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A RETROSPECTIVE ANALYSIS OF THE INTERPLAY BETWEEN HYPERTENSIVE DISORDERS OF PREGNANCY AND ABERRATIONS IN THYROID FUNCTION TESTS

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ABSTRACT

The association between hypertensive disorders of pregnancy (HDP) and thyroid disorders has been a subject of growing interest in maternal fetal medicine. Hypertensive disorders including conditions like preeclampsia and thyroid dysfunction both contribute to maternal morbidity and adverse pregnancy outcomes. Studies have demonstrated a bidirectional relationship between HDP and thyroid disorders. Women with HDP are more likely to experience disruptions in thyroid function such as alternations in thyroid stimulating hormone (TSH) levels and thyroid hormone (T3 and T4). These abnormalities may contribute to the intricate pathophysiology of HDP, influencing vascular function, endothelial dysfunction, and inflammatory process. Conversely thyroid disorders particularly autoimmune thyroid conditions like Hasimoto thyroiditis may predispose to the development of HDP. Understanding the association between HDP and thyroid function has implications for both obstetric and endocrine care. Monitoring thyroid function during pregnancy in women with HDP could aid in early detection and management of potential complication and to develop targeted interventions ultimately improving maternal and fetal outcomes.

KEYWORDS

Hypertensive Disorders Of Pregnancy, Thyroid Disorder, Endothelial Dysfunction, Vascular Function, Thyroid Hormone

INTRODUCTION

Maternal thyroid's adequate functioning is required for an uncomplicated pregnancy. Overt hyperthyroidism due to Graves' disease and overt hypothyroidism have both been associated with adverse pregnancy outcomes including pregnancy loss, intrauterine growth retardation, preterm birth, and preeclampsia. Thyroid hormones are involved in the regulation of placental development, endothelial function and blood pressure regulation, and therefore, thyroid hormone aberrations might have a relevant role in the development of hypertensive disorders during pregnancy. Hypertensive disorders of pregnancy includes gestational hypertension, preeclampsia, and eclampsia whose common characteristic is the increase in blood pressure leading to various degrees of multi-organ compromise. Preeclampsia is a major risk factor for intrauterine growth retardation, placental abruption, and preterm birth. This research study delves into the retrospective analysis of the association between hypertensive disorders of pregnancy (HDP) and abnormal thyroid function tests (TFTs). Drawing on data from 4100 pregnancies spanning [2022(Jan)-2024(Jan)], the investigation aims to elucidate the extent and nature of this association.

OBJECTIVES:

- To assess the prevalence of abnormal TFTs in pregnancies with hypertensive disorders.
- To analyze the temporal relationship between the onset of hypertensive disorders and abnormalities in thyroid function.
- To investigate the impact of concurrent HDP and abnormal TFTs on maternal health.

METHODOLOGY

Study design: Retrospective cohort study

Inclusion Criteria:

Pregnant women who received care at the healthcare institution during a specific 2 year period.

Exclusion Criteria:

- Participants with preexisting thyroid disease.
- Not having thyroid function assessment during pregnancy.
- Taking medications which affect thyroid function.
- Multifetal gestation, chronic hypertension

Participants:

Data was drawn from 4100 pregnancies spanning 2 years in our Institute. Serum TSH, free T4 (FT4), levels were determined in 4100 pregnant women by an electrochemiluminescent immunoassay technique. No interventions were done. The associations of thyroid function with70 excluded without thyroid function test the risk of hypertensive disorders were studied.

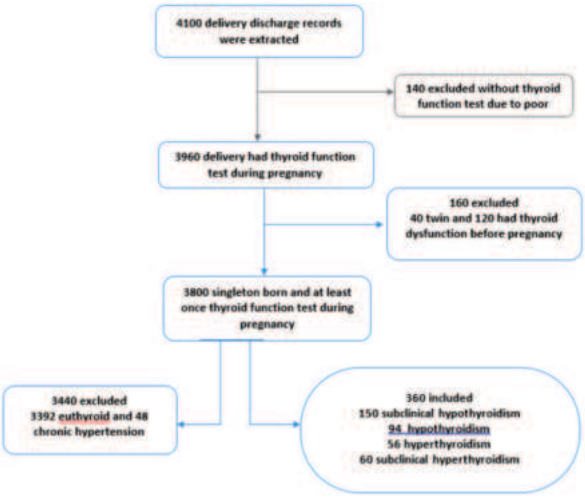
Subclinical hypothyroidism was defined as a TSH concentration above the 97.5th percentile and a FT4 concentration within the reference range (2.5th-97.5th percentile). Overt hyperthyroidism was defined as a TSH concentration below the 2.5th percentile and a FT4 concentration above the 97.5th percentile. Subclinical hyperthyroidism was defined as a TSH concentration below the 2.5th percentile and a FT4 concentration within the reference range. Serum values of TSH and FT4 for all cohorts were log-transformed and then standardized to population-specific standard deviation scores (Z-scores) after removal of outliers (±4 SD from the mean).

Subclinical hypothyroidism	Tsh(>97.5 percentile)	FT4(2.5-97.5 percentile)
Overt hypothyroidism	Tsh(> 97.5 percentile)	FT4(< 97.5 percentile)
Subclinical hyperthyroidism	Tsh(<2.5 percentile)	FT4(2.5-97.5 percentile)
Overt hyperthyroidism	Tsh(< 2.5 percentile)	FT4(>97.5 percentile)

Main outcome measures: Mean blood pressures and hypertensive disorders, including pregnancy-induced hypertension (n = 320) and preeclampsia (n = 180), were measured. 360 70 excluded without thyroid function testpregnant women were with documented abnormal TFTs.

Hypertensive disorders were defined and classified according to a previously described protocol. Briefly, gestational hypertension was defined as persistent blood pressures of 140/90 mm Hg or more, occurring after 20 weeks of gestation, without evidence of proteinuria. Mild preeclampsia was diagnosed in hypertensive women who also had 1+ proteinuria determined by urine dipstick analysis from a catheterized sample as per the protocol of our institution. Severe preeclampsia was diagnosed in hypertensive women with any of the following: 2+ or more proteinuria by dipstick from a catheterized urine sample, blood pressure higher than 160/110 mm Hg, persistent

headache, visual disturbances, right upper quadrant or epigastric pain, serum creatinine 1.2 mg/mL or more, serum aspartate transaminase levels more than twice the upper limit of normal, or thrombocytopenia less than 100,000/mL.



Study population:

RESULTS:

During the time 24 month study, a total of 4100 women who delivered singleton neonate were included in this study. Of these, 3392 (90%) had TSH values within the normal range and were considered to be euthyroid; 150 (3.2%) had TSH levels more than 4.13 milliunits/L along with normal free T4 levels, therefore meeting criteria for subclinical hypothyroidism. 60(1.21%) had TSH levels less than 0.03 milliunits/L along with normal free T4 levels, therefore meeting criteria for subclinical hyperthyroidism.

Maternal demographics of the three cohorts are shown in Table 1, in which women within either the subclinical hyperthyroid cohort or the hypothyroid cohort were compared with those in the euthyroid cohort

Table 1:-Maternal Demographics in Women With Subclinical Thyroid Dysfunction Compared With Euthyroid Women

Demographics factors	Subclinical hypothyroidism (n= 150)	Euthyroidism (n=3392)	Subclinical hyperthyroidism (n=60)
Age (>35 yrs) Yes No	24(17.37) 126(83.50)	406(12.21) 2986(88.30)	12(19.4) 48(80.6)
Ehinicity- Minority (lower) Majority (middle and upper)	6(3.05) 144(96.95)	90(2.71) 3300(97.29)	18(3.2) 42(96.8)
BMI Underweight (<18kg/m2) Optimal(18-22.9) Overweight(23-24.9) Obesity(>25)	16(10.2) 92(62) 30(21.5) 8(5.01)	474(14.34) 2179(64.4) 542(16.32) 134((4.24)	16(26.66) 24(40) 12(20) 8(13.3)
Parity Nulliparous Parous	102(68.30) 46(31.67)	2544(75) 814(24.4)	42(70.6) 16(30.45)
Gestational age at thyroid hormone measurment	85(60-114)	86(60-114)	84(60-118)

Women with subclinical thyroid disorder were more likely than euthyroid women to be parous subclinical hypothyroidism (31.67%), subclinical hyperthyroidism (30.45) vs euthyroid (24.4%), have an advanced age(17.37%,19.4%,12.85% respectively),and have pre pregnancy overweight or obesity(21.5% ,20%,16.32% respectively). In each group of thyroid classifications, no of patients of hypertensive disorders estimated below

Table 2:- shows occurrence of hypertensive disorders in each study groups. Total patients with both hypertensive disorder along with thyroid dysfunction (130)

Thyroid disorders	Hypertensive disorders (Including GHTN; preeclampsia both mild , severe)
Euthyroidism (n=3392)	390(11.49%)
Subclinical hypothyroidism (n=150)	50(33%)
Overt hypothyroidism (n=94)	30(31%)
Overt hyperthyroidism (n=56)	10(17%)
Subclinical hyperthyroidism (n= 60)	40(33%)

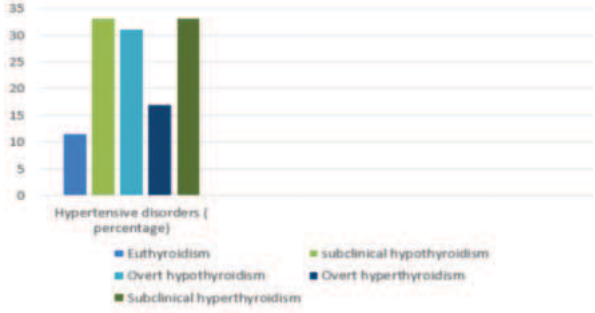


Figure 1:- shows occurrence of hypertensive disorder in each study group

Occurrence of different types of hypertensive disorders in each study group shown in below table 2:

Table 3:- shows occurrence of different types of hypertensive disorders in each study group

Hypertensive disorder	Euthyroidism (n=390)	Subclinical hypothyroidism (n=50)	Overt hypothyroidism (n=30)	Subclinical hyperthyroidism (n=60)	Overt hyperthyroidism (n=10)
Gestational HTN	300 (76%)	24(48%)	14(46%)	10(50%)	6(60%)
Mild preeclampsia	66(16%)	16(32%)	10(33%)	6(30%)	2(20%)
Severe preeclampsia	24(6.1%)	10(2%)	6(2%)	4(20%)	2(20%)

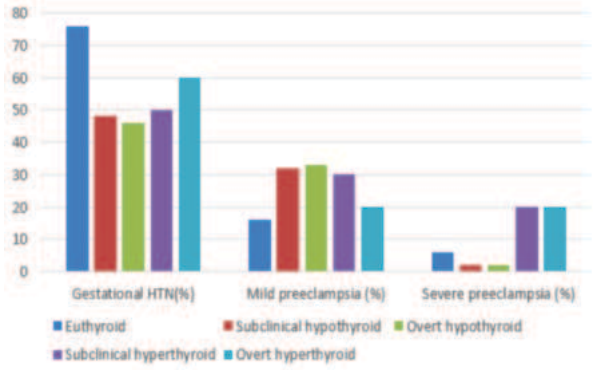


Figure 2:- shows occurrence of different types of hypertensive disorder in each study group

Table 4:: shows outcome of patients of hypertensive disorder along with thyroid disorder

Maternal health outcomes	130 patients of Hypertensive disorder along with thyroid disorder (n)
Early gestational failure	6 (4.61%)
Fetal growth restriction	25 (19.23%)
Low birth weight	27 (20.76%)
Preterm birth(<34 weeks)	30 (23.07%)
Gestational diabetes mellitus	10 (7.69%)
Cesarean section	16 (12.30%)

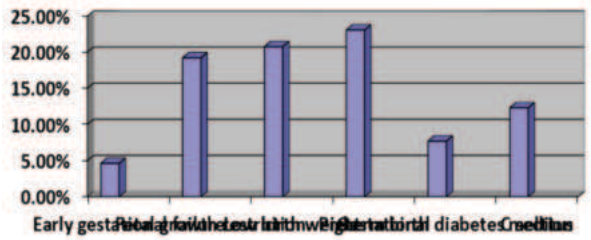


Figure 3:: shows outcome of patients of hypertensive disorder along with thyroid disorder

DISCUSSION

The one significant finding of this study that included nearly 4100 pregnant women was that those identified to have subclinical hypothyroidism had a significantly increased risk for development of severe preeclampsia when compared with euthyroid women. This association is particularly strong because its significance persisted after adjustment for factors known to increase preeclampsia risks, such as age, parity, race, and weight. Hypothyroidism has been associated with endothelial cell dysfunction likely secondary to decreased production of vasoactive substances (e.g., nitric oxide) which leads to impaired vasorelaxation, increased sympathetic tone, and vascular resistance and finally hypertension[1,2,3,4]. Critical processes during placental formation, such as decidual cell migration and angiogenesis are regulated by inflammatory mediators (e.g., interleukin-10, leptin, and nitric oxide synthase 2) and at least in part influenced by thyroid hormones. Consequently, conditions with a low thyroid hormone availability may result in an inadequate anti-inflammatory environment in the developing placenta and therefore in placental vascularity disturbances, which have been associated with adverse pregnancy outcomes such as preeclampsia and miscarriage[5].There are a number of observations that support the biological plausibility of this association. These include the cardiovascular effects of abnormal concentrations of thyroid hormones, the adverse pregnancy outcomes reported for women with overt hypothyroidism, other vascular-related pregnancy complications that have been linked to subclinical hypothyroidism, and, finally, endothelial cell activation from abnormal amounts of thyroid hormones.Up to one fourth of overtly hypothyroid individuals are hypertensive, with a decreased pulse pressure, slowed diastolic filling, decreased ventricular filling and contractility, and increased systemic vascular resistance[6,7]. Although less well-studied, there is evidence that subclinical hypothyroidism in some, usually older, patients can cause hypertension, heart failure, and atherosclerotic vascular disease[6,8,9,10]. Finally, subclinical hypothyroidism has been shown to cause endothelial cell dysfunction characterized by diminished nitric oxide production with impaired vasorelaxation[11].A number of investigators have reported that pregnancies in women with untreated or poorly controlled thyrotoxicosis have increased incidences of cardiovascular and related complications such as preeclampsia, placental abruption, and heart failure[3,12-15].Similarly, reports of pregnant women with untreated overt hypothyroidism describe inordinately high rates of preeclampsia, placental abruption, and heart failure[14,15].The unifying theme of these cited studies is that abnormal levels of thyroid hormones can lead to long-term cardiovascular sequelae that are mediated in part by chronic endothelial cell damage. In this regard, preeclampsia is thought to be a syndrome characterized by multiorgan involvement that results from endothelial cell activation[16]. Thus, it seems reasonable to posit that abnormal levels of thyroid hormones are additive or synergistic toward the development of preeclampsia in women genetically predisposed.

Hyperthyroidism contributes to endothelial cell dysfunction through impairment of protective mechanisms against endothelial damage, such as tissue plasminogen activator and plasminogen activator inhibitor secretion, regulation of interleukin-18 and soluble vascular cell adhesion molecule 1 (VCAM-1)[17,18,19]. Higher FT4 concentrations in early pregnancy have been associated with higher vascular resistance in both the maternal and fetal placental compartment, which may induce adverse pregnancy outcomes[20]. Additionally, the association of hyperthyroidism with hypertensive disorders of pregnancy could in part be related to dysregulation of placental deiodinases, which activate or deactivate thyroid hormones in local tissues (placental deiodinases type 1 [DIO1] and type 2 [DIO2] convert T4 to T3 whereas placental deiodinase type 3 [DIO3] inactivates T4)[21]. It has been suggested that since both hypothyroidism and hyperthyroidism are risk factors for preeclampsia, the existence of divergent molecular mechanisms of placental deiodinase dysregulation in preeclampsia could be implied[21]. Future clinical studies could assess this possibility, for example by assessing the association of maternal FT3 or the FT4/FT3 ratio with gestational hypertension and preeclampsia [21].

In conclusion this retrospective analysis shows that subclinical hypothyroidism during pregnancy was associated with a higher risk of preeclampsia, and that there was a U-shaped association of TSH with preeclampsia. These findings add to the evidence on the risk of adverse maternofetal outcomes of thyroid dysfunction during pregnancy and indirectly informs on the optimal TSH treatment target in women treated with levothyroxine during pregnancy, which needs to be assessed in future interventional studies.

Limitations

Majority of women are of Asian heritage, and hence our observations may not be applicable and may vary in other ethnic and geographic populations. Our study precluded other such risk factors such as chronic hypertension that are known to increase the risk for preeclampsia. The current study we did not identify any evidence of a synergistic risk between TPO antibody positivity and high TSH.

Implications

Our observations add to accruing data that subclinical hypothyroidism, a relatively common finding in women of childbearing age, may be associated with some adverse perinatal outcomes.

These findings imply that optimal TSH treatment target could be in the middle of the reference range, which highlights the relevance of follow-up of thyroid function tests during pregnancy in women treated with levothyroxine to avoid under- or overtreatment.

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