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Dr. K Abiramavalli
Associate Professor Obstetrics & Gynaecology, Government Thiruvannamalai Medical College, Thiruvannamalai, Tamil Nadu, India

Dr. V Vanitha
Associate Professor Obstetrics & Gynecology, Government Chengalpet Medical College, Chengalpattu, Tamil Nadu, India

Correspondence
Dr. K Abiramavalli
Associate Professor Obstetrics & Gynecology, Government Thiruvannamalai Medical College, Thiruvannamalai, Tamil Nadu, India

Foeto maternal outcomes of hypothyroidism in pregnancy: A prospective study

Dr. K Abiramavalli and Dr. V Vanitha

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Abstract
Aim: To study the effects of maternal and fetal outcomes in case of thyroid dysfunction, specifically hypothyroidism.
Methods: The studied subjects included all pregnant women reporting to the hospital for a period of one year. All participants were subjected to detailed history, thorough general physical, systemic, local examinations, and routine investigations, thyroid function tests (serum TSH, T3, T4). All participants were divided into two groups, group-I: pregnant women diagnosed with hypothyroidism, group-II: euthyroid pregnant women (control group). Maternal and fetal outcomes of subjects in both groups were confirmed.
Results: A total of 10045pregnant women who attended OPD were qualified after applying exclusion criteria. Out of these, 9627 pregnant women were found euthyroid and hypothyroidism was identified in 408 (4.05%) women. Statistically, maternal outcomes like gestational hypertension, PROM, preterm premature rupture of membrane and placental abruption were found to be highly significant. (p<0.01).
Conclusions: Early detection and treatment of women with hypothyroidism in early pregnancy will improve the perinatal outcome.

Keywords: Hypothyroidism, maternal outcome, fetal outcome

Introduction

Hypothyroidism during pregnancy is usually asymptomatic, especially when subclinical. Antithyroid antibodies are prevalent in pregnancy, found in approximately 10% of women in the second trimester [1]. Thyroid disease is the second most common endocrine disorder, after diabetes mellitus, affecting women of reproductive age. The incidence of hypothyroidism is estimated to be 0.3-0.5% for subclinical hypothyroidism and 2-5% for overt hypothyroidism [2].
Thyroid physiology is perceptibly modified during normal pregnancy [3]. The most notable change is the increase in thyroxin-binding globulin (TBG). This begins early in the first trimester, plateaus during mid-gestation and persists until shortly after delivery. This is due to stimulation of TBG synthesis by elevated estrogen levels and more importantly due to a reduced hepatic clearance of TBG because of estrogen-induced sialylation [4]. This increased TBG concentration leads to an expansion of the extra-thyroidal pool and results in elevated total T3 and T4 levels due to an increase in maternal thyroid hormone synthesis. Women with hypothyroidism have decreased fertility; even if they conceive, risk of abortion is increased and risk of gestational hypertension, anemia, abruptio placentae and postpartum haemorrhage is increased [5]. The risk of these complications is greater in women with overt, rather than subclinical hypothyroidism.
.Fetal thyroid is capable of trapping iodine by 12 weeks and can synthesize thyroxin by 14 weeks of gestation. Even transient hypothyroidism can cause adverse neurologic outcome in a new-born. Thus, early diagnosis and treatment is recommended [8]. Obstetric complications of hypothyroidism contribute to the overall increase in frequency of adverse neonatal outcomes, which include preterm birth, low birth weight, increased admission to neonatal intensive care and increased perinatal morbidity and mortality [9].
Treatment of maternal hypothyroidism during pregnancy greatly improves both obstetric and neonatal outcomes [10-12]. Women should be made euthyroid as quickly as possible. India is one of the major endemic regions of goitre in the world undue importance should be given at diagnosing and treating hypothyroidism to prevent adverse maternal and neonatal outcome.

Methods

The present study was conducted in the department of obstetrics and gynaecology, Institute of obstetrics and gynaecology, Chennai. The studied subjects included pregnant women with hypothyroidism reporting to the hospital for a period of one year April 2016 to March 2017. Pregnant women diagnosed with hypothyroidism and euthyroid pregnant women were included while pregnant women with hyperthyroidism, other medical disorders- hypertension, diabetes mellitus, renal disorders, etc. and drug-induced hypothyroidism were excluded. All participants included in the study were subjected to detailed history; thorough general physical, systemic, local examinations, routine investigations, thyroid function tests (serum TSH, T3, T4).

All participants were divided into two groups, group-I: pregnant women diagnosed with hypothyroidism and group-II: euthyroid pregnant women (control group). Maternal and fetal outcomes of subjects in the first group were compared with control group. Serum TSH, T3, T4 was measured by radioimmunoassay (RIA) method. The reference values taken in the present study were as per medical college endocrinology laboratory, which are as follows: TSH (0.5 to 5 mU/L), T3 (0.8 to 1.6 ng/mL or 80 to 160 ng/dL) and T4 (60 to 120 ng/mL or 6 to 12 μg/dL).

The data was analyzed. Mean and standard deviation (SD) was calculated and reported for quantitative variables. Chi square test was performed to evaluate statistical significance. A p-value of <0.05 was considered a statistically significance.

Results

51450 pregnant women, reported to labour room and OPD from April 2016 to March 2017. A total of 10045 pregnant women qualified after applying exclusion criteria and 9637 pregnant women were found euthyroid. Hypothyroidism was identified in 408 (4.06%) pregnant women and further observations were made on hypothyroid women, who are as follows: majority of patients (%) were in the age group of 20-25 years (43.6%), 41.4% in age group of 26-30 years. Mean age was 26.89±3.93 years with range of 20- 30 years. {TABLE 1}

Majority of patients (47.5%) were primigravidas, G2 (22.3%), G3 and more (15.1%), BOH (15.1%). {TABLE 2}

Table 1: Age wise Distribution of Study Population

Age	No. of Patients	Percentage
Less than 20	4	0.98%
20 – 25	178	43.6%
26 – 30	169	41.4%
31 - 35	48	11.76%
>35	9	2.2%
Total	408	

Table 2: Parity wise Distribution of Study Population

Parity	No. of Patients	Percentage
Primi	194	47.5
Gravida 2	91	22.3
More Gravida 3	62	15.1
BOH	61	15
Total	408	

Table 3: Mode of Delivery of Study Population

Mode of delivery	No. of patients	Percentage
Vaginal delivery	178	43.6%
LSCS	230	56.3%
Total 408		

Table 4: Gestational age of Study Population

Gestational age	No. of Patients	Percentage
Less than 28 weeks	1	0.002
28 weeks to 34 weeks	42	10.2
34 weeks to 37 weeks	115	28.1
>38 weeks	250	61.2%
Total	408	

Table 5: Birth weight of Study Population

Birth weight	No	Percentage
Less than 1kg	9	2.2
1 kg to 2 kg	38	9.31%
2kg to 2.5 kg	245	60
>3kg	149	36.5

Statistically, maternal outcomes like gestational hypertension, preterm premature rupture of membrane, Premature rupture of membranes and placental abruption were found to be highly significant (p<0.01), while preterm labour, Oligohydramnios, placental previa, postpartum haemorrhage were found to be non-significant (p>0.05) (Table 6).

Statistically, fetal outcomes like fetal distress, low birth weight (<2.5 kg) and premature birth were found to be highly

significant ($p<0.01$), while intrauterine deaths and congenital anomalies were found to be non-significant ($p>0.05$) (Table 2).

Table 6: Comparison of maternal outcome between euthyroid and subclinical hypothyroidism patients.

Maternal Outcome	Hypothyroid (408) Patients (Cases)	Euthyroid Patients (Controls) (9627)	Statistical Significance
PPROM	24	317	p<0.007**
PROM	56	412	p<0.003**
Hypertensive Disorders of Pregnancy	50	1588	p<0.001**
geststional diabetes Mellitus	38	1444	p<0.06*
Preterm Labour	40	654	p<0.52*
Oligohydramnios	26	784	p<0.06
Placental Abruption	20	115	p<0.0001**
Post partumhaemorrhage	3	252	p<0.55*
Placenta previa	24	402	p<0.08

Table 7: Comparison of Foetal/Perinatal outcome between euthyroid and subclinical hypothyroidism patients

Foetal/Perinatal Outcome	Cases	Control	Statistical Significance
Foetal distress	81	962	p<0.002
Low birth weight <2.5kg	280	1058	p<0.0001**
Congenital anomalies	2.04	192	p<0.7
IUD	12.8	198	p<0.8
IUGR	47	244	p<0.004

Discussion

The range of clinical manifestations of hypothyroidism during pregnancy is similar to those that occur in non-pregnant patients and may include fatigue, cold intolerance, constipation, and weight gain. Symptoms may be overlooked or attributed to the pregnancy itself. Many patients are asymptomatic. Hypothyroidism can have additional adverse effects on the mother and child, depending upon the biochemical severity of the hypothyroidism

- The diagnosis of overt primary hypothyroidism during pregnancy is based upon the finding of an elevated population and trimester-specific thyroid-stimulating hormone (TSH) concentration (or above 4.0 mU/L when local reference range is not available) in conjunction with a decreased free thyroxine (T4) concentration (below assay normal using reference range for pregnant women).
- Subclinical hypothyroidism is defined as an elevated population and trimester-specific serum TSH concentration and a normal free T4 concentration.
- The universal screening of asymptomatic pregnant women for thyroid dysfunction during the first trimester of pregnancy is controversial. ACOG suggests a targeted approach (case finding) rather than universal screening. It favour screening pregnant women if they are from an area of moderate to severe iodine insufficiency; have symptoms of hypothyroidism; have a family or personal history of thyroid disease or have a personal history of goiter, thyroid peroxidase (TPO) antibodies, type 1 diabetes or other autoimmune disorder, head and neck radiation, recurrent miscarriage or preterm delivery, morbid obesity, infertility, multiple prior pregnancies (>2), use of amiodarone, lithium or recent iodinated radio contrast; or age >30 years.

In women who meet the case-finding criteria, we measure serum TSH during the first trimester as the screening test for hypothyroidism. If the serum TSH is above 2.5 mU/L, we also measure TPO antibodies, and if the TSH is above the population and trimester-specific upper limit of normal, we measure free T4 to determine the degree of hypothyroidism

In women with normal TSH at initial screening but at particularly high risk for developing hypothyroidism during pregnancy (TPO antibody positive, post-radioiodine treatment, post-hemithyroidectomy, history of childhood exposure to high-dose irradiation of the head or neck region), we reassess TSH during pregnancy (eg, approximately every four weeks during the first trimester, and then once during each of the second and third trimesters).

All pregnant women with newly diagnosed, overt hypothyroidism (TSH above population and trimester-specific normal reference range [or above 4.0 mU/L when local reference range is not available] with low free T4) should be treated with thyroid hormone T4).

Patients with overt hypothyroidism should be started on close to full replacement doses (1.6 mcg/kg body weight per day), while patients with subclinical hypothyroidism may become euthyroid with lower doses and can therefore be started on approximately 1 mcg/kg daily. TSH should be measured every four weeks during the first half of pregnancy because dose adjustments are often required. The goal of treatment is to maintain TSH in the lower half of the trimester-specific reference range (or approximately <2.5 mU/L).

An increased rate of fetal loss and premature delivery has been reported in women with high serum anti-TPO antibody concentrations, and adverse outcomes occur at a lower TSH than in women without TPO antibodies. For pregnant women with a TSH between 2.6 and 4 mU/L, positive TPO antibodies, and a history of recurrent miscarriage, we suggest treatment with T4, typically 50 mcg daily. For pregnant women with TSH in this range and no prior history of miscarriage, we individualize the decision to treat based upon the presence of TPO antibodies and patient values and preference.

Women with preexisting hypothyroidism who are planning to become pregnant should optimize their thyroid hormone dose preconception. The goal preconception serum TSH level is between the lower reference limit and 2.5 mU/L. If possible, women already taking levothyroxine should have a normal serum TSH (ie, <2.5 mU/L) prior to becoming pregnant.

T4 dose requirements may increase during pregnancy in women with preexisting overt or subclinical hypothyroidism. For treated hypothyroid women who are newly pregnant, we suggest preemptively increasing their levothyroxine dose at the time of the positive pregnancy test (Grade 2B). We typically accomplish this by increasing the dose from once-daily dosing to a total of nine doses per week (double the daily dose two days each

week).

50 (12.25%) pregnant women with hypothyroidism had gestational hypertension which was statistically significant (p<0.001). Leung *et al* also reported that gestational hypertension was significantly more common in the overt (22%) and subclinical hypothyroid (15%) patients than in the general population (7.6%) and Casey *et al* reported that gestational hypertension occurred not only in overt hypothyroidism (36.1%) but also in subclinical hypothyroidism compared to general population. [16-18].

20 (4.9%) pregnant women with hypothyroidism had placental abruption which was statistically significant (p<0.0001) while Casey *et al* reported that pregnancies in women with subclinical hypothyroidism were three times more likely to be complicated by placental abruption and it was statistically significant (p=0.026) [16].

Thyroid disorders are common endocrine problems in pregnant women. It is now well established that both overt and subclinical thyroid dysfunction have adverse effect on maternal and fetal outcome. However, pregnant women with thyroid disease do not always develop symptoms, and when they do, these symptoms can sometime be attributed to pregnancy itself and can only get exaggerated. In these situations, accurate laboratory assessment of maternal thyroid function assumes a great importance.

There are several important findings from this prospective analysis of about 10,045women. First, hypothyroidism was identified in 408 (4.08%) women., 24(5.8%) women with hypothyroidism had preterm premature rupture of membranes (PPROM) which was found to be statistically significant with (p=0.007). 56 (13.7%) of hypothyroid patients had PROM and was statistically significant p<0.003. 40(9.8%) women with hypothyroidism had preterm delivery (p=0.02) which was not significant and 292 (71.00%) women delivered low birth weight babies and when compared with euthyroid pregnant women (p<0.0001). Idris *et al* performed a retrospective study of data from 167 pregnancies managed in the antenatal endocrine clinic and reported that maternal hypothyroidism at presentation and in third trimester may increase the risk of low birth weight [7].

81(20%) pregnant women with subclinical hypothyroidism had fetal distress during labour which was statistically significant (p<0.002). Rests of the findings were found not significant.

Conclusion

There is a need for early detection of hypothyroidism in early pregnancy so that adequate treatment could be started at the earliest in order to prevent poor maternal and fetal outcome. In a country like India where pregnancy rate is very high because of sheer magnitude of the population and where majority of women seek antenatal care at government institutions, diagnosing hypothyroidism at the earliest could have profound implication on the health of the nation.

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