) autoantibodies can be detected in 10–20% of women of childbearing age. The majority of women who test positive for thyroid autoantibodies are euthyroid. Sixteen percent of the women who are euthyroid and positive for TPO or TG antibodies in the first trimester will develop a TSH that exceeds 4.0 mIU/L by the third trimester, and 33%–50% of women who are positive for TPO or TG antibody in the first trimester will develop postpartum thyroiditis. Thyroid autoimmunity in pregnancy has been associated with adverse pregnancy outcomes, including miscarriage, recurrent abortion, preterm births, and low IQ [23].

4. Thyroid ultrasound (TUS): to assess size of thyroid gland, in pregnancy there is normally enlarge of size of thyroid gland, but according to the guideline of American Thyroid Association (ATA), the uncomplicated hypothyroidism, there is no recommendation to do TUS[57].

Screening for Thyroid Dysfunction during pregnancy:

Given that most thyroid dysfunction that occurs in pregnant women is SCH, and given the lack of clear data for efficacy of treatment, there is ongoing debate regarding the need for universal screening for thyroid dysfunction during pregnancy versus a case-finding approach versus testing only symptomatic women or those with personal history of thyroid disease or other associated medical conditions [8]. Appropriately dosed LT4 therapy in pregnancy does not confer any risks for the mother or fetus. However, the benefits of treating SCH are unclear based on current published RCTs. The potential risks of universal screening would be:

- Costs of treatment, follow-up, and monitoring.

- Possible misinterpretation of TFTs resulting in inappropriate treatment. - Inappropriately dosed LT4 treatment for SCH women, resulting in over- or under treatment.

- Experienced caregivers should be involved in interpretation of TFTs in pregnancy to avoid misdiagnoses and initiation of inappropriate treatments (e.g., misinterpreting a low TSH as abnormal and inappropriately initiating treatment for hyperthyroidism).

- If patients are started on LT4 therapy, they need close monitoring to ensure euthyroidism. In a survey of a no pregnant population, Canaris et al. demonstrated that over 40 percent of patients taking thyroid medications were not at target range and were either hypo- or hyperthyroid [58].

The most practice guidelines from the American College of Obstetricians and Gynecology (ACOG) recommend thyroid testing only in high-risk pregnant women who are symptomatic, or have a personal history of thyroid disorders, personal history of type I diabetes or other autoimmune disorders [59]. These guidelines specifically do not recommend testing an asymptomatic women or women with small goiters. The Society for Maternal-Fetal Medicine supports the recommendations of ACOG [60].

The American Thyroid Association (ATA) in 2011 recommended against universal screening of healthy women for thyroid dysfunction during pregnancy [61]. However, a case-finding approach was advocated to identify individuals at high risk for hypothyroidism.
In guidelines published in 2012, the Endocrine Society Task Force could not reach agreement on thyroid testing recommendations for pregnant women [55]. Some members recommended screening of all pregnant women for serum TSH abnormalities by the 9th week or at the time of their first visit. Others recommended against universal screening of pregnant women at the time of their first visit and instead supported aggressive case finding to identify high-risk women. This case-finding approach is similar to the 2011 ATA guidelines.

The American Association of Clinical Endocrinologists (AACE)/ATA Hypothyroidism guidelines also currently recommend a case-finding approach [8].

*Cost-Effectiveness Studies:

A recent study comparing ACOG guidelines (screening only symptomatic women or those with history of thyroid or associated diseases) versus universal screening for SCH in pregnancy demonstrated that universal screening was by far the most cost-effective strategy under a wide range of circumstances. The cost-savings were determined from the relatively low cost of thyroid screening tests and treatment of SCH compared to the relatively large additional lifetime costs incurred by individuals with neurodevelopmental impairment. However, a benefit of treatment on offspring neurodevelopment has not to date been demonstrated in interventional studies [23].

Treatment of Overt hypothyroidism and Subclinical hypothyroidism in pregnancy:

However, hypothyroidism is not readily recognized because it usually manifests as non-specific symptoms. Whilst it is generally accepted that optimal treatment of maternal hypothyroidism is important to achieve a successful pregnancy outcome, how to detect and treat maternal hypothyroidism in pregnancy remains a matter of controversy and since the introduction of the Endocrine Society Guidelines for the management of thyroid diseases, including

hypothyroidism, in pregnancy which was at 2007, many new studies – including randomized controlled trials have been evolved and further evidence base for clinical practice in the field had been arise and prompted development of the more recent guidelines from the American Thyroid Association [62].

Most experts and societies suggest treatment of subclinical hypothyroidism if TSH levels are >10 mIU/l based on the available evidence, even though long-time risks and benefits of treatment in this population are not known[63].

For persons with moderately elevated TSH concentrations between 4.5–10 mIU/l, TSH levels should be monitored every 6 to 12 months and treatment outside of a clinical trial is currently not recommended. Current guidelines from the Swiss Society of Endocrinology and Diabetes recommend treatment of individuals with subclinical hypothyroidism according to a risk stratification taking into account a TSH level >10 mIU/l, the presence of goiter, antithyroid antibodies, cardiovascular risk factors or prevalent CHD, smoking, dyslipidemia, clinical symptoms, ovulatory dysfunction or infertility. In pregnant women with TSH levels above the trimester-specific TSH cutoffs and in women with infertility or wishing to become pregnant with TSH values of 2.5 mIU/l or higher, initiation of thyroxin replacement therapy is recommended [64].

*The Role of Iodine in Subclinical hypothyroidism:

In pregnancy there is about a 50% increase in iodine requirement to achieve a dietary intake of 250 µg/day. This increase is due to an increased glomerular filtration and renal iodine clearance as well as iodine transplacental transfer to the fetus, particularly in later gestation [65]. In chronically iodine-deficient pregnant women, depleted iodine thyroid stores are not able to compensate for increased demands; if deficiency is not corrected, it may result in goiter formation and maternal hypothyroidism [66].

According to the WHO, pregnant and lactating women should be provided with 250 µg iodine daily [67]. This may be achieved by administering iodine supplements containing 150–250 µg of iodine in the form of potassium iodide often as prenatal and pregnancy vitamin supplements. Adequate iodine intake during pregnancy (250 µg of iodine daily) should be preferably achieved before conception. In countries with successful salt iodization programs, pregnancy-desiring women should be additionally supplemented with 50 µg of iodine [29]. The daily intake of iodine should not exceed 500 µg.

Hypothyroidism status among pregnant women in Iraq:

Iraq is a country with an inadequate iodine nutrition, with mild, moderate and severe iodine deficiency documented in various parts of this country[68]. Iodine supplementation has been flawed, inadequate and hence ineffective [69].

Previous study pointed out that a study in 1992 showed goiter prevalence of 41.7% among women of childbearing age. A 1993 national survey of 3004 school-age children reported a goiter prevalence ranging between 24-44%, with 51% of children having low urinary iodine levels. Iodized salt production was begun in 1990 and legislation made it mandatory in 1993. The percentage of iodized salt consumption by households varied between 40 and 90% in the late 90's but no data on the amount of iodide in various salts was available [69].

Another study in Iraq found a significant subclinical hypothyroidism throughout three trimesters of pregnancy [70].

Aim of study

To measure the prevalence of undiagnosed overt hypothyroidism and subclinical hypothyroidism among a group of Iraqi pregnant women early in pregnancy.

Patients and Methods

Study design:

The present study is a cross-sectional study.

Study period:

The 1st of January 2015- 1st of January 2016.

Setting:

Al-Elwiya Maternity Teaching Hospital, department of Obstetrics and Gynecology.

The study protocol was approved by the Obstetrics and Gynecology committee of the Iraqi Board for Medical Specialization and Al-Elwiya Maternity Teaching Hospital administration.

Data Collection:

The study includes 240 apparently healthy pregnant women at their early pregnancy up to 23 weeks+6 days, who attended the consulting clinic every Monday for checking of their pregnancy status and whom their acceptance in participation in the study was insured. Eligible criteria for inclusion were singleton pregnancy that complicated by any type of spontaneous miscarriage or not.

Exclusion criteria for participants were:

1- Known cases of thyroid disease.
2- Known cases of diabetes mellitus.
3- Septic miscarriages.
4- Abortion cases (whether they were due to medical indications or by woman wishes).

All the participants were subjected to:

- History: looking for participant age, residency, occupation, parity, gestational age according to the last menstrual period, symptoms of pregnancy, any abdominal pain and vaginal bleeding, previous obstetrical performance, symptoms of hypothyroidism, menstrual history, history of infertility, previous abnormal babies and family history of abnormal thyroid status.

- Examination: looking for signs of thyroid disorders and obstetrical examination including vaginal examination if it is indicated.

- Investigations:

1- Ultrasound: to confirm pregnancy dating and viability status.
2- Laboratory data:

- For all participants:
  - Blood sugar, Hb level, blood group, Rh and GUE.
  - Serum TSH and free T4.
- For women with recurrent miscarriage: tests for exclusion of Immunological disorders and thrombophilia and otherwise accordingly.

Blood samples were collected by aseptic technique, serum was isolated after centrifugation and stored at –80uC until testing. The serum was tested for TSH and free T4 by Addendeum-Mini VIVAS apparatus (VIDAS) 12 mode 10, 1992, Biomreieux Company, France, though an enzyme linked fluorescent assay (ELFA) technique, USA[71].

Criteria for abnormal test results:

Overt hypothyroidism was define as a serum TSH greater and a free T4 lower than the reference values for specific trimester. While subclinical hypothyroidism was define as a serum TSH level greater than the reference values for the gestational age with a normal free T4 adjusted for gestational age. Those reference values were shown in the table below.

Table 1- serum level of free T4 and TSH[72].

Free T4	pmol/L	11.1 - 24.1	8.2 - 24.7	8.2 - 24.7	72
TSH	µU/mL OR mU/L	0.2 - 3.5	0.2 - 3.5	0.2 - 3.5	72

Subsequent measures to the participants:

Those women who were aborted they were managed accordingly with counseling. While women who had been not aborted were followed till 23 weeks+6 days, and cases of recurrent miscarriage were investigated and managed accordingly. Those cases that had been discovered to have OH, were referred to an endocrine unit for treatment.

Statistical analysis:

Data were translated into a computerized database structure. The database was examined for errors using range and logical data cleaning methods, and inconsistencies were remedied. An expert statistical advice was sought for. Statistical analyses were done using IBMSPSS version 21 computer software (Statistical Package for Social Sciences) in association with Microsoft Excel 2016.

The 95% confidence interval is a statistical procedure to anticipate or predict the expected range of possible values of the calculated sample estimate of any statistic in the reference population with 95% confidence.

The statistical significance, direction and strength of linear correlation between 2 quantitative normally variables, one of which being non-normally distributed was measured by Spearman's rank linear correlation coefficient.

Compliance of quantitative random variables with Gaussian curve (normal distribution) was analyzed using the Kolmogorov-Smirnov test. Serum TSH and free T4 were shown to be normally distributed quantitative continuous outcome variables. Such variables are described by mean, SD (standard deviation) and SE (standard error). The statistical significance of difference in mean between 2 groups was assessed using students t-test, while between more than 2 groups ANOVA test was used. Associations between 2 categorical variables was explored by cross-tabulation. The statistical significance of such associations was assessed by Chi-square (χ^2) test. An estimate was considered statistically significant if its P value was less than an α level of significance of 0.05.

A multiple linear regression model was used to study the net and independent effect of a set of explanatory variable on a quantitative outcome (dependent) variable. The model provides the following parameters:

1. P (model): In order to generalize the results obtained, the model should be statistically significant.
2. Unstandardized partial regression coefficient: Measures the amount of change expected in the dependent variable for each unit increase in the independent variable after adjusting for other explanatory variables included in the model.
3. P for regression coefficient: reflects the statistical significance of the calculated partial regression coefficient of each explanatory variable included in the model.
4. R^2 (Determination coefficient): measures the overall performance of the model since it reflects the amount of variation in the dependent variable explained by the model. The closer its value to 100% the better the model fit.

Results

The results presented in this chapter were based on the analysis of a cross-sectional study sample of 240 pregnant women attending a secondary referral teaching maternity hospital.

As shown in the table 2, the mean age was significantly higher (30 years) among those with recurrent miscarriages compared to the remaining groups (26.3 and 27.8 means). The difference in age although significant was small in magnitude.

Table 2: The difference in mean age (years) between the 3 study groups.

	Classification of miscarriage incidents			
	Negative	**1-2 incidents**	**Recurrent (3+)**	**P**
Age (years)				0.003
Range	(18 to 43)	(17 to 44)	(18 to 44)	
Mean	26.3	27.8	30	
SD	5.9	6	5.6	
N	69	117	54	

The study sample was classified according to the history of miscarriage into three categories. As shown in table 3:

Table 3: The difference in mean serum T4 and TSH between the 3 study groups.

	Classification of miscarriage incidents			
	Negative	**1-2 incidents**	**Recurrent (3+)**	**P**
Serum Free T4				0.36[NS]
Range	(7.3 to 17.54)	(6.8 to 110.86)	(7.33 to 21.47)	
Mean	11.6	12.9	11.8	
SD	2.1	9.4	2.8	
N	69	117	54	
r=0.007 P=0.91[NS]				
Serum TSH				
Range	(0.22 to 5.24)	(0.42 to 5.72)	(0.34 to 4.32)	0.09[NS]
Mean	2.2	2	1.8	
SD	1.2	1.1	1	
N	69	117	54	
r=-0.121 P=0.06[NS]				

Those with no reported incidence of miscarriage were 69 in number, those with recurrent miscarriages (three and more miscarriage incidents) were 54 in number. The last remaining category was those women with 1-2 miscarriage incidence (N=117). There was no obvious or statistically significant differences in mean serum TSH and serum free T4 between the three miscarriage categories. In addition, there was no important or significant liner correlation between these hormonal levels and count of miscarriage incidents.

Prevalence rate of selected hypothyroidism status:

The most frequently observed hypothyroidism status in the current study sample was "isolated low free T4" documented in 10% of pregnant females (with an anticipated 95% confident interval in the reference population ranging between 6.5% to 14.5%). Ranked second was Subclinical hypothyroidism (High TSH) observed in 7.1% of subjects (95% confidence interval 4.2% to 11.1%). Overt hypothyroidism (both high TSH and low F4) was observed in only 1.7% of cases (95% confidence interval 0.5% to 4.3%). In conclusion, a laboratory evidence of low thyroid status (Any low thyroid status) was observed in 18.8% of the study sample (95% confidence interval 14.1% to 24.3%), table 4, figure 4.

Table 4: The relative frequency (prevalence rate) of selected thyroid status in the total study sample.

Total study sample (n=240)	N	%	95% Confidence Interval
Subclinical hypothyroidism (High TSH)	17	7.1	(4.2% to 11.1%)
Isolated low free T4	24	10.0	(6.5% to 14.5%)
Overt hypothyroidism (both high TSH and low F4)	4	1.7	(0.5% to 4.3%)
Any low thyroid status	45	18.8	(14.1% to 24.3%)

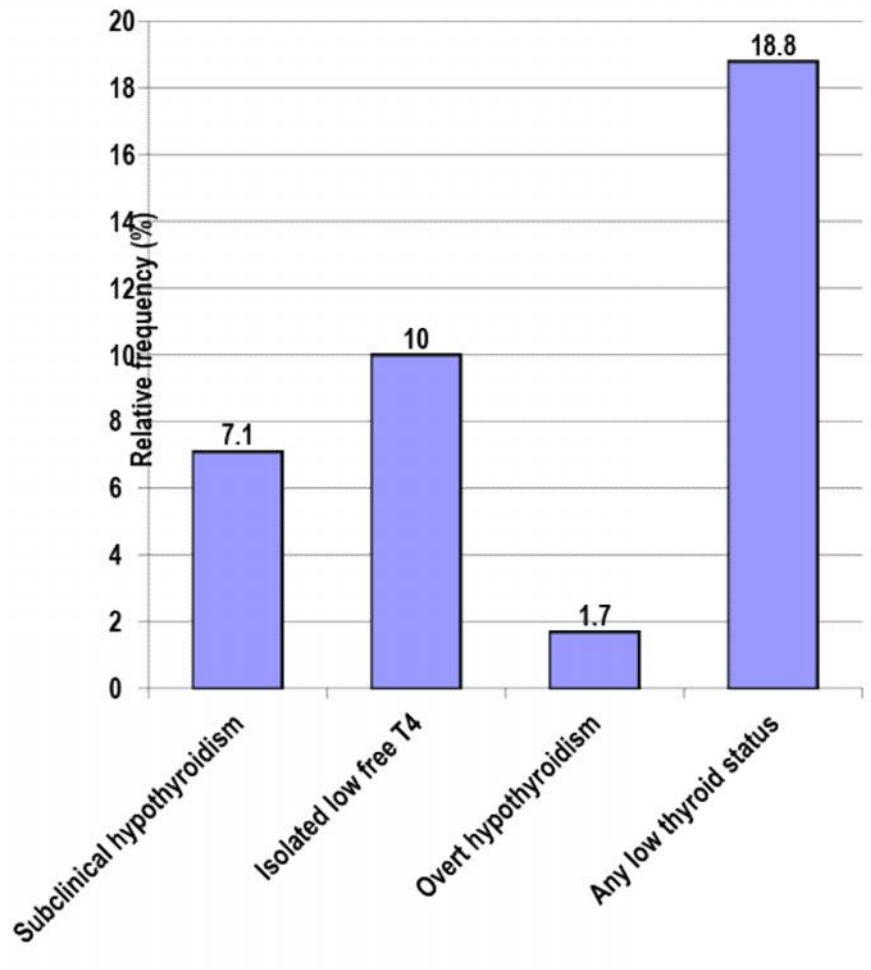

Figure 4: Bar chart showing the relative frequency (prevalence rate) of selected thyroid status in the total study sample

The association between miscarriage and low thyroid status:

As shown in table 5, there was no statistically significant difference in relative frequency (rate) of any low thyroid status between the three miscarriage categories. The rate of any low thyroid status was slightly higher in those with recurrent miscarriages (24.1%) compared to the remaining two categories (negative miscarriage = 21.7%, 1-2 miscarriages = 14.5%), but the difference was not significant statistically, figure 5.

Table 5: The difference in rate of selected thyroid status functions by classification of miscarriage status incidents.

	Classification of miscarriage incidents						
	Negative (n=69)		1-2 incidents (n=117)		Recurrent (3+) (n=54)		P (Chi-square)
Thyroid function	N	%	N	%	N	%	
Subclinical hypothyroidism (High TSH)	7	10.1	7	6.0	3	5.6	0.5[NS]
Isolated low free T4	7	10.1	8	6.8	9	16.7	0.14[NS]
Overt hypothyroidism (both high TSH and low F4)	1	1.4	2	1.7	1	1.9	0.98[NS]
Any low thyroid status	15	21.7	17	14.5	13	24.1	0.25[NS]

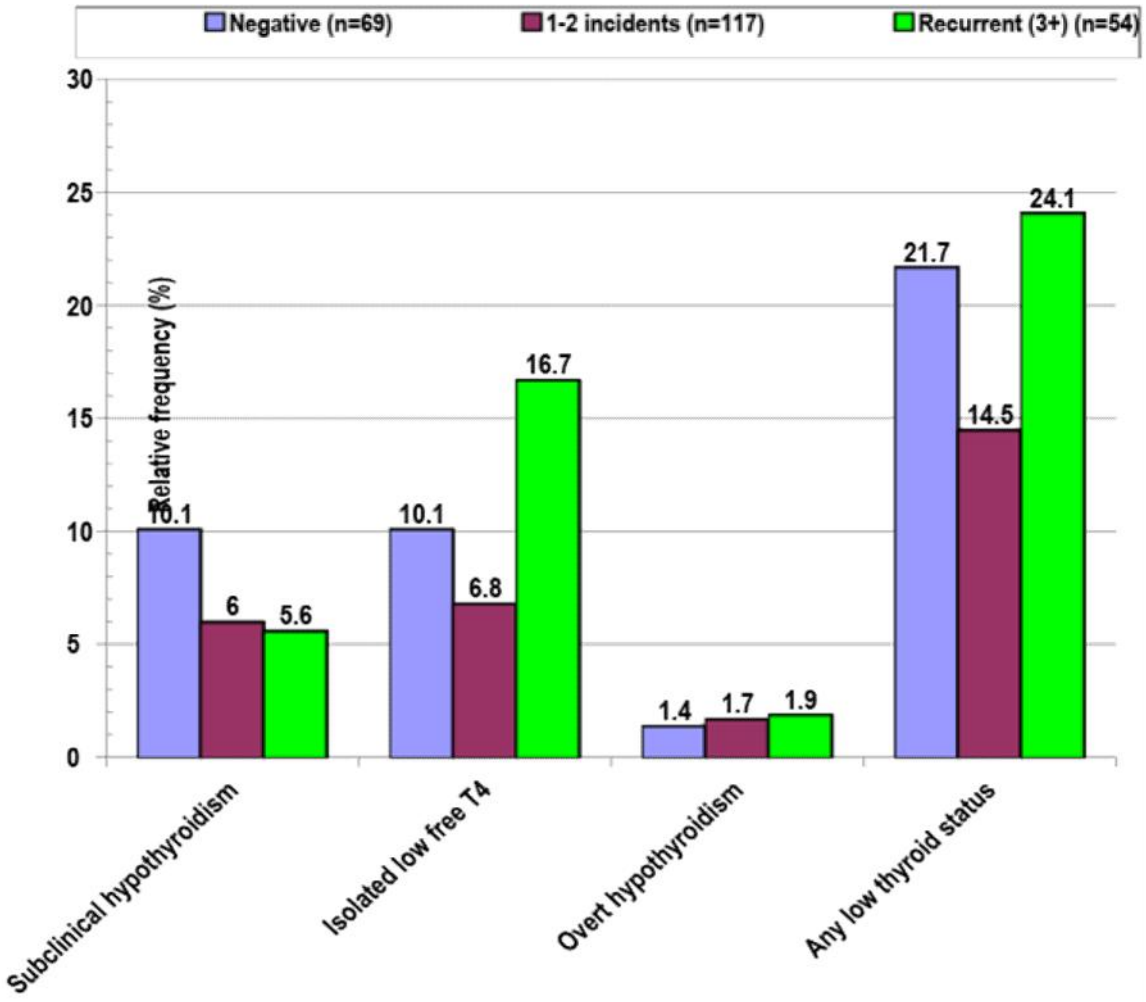

Figure 5: Bar chart showing difference in rate of selected thyroid status functions by classification of miscarriage status incidents.

The association between the outcome of current pregnancy (being miscarried or not) and low thyroid status:

When we related the outcome of current pregnancy, whether it end with miscarriage or not with the thyroid status (regardless of the previous history). Table 6 had shown that the rate of any low thyroid status was significantly higher in women who had no miscarriage (25.7%) compared to women who end with miscarriage (9%). In specific the SCH (high TSH) was significantly higher in women whom pregnancy was proceed beyond 23 weeks + 6 days (10.7%) compared to miscarriage group (2%), figure 6.

Table 6: The difference in rate of selected thyroid status functions by outcome of current pregnancy.

	Non miscarriage (n=140)		Miscarriage (n=100)		P (Chi-square)
Hypothyroidism	N	%	N	%	
Subclinical hypothyroidism (High TSH)	15	10.7	2	2.0	0.009
Isolated low free T4	17	12.1	7	7.0	0.19[NS]
Overt hypothyroidism (both high TSH and low F4)	4	2.9	0	0.0	0.14[NS]
Any low thyroid status	36	25.7	9	9.0	0.001

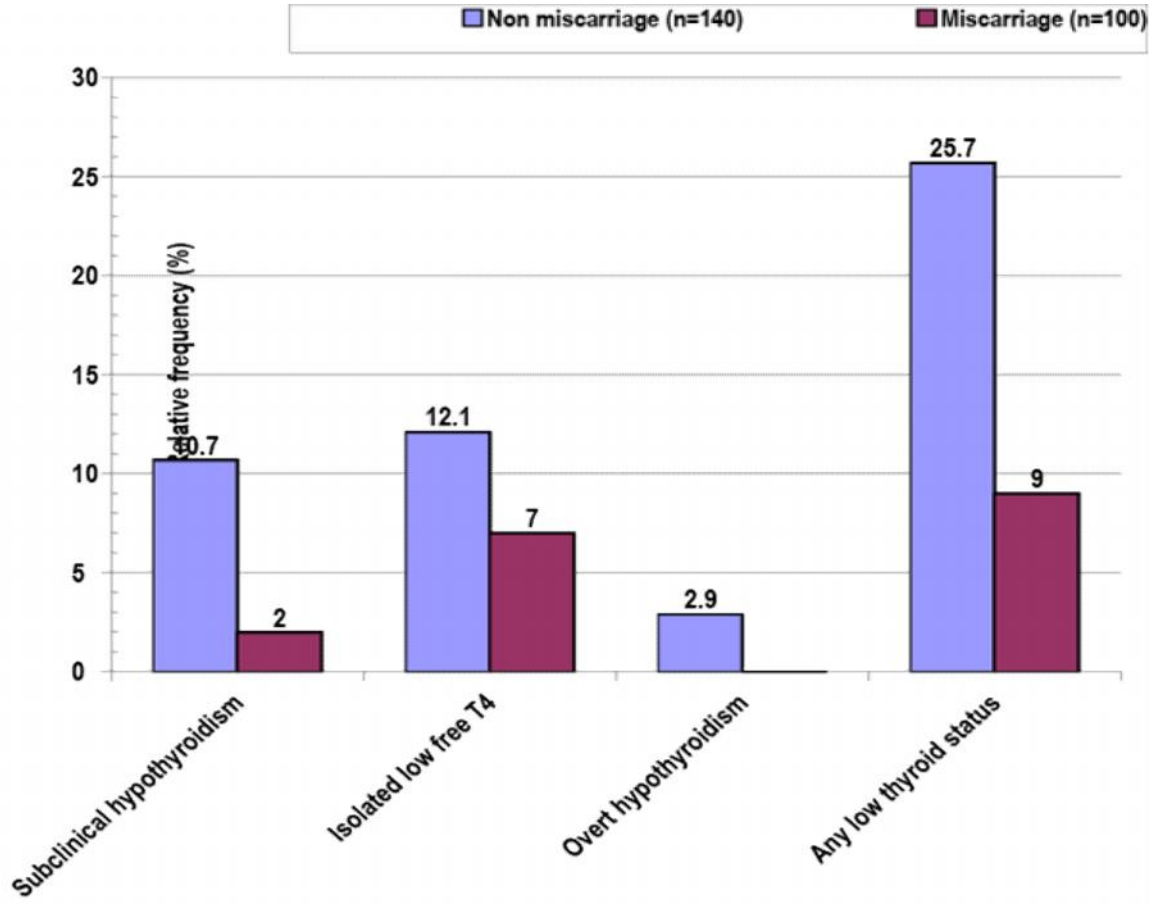

Figure 6: Bar chart showing difference in rate of selected thyroid status functions by outcome of current pregnancy.

The association between gestational age and low thyroid status:

As shown in table 7, the rate of isolated low T4 was significantly higher among women tested in the first trimester of pregnancy (22%) compared to those tested in the 2nd trimester (3.8%). In addition, the rate of any low thyroid status was significantly higher among women tested in the first trimester of pregnancy (30.5%) compared to those tested in the 2nd trimester (12.7%). The relative frequency of the remaining two low thyroid status parameters was not obviously or significantly different, figure 7.

Serum Free T4 showed a weak, but statistically significant negative (inverse) linear correlation with the gestational age (r=-0.258, P<0.001). Serum TSH on the other hand had no obvious or statistically significant linear correlation with gestational age (r=0.063, P=0.33[NS]).

Table 7: The difference in rate of selected thyroid status functions by Trimester of pregnancy.

	First Trimester (n=82)		Second Trimester (n=158)		P (Chi-square)
Hypothyroidism	N	%	N	%	
Subclinical hypothyroidism (High TSH)	5	6.1	12	7.6	0.67[NS]
Isolated low free T4	18	22.0	6	3.8	<0.001
Overt hypothyroidism (both high TSH and low F4)	2	2.4	2	1.3	0.61[NS]
Any low thyroid status	25	30.5	20	12.7	<0.001

Serum Free T4 r=-0.258 P<0.001
Serum TSH r=0.063 P=0.33[NS]

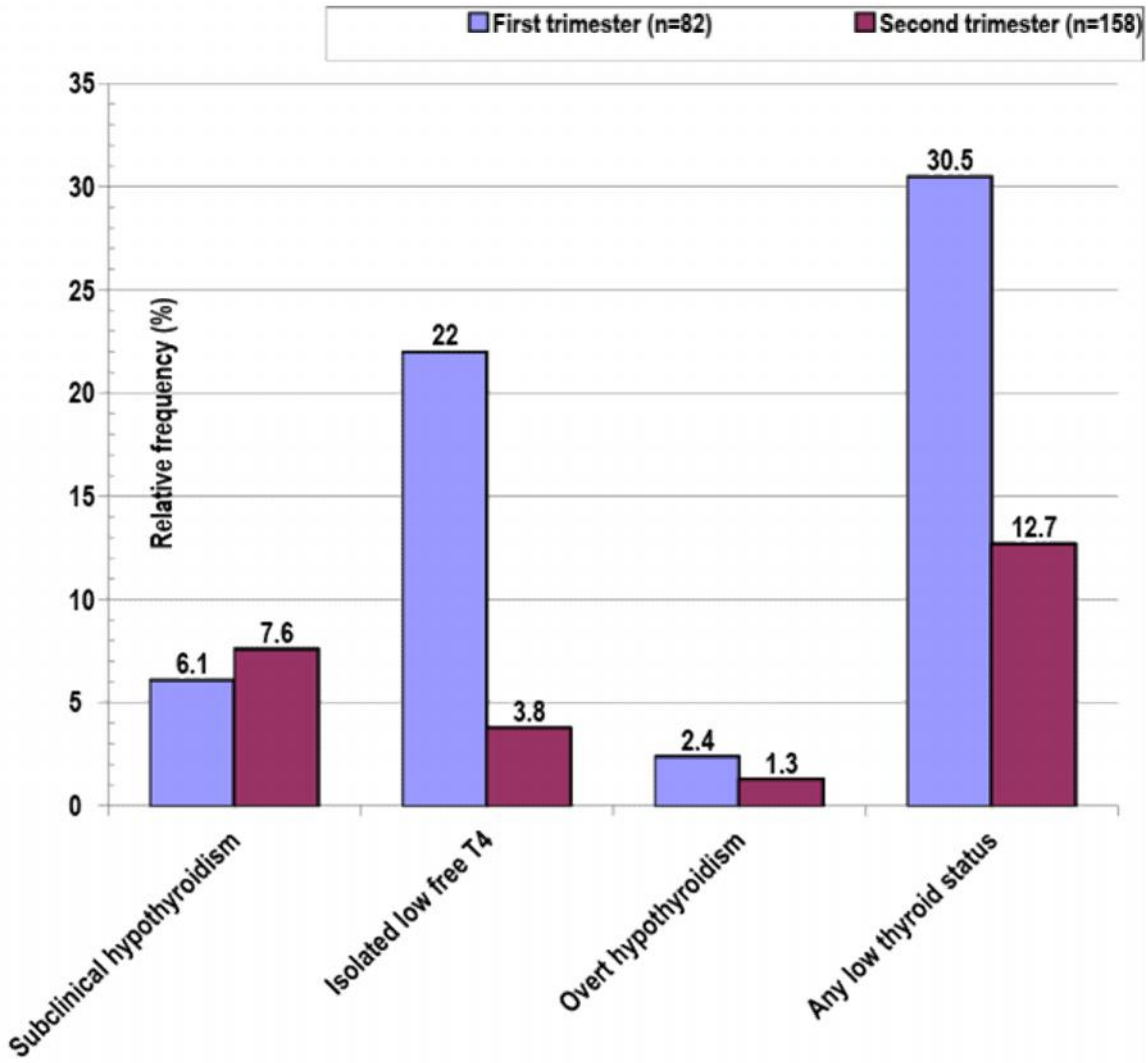

Figure 7: Bar chart showing difference in rate of selected thyroid status functions by Trimester of pregnancy.

The association between age and low thyroid status:

As shown in table 8, only the rate of isolated low T4 (13.6%) was significantly higher among younger age women (13.6% among <30 years old females) compared to those aged between 30-45 years old (4.3%). The remaining thyroid parameters were not significantly different between the tested age groups, figure 8. In addition, both Serum free T4 and TSH had no obvious or statistically significant linear correlation with age (r=0.057 P=0.38[NS] and r=-0.062 P=0.34[NS] respectively).

Table 8: The difference in rate of selected thyroid status functions by age group.

	Age group (years)				
	<30 (n=147)		30-45 (n=93)		P (Chi-square)
Hypothyroidism	N	%	N	%	
Subclinical hypothyroidism (High TSH)	12	8.2	5	5.4	0.41[NS]
Isolated low free T4	20	13.6	4	4.3	0.019
Overt hypothyroidism (both high TSH and low F4)	1	.7	3	3.2	0.3[NS]
Any low thyroid status	33	22.4	12	12.9	0.06[NS]

Serum Free T4 r=0.057 P=0.38[NS]
Serum TSH r=-0.062 P=0.34[NS]

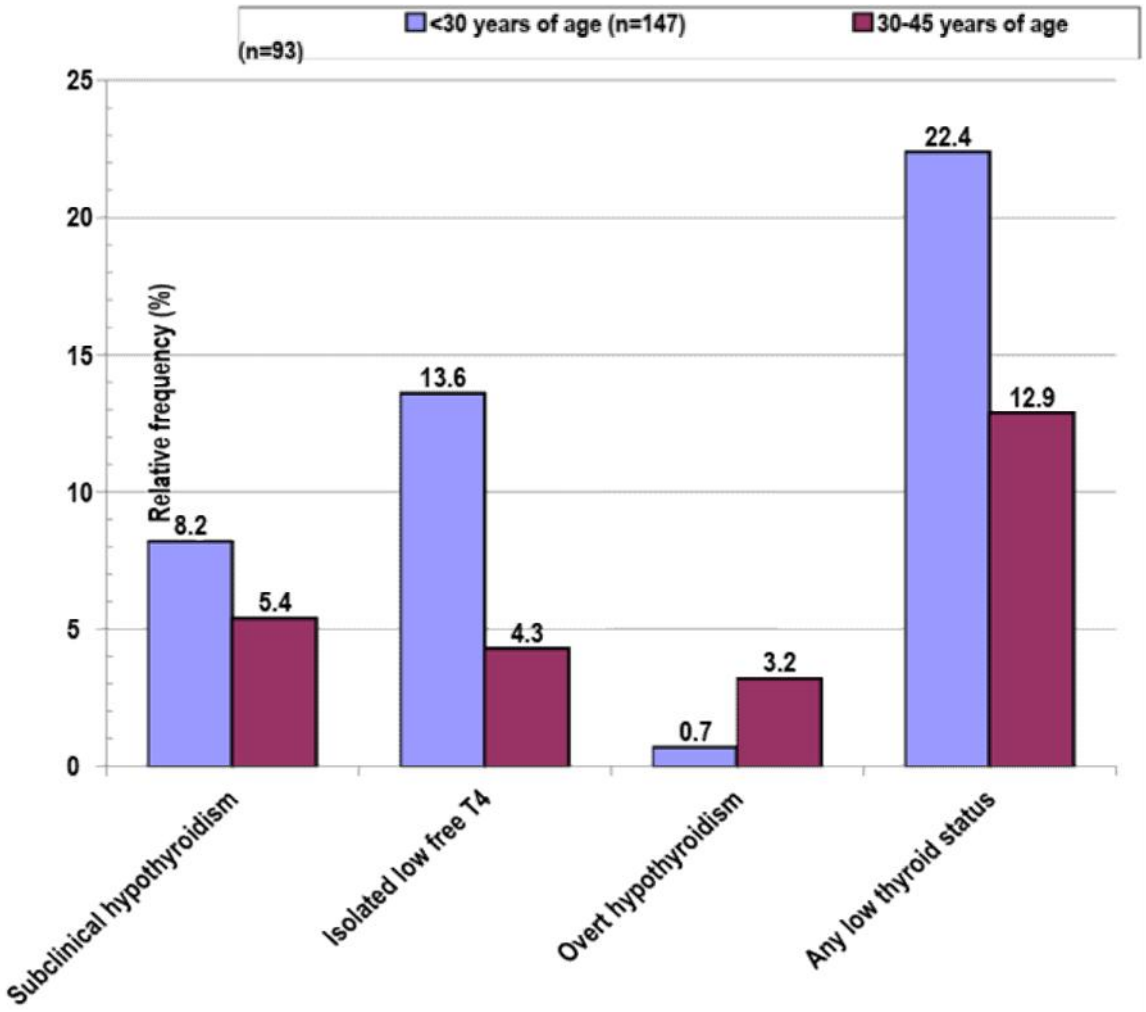

Figure 8: Bar chart showing difference in rate of selected thyroid status functions by age group.

The association between parity and low thyroid status:

The rate of selected thyroid status parameters was not significantly different between the tested parity groups, table 9 and figure 9. In addition, both Serum free T4 and TSH had no obvious or statistically significant linear correlation with parity (r=0.029, P=0.65[NS] and Serum TSH r=-0.027, P=0.68[NS] respectively).

Table 9: The difference in rate of selected thyroid status functions by parity.

	Parity group						
	Nullipara (n=84)		1-2 (n=86)		3+ (n=70)		P (Chi-square)
Hypothyroidism	N	%	N	%	N	%	
Subclinical hypothyroidism (High TSH)	4	4.8	6	7.0	7	10.0	0.45[NS]
Isolated low free T4	7	8.3	10	11.6	7	10.0	0.77[NS]
Overt hypothyroidism (both high TSH and low F4)	0	0.0	1	1.2	3	4.3	0.11[NS]
Any low thyroid status	11	13.1	17	19.8	17	24.3	0.2[NS]

Serum Free T4 r=0.029 P=0.65[NS]
Serum TSH r=-0.027 P=0.68[NS]

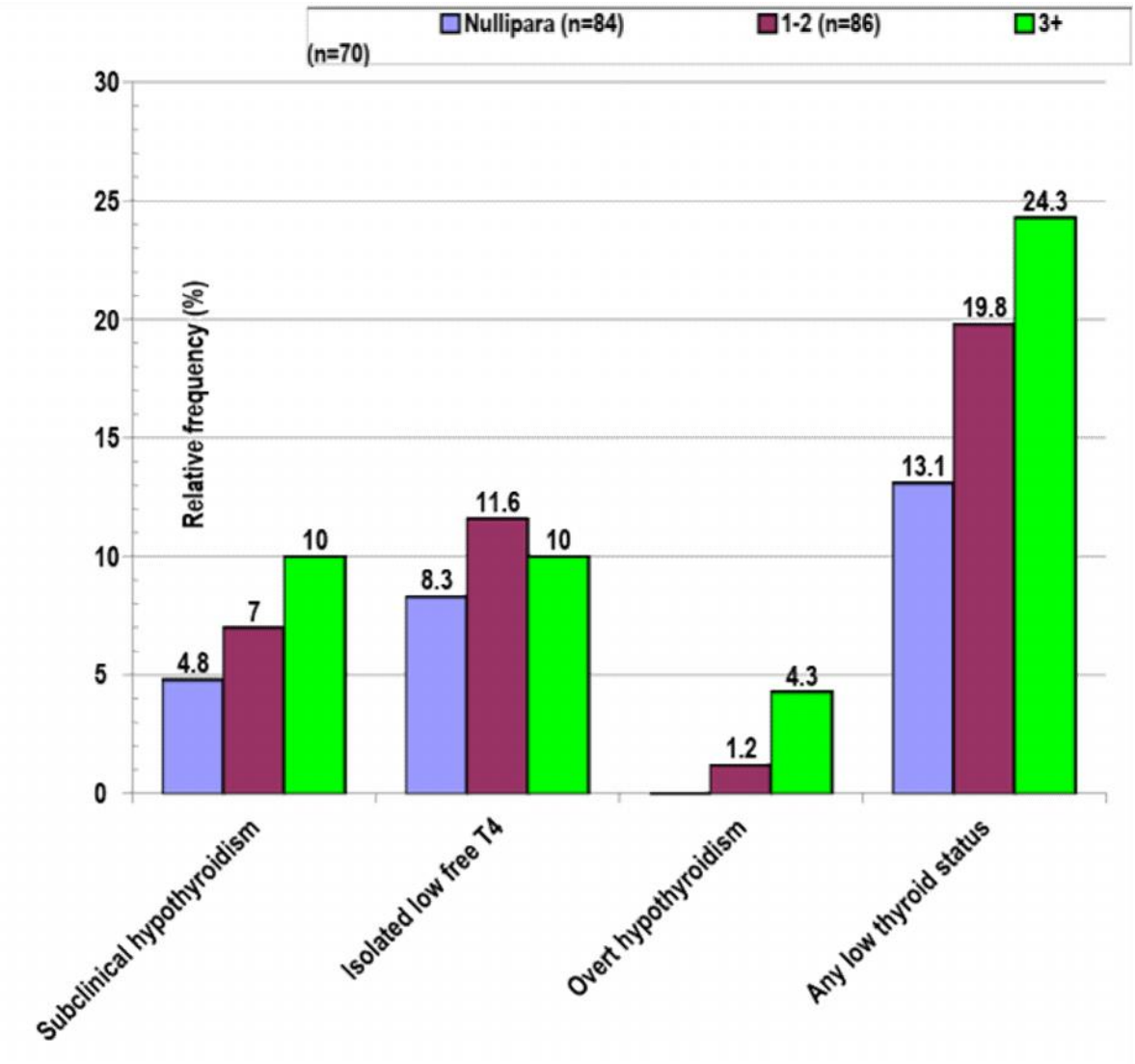

Figure 9: Bar chart showing difference in rate of selected thyroid status functions by parity.

Multivariate modeling

The association between counts of reported miscarriage incidents in a woman was tested for its association with serum free T4 and TSH after adjusting for the possible confounding effect of gestational age, age and gravidity. Both models failed to show any obvious or noticeable association between miscarriage and serum level of T4 and TSH, table 10 and 11.

Table 10: Multiple linear regression model with Serum Free T4 as the dependent outcome variable.

	Partial regression Coefficient	P	Standardized Coefficients
(Constant)	13.514	<0.001	
Age (years)	.040	0.6[NS]	.035
Gestational age (weeks)	-.127	0.29[NS]	-.071
Gravida	-.082	0.69[NS]	-.031
Abortion	-.038	0.89[NS]	-.011

R^2=0.006

P (Model) = 0.84[NS]

Table11: Multiple linear regression model with Serum TSH as the dependent outcome variable.

	Partial regression Coefficient	P	Standardized Coefficients
(Constant)	2.141	<0.001	
Age (years)	-.014	0.25[NS]	-.076
Gestational age (weeks)	.016	0.39[NS]	.057
Gravida	.044	0.17[NS]	.106
Abortion	-.094	0.032	-.166

R^2=0.029
P (Model) = 0.14[NS]

While table 12 failed to show a significant association between any low thyroid status and selected features related to the women history or findings on examination.

Table 12: The association between selected clinical features and having any biochemical evidence of low thyroid function.

	Normal thyroid function (n=195)		Any low thyroid status (n=45)		
Positive findings	N	%	N	%	P
Dry skin	83	42.6	19	42.2	0.95[NS]
Hair loss	30	15.4	7	15.6	1[NS]
Constipation	77	39.5	20	44.4	0.54[NS]
Cold intolerance	68	34.9	19	42.2	0.36[NS]
Myxoedema	57	29.2	16	35.6	0.41[NS]
Bradycardia	73	37.4	14	31.1	0.41[NS]
Irregular menses	83	42.6	17	37.8	0.54[NS]
Oligomenorrhoea	73	37.4	17	37.8	0.97[NS]
Heavy menses	66	33.8	13	28.9	0.51[NS]
History of Infertility	106	54.4	22	48.9	0.51[NS]
History of Primary infertility	72	36.9	21	46.7	0.23[NS]
History of Secondary infertility	82	42.1	20	44.4	0.77[NS]
Abnormal baby	40	20.5	7	15.6	0.45[NS]
Goitre	77	39.5	14	31.1	0.3[NS]

Discussion

Thyroid disorders are the second most common endocrinological disorders affecting women of child-bearing age, with more than half of the cases being undiagnosed. While both thyroid dysfunctions are important, the state of hypothyroidism is considered to be the more serious regarding pregnancy[73].

Main Findings:

In our study, laboratory evidence of low thyroid status (Any low thyroid status) was observed in 18.8% of the study sample (95% confidence interval 14.1% to 24.3%). The most frequently observed hypothyroidism status was "isolated low free T4" documented in 10% of pregnant females (with an anticipated 95% confident interval in the reference population ranging between 6.5% to 14.5%). Ranked second was SCH observed in 7.1% of subjects (95% confidence interval 4.2% to 11.1%), while OH was observed in only 1.7% of cases (95% confidence interval 0.5% to 4.3%), which is higher than had been reported in the other studies.

The literatures review in this field regarding the prevalence of thyroid status abnormality, Hypothyroidism is common in pregnancy with an estimated prevalence of 2-3% and 0.3-0.5% for subclinical and overt hypothyroidism, respectively in West and it is dependent on the TSH and FT4 level thresholds applied, and this represents most women who would be identified with thyroid deficiency through routine screening[74].

There are a few reports of prevalence of hypothyroidism during pregnancy from India with prevalence rates ranging from 4.8% to 11%[75]. It seems that prevalence of hypothyroidism is more in Asian countries compared with the West. In Iraq, we got higher prevalence than had been reported previously by Hashim BA study as they have a prevalence of 16.3% [76]. This difference might be attributed to the difference in the inclusion criteria and sample size. Our SCH cases were also higher; 7.1% than had been reported by other area in the region as the Iranian study; 4.1% that include 3158 pregnant women[76]. In a large Chinese study, which included 2,899 pregnant women, the prevalence of hypothyroidism was significantly higher in the high-risk group than in the non-high-risk group (10.9% vs 7.0%, p = 0.008) [75]. Another study that had been done by Azriny Shaziela, looking to the prevalence of SCH and OH, he had found that in a control population, 1.98% (7/354) were subclinical, and surprisingly 2.82% (10/354) were overt[77].

When we adjusted thyroid status to the trimester of pregnancy, we found that the rate of any low thyroid status was significantly higher among women tested in the first trimester of pregnancy (30.5%) compared to those tested in the 2nd trimester (12.7%) and isolated low free T4 was also significantly higher in the first trimester. While a study in Columbia University Center found that Subclinical hypothyroidism was documented in 2.2% (240 of 10,990) in the first and 2.2% (243 of 10,990) in the second trimester and hypothyroxinemia was documented in 2.1% (232 of 10,990) in the first and 2.3% (247 of 10,990) in the second trimester [6978].

Where is in North India, there is a high prevalence of hypothyroidism (14.3%), majority being subclinical in pregnant women during first trimester as shown by Dhanwal et al, that necessitating routine screening [7879].

In our study, the rate of any low thyroid status, isolated low T4 and OH were slightly higher in those with recurrent miscarriages (24.1%, 16.7% & 1.9% respectively) compared to the remaining two categories (negative miscarriage & 1-2 miscarriages), though the difference was not significant statistically. Comparing that with other studies, there were controversies regarding the available evidences that relate the current thyroid dysfunction with early pregnancy loss. A study done in Bangladesh found a higher risk of abortion among pregnant women with SCH and OH, and that risk being mainly with OH [75].

Another previous one had shown that maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes and SCH was not associated with adverse outcomes, while hypothyroxinemia in the first trimester and in the second trimester was associated with preterm labor, macrosomia and gestational diabetes [69]. Where is AS Khalid found that the prevalence of SCH and undiagnosed OH in the pregnancy loss group (mainly late pregnancy loss and still birth) was significantly higher than the control group (p-value 0.0032) and 7% of women with recurrent miscarriage were either overtly or sub clinically hypothyroid. Another study has demonstrated the prevalence of hypothyroidism to be 4.12% in women with recurrent miscarriage [77].

Looking to the impact of low thyroid status on the outcome of current pregnancy, we had found that the rate of any low thyroid status was significantly higher in women who had no miscarriage (25.7%) compared to women who end with miscarriage (9%), especially the SCH which was significantly higher in women whom pregnancy was proceed beyond 23 weeks + 6 days; (10.7%) compared to miscarriage group (2%), where is De Vivo A, had found that SCH and autoimmune disorder are independently associated with very early embryo loss, but women suffering from SCH have a lower gestational age at the time of miscarriage[78]. In a post hoc analysis, Negro et al. reported the rate of pregnancy loss was statistically significantly higher in women with SCH compared with euthyroid women (6.1% vs. 3.6%; P=006). In contrast, a post hoc analysis of the FASTER Trial, found no association between SCH and adverse pregnancy outcomes [79].

We had found that there was no significant association between any low thyroid status and selected features related to the women history as menstrual history or history of infertility, neither any significant relation with the symptoms and signs related to abnormal thyroid status. Other studies had documented that even in OH individuals there can be a major discrepancy between symptoms and thyroid status. Canaris et al. demonstrated that although OH patients were more likely to report hypothyroid symptoms than euthyroid individuals, only 30% of OH patients were symptomatic whereas 17% of controls reported hypothyroid symptoms [63]. In addition, close to 20% of OH patients reported no symptoms at all. Thus, while the presence of symptoms may be suggestive of either OH or SCH, their absence fails to exclude it.

Strengths and limitations:

To our knowledge, this study is the first one in Iraq that looking to the association of abnormal thyroid function and its potential relation to miscarriage. All the women engaged in the study were interviewed by the same person. The method used to measure the TSH and free T4 by enzyme linked fluorescent assay (ELFA) technique; the best available method nowadays uses to take this measurement. TSH and freeT4 were measured by Addendeum-Mini VIVAS apparatus (VIDAS)12 mode 10, 1992, Biomreieux Company, as it is the newest method use for measurement of thyroid stimulating hormone (TSH) and free T4, that was in agreement with 2 consultants in the field and a consultant statistician.

All the confounders that could affect the result had been excluded when possible, having diagnosed overt hypothyroidism or taken any drugs that could affect the thyroid function.

Because of selection criteria, time constrains and financial issues, we opted to have a small sample size that could affect our result.

We were unable to examine the prevalence of thyroid autoimmunity in this population, as this test was not routinely available at the time of the study.

Conclusion

1. There is a high prevalence of abnormal low thyroid status, in the form of (isolated low free T4, SCH and undiagnosed OH) tested in early pregnancy in the sample that had been studied.
2. Isolated Low free T4 followed by SCH have the highest rate of occurrence in the study sample.
3. Though the occurrence of any low thyroid status, low isolated free T4 are more common in women with recurrent miscarriage, but the difference was not significant statistically.
4. No clear association had been found between the abnormal thyroid tests and the incident of abortion in the current pregnancy.
5. No significant association had been found between abnormal thyroid status and symptoms of hypothyroidism.

Recommendation

1. Larger sample study needed to be established in Iraq to know the real magnitude of this problem.
2. Further studies are needed to determine the optimum thyroid function level in Iraqi women during pregnancy and possibly to define the Trimester-specific reference cut off values for TSH and T 4 (free).
3. Further researches are needed to determine the possible need for screening program in Iraq by testing TSH levels early in pregnancy.
4. Further studies are required in Iraq to determine the precise effects of SCH on obstetric outcome in addition to their effects on childhood neuro-intellectual development.

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