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Original Research Article

Feto-Maternal Outcome Assessment in Pregnant women with Thyroid Disorders: An Observational Study

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Abstract

Aim: To evaluate the impact of thyroid disorders on the health of both fetus and the mother during pregnancy.

Material and Methods: This observational study was conducted in the Department of Obstetrics and Gynaecology, NMCH Patna, Bihar, India for one year. We recruited 294 antenatal women in third trimester admitted into the obstetric ward with singleton pregnancy for other obstetric indications. Informed consent was obtained from all subjects. Subjects were chosen irrespective of age, parity, residence and socioeconomic status. Women with multiple pregnancies, a known case of thyroid disorder, on any treatment or with any pre-existing medical disorder, such as diabetes mellitus, or cardiac or pulmonary disease were excluded. Routine hematological parameters and estimation of T3, T4 and TSH was conducted. Patients with a deranged thyroid profile were subsequently assessed for maternal and fetal complications. Infertility, family history of thyroid disorder, menstrual history, recurrent abortions, mean T3, T4, TSH levels, haemoglobin levels, maternal and fetal outcome were the main study variables.

Results: Of the 294 women screened, 46 (15.64%) had abnormal thyroid function. Prevalence of subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism was 7.48% ($n = 22$), 5.10% ($n = 15$), and 3.06% ($n = 9$), respectively demonstrating that the occurrence of subclinical hypothyroidism is more common during pregnancy. Of the 46 women with dysfunction, 23.91% had a history of irregular menstrual rhythm; 4.34% had history of infertility treatment; 4.34% had family history of thyroid disorder and 4.34% had history of recurrent miscarriage. There was no statistically significant association between any of these factors and the occurrence of thyroid disorder (p values were 0.655, 0.217, 0.079, and 0.752, respectively).

Conclusion: Association of maternal anemia, preeclampsia, increased cesarean delivery, presence of LBW babies, low Apgar score and increased number of NICU admission; is a major finding of this study.

Keywords: Hyperthyroidism, Hypothyroidism, Oligohydramnios, Pregnancy, Thyroid dysfunction

Introduction

Thyroid disorders are the second most common cause of endocrine dysfunction in women of child bearing age after diabetes mellitus. [1-3] Development of maternal thyroid disorders during early pregnancy can influence the pregnancy outcome and fetal development. It is now well established that not only overt, but also subclinical thyroid dysfunction has significant adverse effects on pregnancy and fetal development. [4-9] Iodine deficiency significantly raises the risk of still birth and abortion amongst pregnant women and also leads to decreased availability of iodine to the fetus. It retards the neurological development in fetus and also impairs the cognitive development in later age. [10,11] Neonatal Graves' disease can be seen because of the passage of TRAb to the fetus from the mother and may be seen in about 1-5% of the babies. [12] In view of potential adverse outcomes associated with maternal thyroid disorders, routine thyroid function screening has been suggested in all pregnant women. The present study is being undertaken to establish the maternal and fetal outcome in pregnant women with thyroid disorders.

Material and Methods

This observational study was conducted in the Department of Obstetrics and Gynaecology, NMCH Patna, Bihar, India for one year. We recruited 294 antenatal women in third trimester admitted into the obstetric ward with singleton pregnancy for other obstetric indications. Informed consent was obtained from all subjects. Subjects were chosen irrespective

of age, parity, residence and socioeconomic status. Women with multiple pregnancies, a known case of thyroid disorder, on any treatment or with any pre-existing medical disorder, such as diabetes mellitus, or cardiac or pulmonary disease were excluded. Routine hematological parameters and estimation of T3, T4 and TSH was conducted. Patients with a deranged thyroid profile were subsequently assessed for maternal and fetal complications. Infertility, family history of thyroid disorder, menstrual history, recurrent abortions, mean T3, T4, TSH levels, haemoglobin levels, maternal and fetal outcome were the main study variables. Uni variate analysis was conducted to assess co-relation of thyroid disorders with other clinical features like menstrual rhythm, infertility, family history of thyroid disorder and miscarriage. Estimation for TSH was conducted using the Enhanced Chemiluminescence method. Estimation of free T3 and free T4 was subsequently carried out when TSH levels were abnormal. Cut off values used for TSH were those indicated by the American Pregnancy and Thyroid Association: 1st trimester: 0.1–4.0mIU/L, 2nd trimester: 0.2–4.5mIU/L, 3rd trimester: 0.3 -5mIU/L. Normal free T4 level is 0.7 to1.8 ng/dl and free T3 level is 1.7 to 4.2 pg/ml. Patients with normal fT4 and high TSH were considered to have subclinical hypothyroidism (SCH); those with low fT4 and high TSH were considered to have overt hypothyroidism; those with normal fT4 and low TSH were considered to have subclinical hyperthyroidism; and those with high T4 and low TSH were considered to have overt hyperthyroidism. [7] Maternal co-morbidities pertaining to thyroid dysfunction include history of miscarriage, anemia (haemoglobin level less than 10 g/dl), preeclampsia (blood pressure more than 140/90 with proteinuria after 20 weeks gestation), gestational hypertension (blood pressure more than 140/90 without proteinuria after 20 weeks gestation), oligohydramnios (amniotic fluid Index ≤5), preterm delivery (delivery before completion of 37 weeks of gestation) and increased rate of caesarean section. Fetal outcomes include LBW (neonatal birth weight less than 2.5 kg), Low Apgar score (1-min Apgar less than 5), and increased NICU admission.

Data management and analysis was conducted using Statistical Package for the Social Sciences (SPSS Version 25). The categorical variables were assessed using Pearson chi-square test. Association of risk factors was calculated by binary logistic regression. The test was considered significant only when the p value is less than 0.05.

Results

Of the 294 women screened, 46 (15.64%) had abnormal thyroid function. Prevalence of subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism was 7.48% (n = 22), 5.10% (n = 15), and 3.06% (n = 9), respectively demonstrating that the occurrence of subclinical hypothyroidism is more common during pregnancy. Mean serum TSH levels among women with subclinical hypothyroidism, overt hypothyroidism and subclinical hyperthyroidism were 8.02 ± 1.25mIU/ml, 11.92 ± 5.34mIU/ml and 0.07 ± 0.03mIU/ml, respectively. Mean serum fT3 levels among women with subclinical hypothyroidism, overt hypothyroidism and subcli nical hyperthyroidism were 2.92 ± 0.454 pg/ml, 1.58 ± 1.43 pg/ml, and 4.16 ± 0.40 pg/ml, respectively. Mean serum fT4 levels among women with subclinical hypothyroidism, overt hypothyroidism and subclinical hyperthyroidism were 1.09 ± 0.30 ng/dl, 0.36 ± 0.24 ng/dl and 1.2 ± 0.10 ng/dl, respectively. (Table 1).

Table 1 Prevalence of thyroid disorders in 3rd trimester of pregnancy

Thyroid status	Prevalence	Mean TSH (mIU/L)	Mean fT4 (ng/dl)	Mean fT3 (pg/ml)
Subclinical hypothyroidism n = 22	7.48%	8.02 ± 1.25	1.09 ± 0.30	3.07 ± 0.56
Overt hypothyroidism n = 15	5.10%	11.92 ± 5.34	0.36 ± 0.24	0.81 ± 0.66
Subclinical hyperthyroidism n = 9	3.06%	0.07 ± 0.03	1.2 ± 0.10	4.1 ± 0.40

Of the 46 women with dysfunction, 23.91% had a history of irregular menstrual rhythm; 4.34% had history of infertility treatment; 4.34% had family history of thyroid disorder and 4.34% had history of recurrent miscarriage. There was no statistically significant association between any of these factors and the occurrence of thyroid disorder (p values were 0.655, 0.217, 0.079, and 0.752, respectively) (Table 2).

Table 2: Prevalence and associated risk factors in thyroid disorder

Risk factors	%(n)	P value
Irregular menstrual rhythm	23.91% (11)	0.655
History of infertility treatment	4.34% (2)	0.217
Family history of thyroid disorder	4.34% (2)	0.079
Miscarriage	4.34% (2)	0.752

Of the women with hypothyroidism, 26.08% had anaemia, and the association between occurrence of hypothyroidism and anaemia was statistically significant (p = 0.008). Preeclampsia was observed in 15.21% of women, and the association between occurrence of hypothyroidism and preeclampsia was statistically significant(p = 0.041). Cesarean delivery occurred in 26.08% of women with hypothyroidism having significant association (p = 0.012) and oligohydramnios (p = 0.072). Preterm delivery occurred in 4.34% of hypothyroidism and was not significantly associated with hypothyroidism. 32.60% had LBW babies, and the association between LBW and hypothyroidism was significant (p = 0.001). For 1-min Apgar score cut off value considered was 5, as an indicator for fetal asphyxia. 21.73% had babies with low Apgar scores which was significantly associated (p = 0.042). NICU admission 43.47% was significantly associated with hypothyroidism (p = 0.000). The risk of anemia in women with hypothyroidism is 4.8 times (95% CI = 1.5–15.8) higher than in women with euthyroidism. It is likely that hypothyroidism may add to the severity of anaemia. Risk of delivery of LBW babies is 6.3 times higher in women with hypothyroidism (95% CI = 2.03–19.5) than in women with euthyroidism. Risk of NICU admission and low Apgar score were 0.14 times (95% CI = 0.048–0.39) and 3.6 times (95% CI = 1.04–12.7) higher in babies born to women with hypothyroidism compared to those born to women with euthyroidism (Table 3).

Table 3 Association of maternal and fetal risk factors in women with hypothyroidism (n = 19)

Outcome %(n)	95% CI	Odds Ratio	p value
Anaemia 26.08% (12)	1.50–15.8	4.88	0.008
Preeclampsia 15.21% (7)	1.06–19.22	4.52	0.041
Preterm 4.34% (2)	0.253–22.54	2.39	0.447
Oligohydramnios 10.86% (5)	0.034–1.15	0.19	0.072
Caesarean section 26.08% (12)	1.39–14.38	4.47	0.012
Low birth weight (LBW) 32.60% (15)	2.03–19.54	6.30	0.001
Low Apgar Score 21.73% (10)	1.04–12.70	3.64	0.042
NICU admission 43.47% (20)	0.048–0.391	0.14	0.000

Discussion

As this study was conducted in 3rd trimester pregnant women, we do not report any outcomes for 1st or late 1st trimester. As per older guideline, considering TSH cut off values for each trimester as, 1st trimester: 0.1–2.5mIU/L, 2nd trimester: 0.2–3.0mIU/L, 3rd trimester: 0.3 -3mIU/L is questionable [2]. In view of scarcity of recent reports from India we follow standard ATA 2017 guideline. The observed prevalence of thyroid disorder in 3rd trimester of pregnancy in the present study is 15.64%, which is higher than prevalence observed in a study conducted by Weiwei Wang et al. (10.2%) [8] and Ajmani et al. (13.25%) [9]. Variations in different areas may be due to non-uniformity in the study setting or in laboratory techniques, personal human error, and differences in sample size. In India, the prevalence of hypothyroidism in pregnancy is much higher compared to that in Western countries. Iodine deficiency could be a contributing cause. The percentage of households consuming iodised salt in India, as per the Iodine Network Global score card 2010, is 51% [10]. Hashimoto's thyroiditis is a cause of hypothyroidism in iodine-sufficient areas, such as North America and Western Europe.

In the present study, the prevalence of subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism in pregnancy is 7.48, 5.10, and 3.06%, respectively (Table (Table1).1). This is in agreement with the findings of some Indian studies in which the prevalence of subclinical hypothyroidism and overt hypothyroidism is 6.1 and 0.7% respectively [11]. Another Indian study in 2016 reports prevalence of SCH 8% in 3rd trimester [12]. In a recent review and meta-analysis, prevalence rates reported were 0.50, 3.47, and 2.05% for overt hypothyroidism, subclinical hypothyroidism and isolated hypothyroxinaemia respectively [6]. We report mean serum TSH levels in women with subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism being 8.02 ± 1.25mI U/ml, 11.92 ± 5.34mIU/ml, and 0.07 ± 0.03mIU/ml respectively. Mean serum fT3 levels among women with subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism were 2.92 ± 0.454 pg/ml.,1.58 ± 1.43 pg/ml and 4.1 ± 0.40 pg/ml respectively. Mean serum fT4 levels among subclinical hypothyroid, overt hypothyroidism, and subclinical hyperthyroid women were 1.09 ± 0.30 ng/dl, 0.36 ± 0.24 ng/dl and 1.2 ± 0.10 ng/dl, respectively while a report from India in 2016 quotes reference values for TSH, fT3 and fT4 as 0.47–5.78 (uIU/ml), 0.24–3.61(ng/100 ml) and 0.47–5.1 (ng/100 ml) in 3rd trimester [12]. A recent review suggests that stricter criteria of TSH values with a 2.5 cut-off may be considered too low. Many women would be unnecessarily diagnosed as having SCH and may be subjected to the therapeutic burden of LT4 treatment [13]. Thyroid dysfunction results in an ovulatory cycles, luteal phase defect, high prolactin (PRL)

levels, and sex hormone imbalances. All of these factors may result in infertility and irregular menstrual cycles, as documented by various authors [14]. In the present study, among women with hypothyroidism, 4.34% had a history of infertility treatment, compared to 3.8, and 4.0% women with hypothyroidism observed in other studies [15, 16]. We observed that, 23.91% of women with hypothyroidism had irregular menstrual rhythm. Thyroid peroxidase (TPO) enzyme is responsible for the oxidation and organization of iodine, and for the formation of fT4 and fT3 hormones [17]. Thyroglobulin (TG) is a glycoprotein that acts as a substrate for synthesis and storage of thyroid hormones [18]. Autoimmune thyroid disorders present with antibodies to both resulting in hypothyroidism. Thyroid autoimmunity is associated with recurrent miscarriage likely to be due to generalized activation of the immune system and transplacental transfer of antibodies, causing fetal rejection [19, 20]. The presence of antibodies to thyroid peroxidase (TPO-Ab) or thyroglobulin in pregnancy is associated with significant increase in miscarriages, premature deliveries, gestational diabetes, postpartum thyroiditis and permanent hypothyroidism [21–23]. In the present study, miscarriage rate in women with hypothyroidism was 4.34%, which is similar to results of other studies, reporting rates of 5.6 and 5.0% [8, 15]. Hypothyroidism in pregnancy has immense relevance in clinical obstetric abnormalities.

First-degree relatives of patients with hypothyroidism due to Hashimoto's thyroiditis have a nine-fold higher risk of developing this disease compared to the general population [24]. Family history of thyroid disorder was seen in 4.34% of women with hypothyroidism, which is lower than prevalence observed in other studies: 12.7% [8]. In this study, no statistically significant association was observed between thyroid dysfunction and clinical obstetrics and gynecological features, including miscarriage, menstrual irregularity, family history of thyroid disorder, and infertility (Table 2). Iron deficiency causes impairment of the heme-dependent enzyme thyroid peroxidase, thereby limiting synthesis of thyroid hormones, which can lead to a reduction in circulating levels of tT3 and tT4. Iron repletion may reverse hypothyroidism [25]. In the present study, anemia was observed in 26.08% of women with hypothyroidism ($p = 0.008$) while other authors have observed occurrence of anemia in 4.2% of women with hypothyroidism [26]. In one study, prevalence of anemia in women with hypothyroidism was as high as 60% due to iron deficiency [27]. As per a report from North India anemia and hypothyroidism are very commonly associated [28]. The results of this study support an important clinical picture of an association between anemia and hypothyroidism. Hypothyroidism causes vascular smooth muscle contraction both in systemic and renal vessels, which leads to increased diastolic pressure, peripheral vascular resistance, and decreased tissue perfusion, which could be the pathophysiology of preeclampsia in hypothyroidism [29, 30]. Thyroid dysfunction can be associated with proteinuria, which is known to result in increased excretion of thyroxine and thyroid-binding globulins. Rare cases have been reported in which proteinuria is severe enough to result in losses of thyroid-binding globulins and thyroxine that cannot be compensated by the body [31–33]. In the present study, pre-eclampsia was observed in 15.21% of women ($p = 0.041$) with hypothyroidism. These results are comparable to those of other studies, in which preeclampsia was observed in 13.6% women with SCH and 14.7 in overt hypothyroidism [15, 34]. Increased rate of cesarean delivery is another outcome, observed in 26.08% ($p = 0.012$) of women with hypothyroidism. Other authors have reported rates of cesarean delivery of 22.9% in women with hypothyroidism [34]. The reason for the increased risk of cesarean delivery may be due to the associated pregnancy complications, such as hypertensive disorders, gestational diabetes, and preterm birth. Whether otherwise uncomplicated hypothyroidism increases risk of cesarean section warrants further study [35–37]. Some authors reported, pre-eclampsia ($p = < 0.001$), preterm labor ($p = 0.001$) and abruption ($p = 0.03$) being significantly related to hypothyroidism [38].

Complications that were observed to have lower prevalence in women with hypothyroidism in this study were oligohydramnios (10.86%) and preterm labor (4.34%). These findings are similar to those of other reports [20, 27]. Low birth weight is associated with hypothyroidism due to its association with preeclampsia. Reduced fetal thyroxine may cause disruption to the development of the pituitary-thyroid axis of the newborn, fetal pituitary growth hormone secretion, vascular responsiveness and maturation, and cardiovascular homeostasis in utero [39–41]. These factors are causative for the observation of reduced neonatal birth weight of offspring born to mothers with inadequately controlled hypothyroidism at initial presentation or at third trimester. In this study LBW was observed in 32.60% of women with hypothyroidism, as compared to 20% observed in another study [42]. NICU admission in thyroid dysfunction was 43.4%, which is similar to the rates of 46.6 and 42% [10, 42]. Low Apgar scores occurred in 21.73% of babies born to women with hypothyroidism, compared to 20% observed in another study [15]. We did not find Intrauterine death as a fetal complication of hypothyroidism, unlike the findings of one report [38]. In the present study, hypothyroidism was found to be significantly associated with LBW ($p = 0.001$) and NICU admission ($p = 0.000$) similar to study conducted by Gupta HP et al. [38].

Considering the results, we feel that estimation and diagnosis of thyroid parameters has high clinical relevance. However, there is an ongoing debate regarding cost-effectiveness of universal vs. targeted screening in pregnant women. Current recommendations suggest targeted TSH screening for women at high risk for thyroid disease before or during early pregnancy [7]. Recommendations also focus on TPO abs- positive and negative women. It states that risk of pregnancy loss is more in TPO abs-positives at 1st trimester cut off TSH 2.5 mU/L and more. In an RCT authors advice benefit of levothyroxine treatment around 9 weeks gestation [43]. They also document improvement in adverse pregnancy outcomes only in TPO abs-positive women with mild hypothyroidism (defined as a TSH > 2.5 mU/L) with thyroxin therapy. The Task Force advocates evaluation of TPO abs for asymptomatic women with higher TSH (2.5 mU/L) in first trimester. In this study we have not carried out TPO abs status of study subjects. Based on our sample size (n = 294) the study is 80.7% powered for 8 independent variable comparison for the outcome, which is adequate.

Conclusion

This study concludes that there is a high prevalence of thyroid dysfunction in pregnancy (15.64%), with the majority of women being subclinical hypothyroidism. Association of maternal anemia, preeclampsia, increased cesarean delivery, presence of LBW babies, low Apgar score and increased number of NICU admission; is a major finding of this study.

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