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RESEARCH ARTICLE

PREVALENCE OF SUBCLINICAL AND UNDIAGNOSED OVERT HYPOTHYROIDISM IN HABITUAL ABORTION

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Abstract

Background: Hypothyroidism is the second most common endocrine disorder in women of childbearing age with an increased risk of pregnancy loss. Pregnancy loss associated with subclinical hypothyroidism (SCH), defined as elevated thyroid-stimulating-hormone level, with normal free thyroxine. In overt hypothyroidism (OH), the free thyroxine is low.

Materials and methods: Cases recruited from those attending high risk pregnancy unit of obstetrics and gynecology department of Benha university hospital Egypt from 2019 till 2020. We examined the prevalence of subclinical and undiagnosed overt hypothyroidism in women with recurrent miscarriage, late miscarriage and stillbirth. Cases with sporadic miscarriages, autoimmune disorders, thrombophilias and known hypothyroidism were excluded.

Sample size: Two-hundred women were included. Median maternal age was 35 years (range 18-47). Subclinical and undiagnosed overt hypothyroidism was found in 24 cases (12%) of women. Sixteen women (8%) had subclinical hypothyroidism, eight (4%) had undiagnosed overt hypothyroidism. Results were compared to women with ongoing pregnancies.

Results: The prevalence of subclinical and undiagnosed overt hypothyroidism in the pregnancy loss population was 12% (24/200), where 8% (16/200) were subclinical, and 4% (8/200) were undiagnosed overt. In the control population, prevalence of hypothyroidism was 1.5% (3/200).

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Introduction:-

Hypothyroidism is a frequent disorder in pregnant women and the second most common endocrine disorder in women of childbearing age. Both types of hypothyroidism overt or subclinical type associated with an increased risk of pregnancy loss in the form of habitual abortion, mid-trimester abortion, and still birth. (1)

Thyroid dysfunction is not uncommon in pregnant women, with 2–3% caused by chronic autoimmune thyroiditis. 5–15% women of reproductive age are diagnosed with thyroid autoimmunity, resulting in high risk of adverse pregnancy outcomes. Hypothyroidism is more common type of thyroid disorders, and subclinical hypothyroidism (SCH) more prevalent than overt clinical hypothyroidism (OH) (2).

Subclinical hypothyroidism is defined by elevated thyroid stimulating hormone(TSH), with normal free thyroxine (T4) levels. In overt hypothyroidism, free T4 is low.

The antibodies that appear most frequently are:

First group of antibodies: Antithyroid Peroxidase Antibody or TPO Ab (Ab is short for antibody) this is also known as Antithyroid Microsomal Ab.

Second group of antibodies: Antithyroglobulin Antibody or TG Ab.

Third group of antibodies: Thyroid Stimulating Immunoglobulin or TSI Ab.

The first group, the TPO Ab, are found raised in Hashimoto's disease - otherwise known as autoimmune thyroiditis. Here the cells of the thyroid gland are attacked and slowly destroyed. Patients with these antibodies present either have Hashimoto's, or are going to have it with subsequent reduction of thyroid function. (Elevated levels are found in virtually all cases of Hashimoto's disease and they will also be raised in 65% of patients with Graves' disease).

The next group is the TG Ab. These levels rise as well as the TPO Ab levels in autoimmune thyroiditis, but to a lesser degree.(2-7)

The third group, the TSI Abs, exert their effect by targeting the TSH (thyroid stimulating hormone) receptors in the thyroid gland, and activate them abnormally, thus stimulating the thyroid gland to overproduce thyroid hormones. This of course is Graves' disease and these Thyroid Stimulating Immunoglobulins are the chief cause of it. (7-8)

Both the thyroid stimulating immunoglobulin antibodies and the antithyroid peroxidase antibodies may be present in an autoimmune (Hashimoto's) thyroiditis and in Graves' disease in some degree at least.

Thyroid autoantibodies are found in 5–15% of women of childbearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism during pregnancy. (3)

The alteration in thyroid hormone regulation in pregnancy due to the increase in plasma volume expansion, the increase in thyroid binding globulin (TBG) caused by human chorionic gonadotrophin (HCG), and the relative iodine deficiency in pregnancy, results in a 10-15% lower free T4 level compared to non-pregnant women(9).

The benefits of universal screening for thyroid dysfunction (primarily hypothyroidism) are not justified by current evidence. Undertake a high-risk screening for thyroid disease by measurement of TSH in women with: History of hyperthyroid or hypothyroid disease, PPT, or thyroid lobectomy.

Symptoms or clinical signs suggestive of thyroid under-function or over-function including anaemia, elevated cholesterol, and hyponatraemia.

Family history of thyroid disease.

Thyroid antibodies (when known).

Other autoimmune disorders.

Previous therapeutic head or neck irradiation.

Goitre.

Type 1 diabetes.

History of recurrent miscarriage or PTD. (10)

Other causes of thyroid insufficiency – treatment of hyperthyroidism (radioiodine ablation or surgery) or surgery for thyroid tumours.

The demands of thyroid hormone, however, increase due to the initial increase in TBG, the thyrotropic action of HCG, which causes an increase in TBG and free T4 and alterations in thyroid metabolism, particularly at placental level at later gestation. Adapt to these changes result in subclinical or even overt hypothyroidism in normally euthyroid women.

Maternal hypothyroidism is associated with adverse pregnancy outcome, including pre-eclampsia, preterm delivery, placental abruption and fetal death (8-13).

Thyroid hormone is an important contributory factor to normal fetal brain development.

At early gestational stages the presence of thyroid hormones in fetal structures can only be explained by transfer of maternal thyroid hormones to the fetal compartment because fetal production of thyroid hormones does not become efficient until mid-gestation.

Prior to 12 weeks' gestation, maternal thyroxine (but not fT3) crosses the placenta. From 12 weeks onwards, fetal thyroid function is controlled independently of the mother, provided that her iodine intake is adequate.

The fetal thyroid begins concentrating iodine at 10–12 weeks and is under control of fetal pituitary TSH by approximately 20 weeks. (14)

TSH does not cross the placenta. However, clinically significant amounts of maternal T4 do cross the placenta. In addition, TSH-releasing hormone (TRH), iodine, TSH receptor (TSH-R) antibodies, and antithyroid drugs (ATDs) cross the placenta readily.

The incidence of pregnancy loss is 15-20%. Recurrent miscarriage, defined as at least three consecutive miscarriages, occurs in 1% of women (24).

Late miscarriage, or mid-trimester miscarriage, defined as miscarriage between 14-24 weeks of gestation, occurs in 1-5% of pregnancies.

Stillbirth occurs in 1 in 200 pregnancies. Both overt and subclinical hypothyroidisms are associated with stillbirth. Three proposed hypotheses for the association of thyroid autoimmunity and pregnancy loss are; firstly, it may reflect a generalized activation of the maternal immune system, secondly it delays conception, therefore increasing the risk of miscarriage due to older maternal age and thirdly, it may reflect a subtle deficiency in thyroid hormone (14, 15, 16).

In overt hypothyroidism, treatment with levothyroxine is known to alleviate maternal symptoms and improve pregnancy outcome (8).

In subclinical hypothyroidism, the evidence for treatment is lacking. However, The Endocrine Society Clinical Practice Guidelines concluded that there is benefit to treatment, with low incidence of adverse outcomes, and therefore advocated levothyroxine treatment in subclinical hypothyroidism (1).

Levothyroxine requirements in patients with overt hypothyroidism increase from early first trimester and the dosage of levothyroxine may need to be increased 30-50% by 4-6 weeks gestation. A target level of TSH less than 2.5 μ U/mL is recommended (17, 18).

Methods:-

We conducted a prospective analysis of thyroid function tests (TFT) in women attending the high risk pregnancy unit of Benha university hospital obstetrics and gynecology department between January 2015 and January 2017 attended by women with a history of recurrent miscarriage, late miscarriage, or perinatal death.

Women have the indicated medical investigations done at the time of pregnancy loss to ensure availability of the results during consultation. Investigations include a thrombophilia screen, thyroid function, autoimmune screening, and parental karyotyping.

Inclusion criteria

Women with recurrent miscarriage, mid-trimester miscarriage and stillbirth were included. Recurrent miscarriage was defined as three or more consecutive first trimester miscarriages, mid-trimester miscarriage was defined as miscarriage between 14 to 24 weeks, and stillbirth was defined as intrauterine fetal death after 24 weeks

Exclusion criteria

Those with sporadic or non-recurrent miscarriage were excluded.
 Women with known thyroid and autoimmune disorders were excluded.
 Women found to have other causative factors were also excluded.

Laboratory evaluation

Thyroid function tests (TFT) were performed at the time of diagnosis of pregnancy loss. Cases with overt or subclinical hypothyroidism have repeated at their follow-up high risk pregnancy unit (HRPU) visit.

Reference ranges for free T4 and TSH in the first, second and third trimester used were 12.05-19.60 pmol/L and 0.33-4.59 mIU/L; 9.63-17.00 pmol/L and 0.35-4.10 mIU/L; and 8.39-15.60 pmol/L and 0.21-3.25 mIU/L respectively.

Cases divided into two groups:

(Group 1 pregnancy loss group PLG) 200 women were included in the pregnancy loss cohort. Median Age of cases was 35 years (range 18-43). One-hundred women (100/200; 50%) had recurrent miscarriage, sixty (60/200; 30%) had late miscarriage and forty (40/200; 20%) had a stillbirth.

In the pregnancy loss population, median TSH was 1.74 mIU/L and median free T4 was 15.20 pmol/L. Median free T4 and TSH in the recurrent miscarriage, late miscarriage and stillbirth groups were 15.70 pmol/L and 1.60 mIU/L; 14.00 pmol/L and 1.69 mIU/L; and 15.00 pmol/L and 2.13 mIU/L respectively.

(Group 2) (Control group) Two hundred patients were included in the control group. Median age was 30 years (range 18-43).

Median free T4 and TSH in the first, second, and third trimesters were 14.40 pmol/L and 1.16 mIU/L, 12.90 pmol/L and 1.16 mIU/L, and 11.40 pmol/L and 1.59 mIU/L respectively.

Free T4 levels in the late miscarriage group and the stillbirth group were significantly lower than those in the recurrent miscarriage group (p-value 0.001 and 0.03 respectively), likely due to the later gestation of these pregnancies. Free T4 levels between the late miscarriage group and the stillbirth group did not differ significantly.

TSH levels did not differ significantly between all three groups.

Median TSH levels in all pregnancy loss groups were higher than the assay median in each trimester. The prevalence of subclinical and undiagnosed overt hypothyroidism in the pregnancy loss population was 12% (24/200), where 8% (16/200) were subclinical, and 4% (8/200) were undiagnosed overt.

In the control population, 1.5% (3/200) were subclinical, and overt hypothyroidism

The prevalence of subclinical and undiagnosed overt hypothyroidism in the pregnancy loss group was significantly higher than the control group (p-value 0.0032).

In the pregnancy loss group (PLG), 12% (24/200) had TSH levels above 2.5 mIU/L, compared to 1.5% (3/200) in the control group (p-value 0.003).

According to each pregnancy loss group, subclinical or undiagnosed overt hypothyroidism were diagnosed in 9.3% (9/96) women with recurrent miscarriage, 12.5% (8/64) women with late miscarriage and 15% (6/40) women with stillbirth.

item	Pregnancy loss group	Control group
Number of cases	200	200
TSH above 2.5 mIU/ml	24(12%)	3(1.5%) p value 0.0003

subclinical	16(8%)	All are subclinical
overt	8(4%)	

Discussion:-

In the current study, the prevalence of subclinical and undiagnosed overt hypothyroidism in the pregnancy loss cohort was 12%, of which 8% were subclinical and 4% overt hypothyroidism. In the general pregnant population, the prevalence of overt and subclinical hypothyroidism is reported as 1.5%. These findings support the association of overt and subclinical hypothyroidism with pregnancy loss. (1)

A previous study demonstrated that in untreated hypothyroid women, 60% of the overtly hypothyroid women and 71% of the subclinically hypothyroid women had miscarriage (2).

Several reasons may account for the changes of thyroid function in pregnant women: (1) relative iodine deficiency during pregnancy; (2) the effects of human chorionic gonadotropin (hCG) on the activation of thyroid function stimulates the secretion of thyroid hormones, which could inhibit adenohypophysis function and suppress the levels of thyrotropin; (3) elevated levels of oestrogen during pregnancy, increasing serum thyroid binding globulin (TBG) and raising the concentrations of serum total thyroxine; and (4) the effect of the placenta on thyroxine deiodination (25)

In adequately treated women, the risk was minimal. In current study, 12% of women with habitual abortion were hypothyroid.

Another report showed that 3.8% of women with first trimester miscarriages had subclinical hypothyroidism. Study included women with sporadic miscarriage (6).

In the current study According to each pregnancy loss group, subclinical or undiagnosed overt hypothyroidism were diagnosed in 9.3% (9/96) women with recurrent miscarriage, 12.5% (8/64) women with late miscarriage and 15% (6/40) women with stillbirth.

Most recently, an increased incidence of pregnancy loss in women with TSH between 2.5-5.0 mIU/L in the first trimester was demonstrated, calling for redefining the upper limits of TSH in the first trimester of pregnancy (4).

Our study showed that 12% of women with pregnancy loss had TSH levels above 2.5 mIU/L, supporting the evidence that increased TSH alone can be associated with pregnancy loss.

Recently, Maraka, et al. reported that pregnancy with SCH (subclinical hypothyroidism) is closely associated with a higher foetal mortality (miscarriage rate and stillbirth rate) in a systematic analysis (22)

Universal screening has never been clinically justified due to the lack of evidence supporting treatment of subclinical hypothyroidism, and the lack of quality studies demonstrating its cost-effectiveness (19, 20).

Targeted screening of women at risk is advocated instead (19, 21). However, this can potentially miss 30% of those with thyroid disorders. Universal screening can detect twice as many women with thyroid disorders in early pregnancy compared to targeted screening, but whether treatment should then be initiated for all is unclear (21-23).

Meta-analysis of pregnant women before 20 weeks done by Yibing Zhang in 2017 revealed an increase in the rate of habitual abortion when cases proved to have subclinical hypothyroidism (25)

Compared to OH (overt hypothyroidism), the incidence of complications related to SCH (subclinical hypothyroidism) is lower. However, the prevalence of adverse outcomes, including spontaneous miscarriage, placental abruption, preterm birth, fetal distress and preeclampsia, has increased in recent studies [3].

In conclusion, this study has demonstrated a significant prevalence of undiagnosed overt and subclinical hypothyroidism in women with pregnancy loss, supporting the association between pregnancy loss and hypothyroidism.

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