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ORIGINAL ARTICLE

Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome

Meenakshi Titoria Sahu · Vinita Das · Suneeta Mittal · Anjoo Agarwal · Monashis Sahu

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Abstract
Purpose Thyroid disorders are among the common endocrine problems in pregnant women. It is now well established that not only overt, but subclinical thyroid dysfunction also has adverse effects on maternal and fetal outcome. There are few data from India about the prevalence of thyroid dysfunction in pregnancy. With this background, this study aims to find prevalence of thyroid dysfunction in pregnancy and its impact on obstetrical outcome in Indian population.
Methods Six hundred and 33 pregnant women in second trimester were registered. Detailed history and examination was done. Apart from routine obstetrical investigations, TSH level estimation was done. If TSH level was deranged then free T_4 and thyroperoxidase antibody level estimation were done. Patients were managed accordingly and followed till delivery. Their obstetrical and perinatal outcomes were noted.
Results Prevalence of thyroid dysfunction was high in this study, with subclinical hypothyroidism in 6.47% and overt hypothyroidism in 4.58% women. Overt hypothyroids were prone to have pregnancy-induced hypertension ($P = 0.04$), intrauterine growth restriction ($P = 0.01$) and intrauterine demise ($P = 0.0004$) as compared to control. Cesarean section rate for fetal distress was significantly higher among pregnant subclinical hypothyroid women ($P = 0.04$). Neonatal complications and gestational diabetes were significantly more in overt hyperthyroidism group ($P = 0.03$ and $P = 0.04$, respectively).
Conclusions Prevalence of thyroid disorders, especially overt and subclinical hypothyroidism (6.47%) was high. Significant adverse effects on maternal and fetal outcome were seen emphasizing the importance of routine antenatal thyroid screening.

Keywords Pregnancy · Thyroid dysfunction · TSH screening

V. Das · A. Agarwal
Department of Obstetrics and Gynaecology,
King George's Medical University, Lucknow, UP, India

M. T. Sahu · S. Mittal
Department of Obstetrics and Gynaecology,
All India Institute of Medical Sciences, New Delhi, India

M. Sahu
Consultant Endocrinology, New Delhi, India

M. T. Sahu (✉)
SF-43, F-Block, Shastrinagar, Ghaziabad 201001, UP, India
e-mail: meenakshi_sahu@rediffmail.com

Introduction

Thyroid disorders constitute one of the most common endocrine disorders seen in pregnancy. In one study, overt hypothyroid disorder was found in 1.3 per 1,000 and subclinical disease in 23 per 1,000 [1]. Vanderpump and Tunbridge [2] reported prevalence of overt hypothyroidism between 1 and 2% and subclinical hypothyroidism in 8% of women. Women with hypothyroidism have relatively increased infertility, miscarriage rates and carry an increased risk for obstetric and fetal complications [3]. The main obstetric complications are anemia, preeclampsia, cardiac dysfunction, placental abruption and postpartum hemorrhage. Fetal complications include prematurity, low-birth weight (LBW), fetal distress in labor, fetal death, perinatal death and congenital hypothyroidism [4, 5].

Overt hyperthyroidism complicates 0.2% of all pregnancies. Subclinical hyperthyroidism is found in 0.4% of

pregnancies [6]. Maternal and fetal complications of hyperthyroidism include congestive heart failure, thyroid storm, preterm delivery, fetal growth restriction, still birth, fetal and neonatal thyrotoxicosis [7].

There is now increasing understanding of the association between not only overt, but also subclinical thyroid disorders and dysfunctions with adverse consequences on both obstetric outcome and long-term neurological development of the offspring.

All these data have been collected from studies in the developed countries. In developing countries, such as India, there is a paucity of available data in relation to thyroid dysfunction, especially subclinical thyroid dysfunction.

With this in mind, this prospective study was undertaken to determine the prevalence of thyroid disorders, both clinical and subclinical among pregnant Indian women attending antenatal clinic of two tertiary care teaching hospitals in Northern India and to see the effect of thyroid disorders on pregnancy outcome. It also aims to identify the importance of thyroid screening among pregnant women in our population.

Materials and methods

This study was a prospective evaluation of 633 women with singleton pregnancies carried out at King George Medical University, Lucknow; and All India Institute of Medical Sciences, New Delhi, India. Both of these hospitals are tertiary care teaching hospital that caters predominantly to low and middle socioeconomic group. This study was done over a period of 3 years from May 2005 to April 2008. Approval from the institutional ethics committee was obtained.

All healthy pregnant women with singleton pregnancy between 13 and 26 weeks of gestation were registered. Women were not enrolled if they planned to be delivered at another hospital, or not willing to be a part of study. Women were excluded if they had multi-fetal gestation, known chronic disorders, such as diabetes, hypertension or had previous bad obstetric history with known cause. Since the study was carried out in tertiary care centers catering to high-risk pregnancy, majority of women were in exclusion criteria.

Detailed history and examination were performed with special regard to maternal age, parity, smoking or alcohol consumption, gestational age, prior obstetric, medical, surgical history and clinical features suggestive of thyroid dysfunction. Informed consent to participate in this study was taken. Serum samples were collected in plain vial for TSH estimation. TSH was measured by CLIA (chemiluminescence's immunoassay) technique from a central laboratory. The normal range for TSH is 0.5–5.5 mIU/L for this laboratory. Values above 5.5 mIU/L or below 0.5 mIU/L were considered abnormal. Complete profile of thyroid hormone and TPO antibody estimation were not carried out in all pregnant women, for cost effectiveness in a low resource setting. Thus, free T4 estimation was done only when TSH value was abnormal. TPO-Ab estimation was done in overt hypothyroid group only. Women diagnosed with abnormal hormone values were referred to endocrinology clinic of respective institution for a simultaneous treatment and follow-up. Routine antepartum management was done and women were followed till delivery. Maternal outcome variables included were the occurrence of anemia, preeclampsia, gestational diabetes and obstetric complications, such as abruptio placenta, overall rate of cesarean section, cesarean section for fetal distress, assisted vaginal delivery and postpartum hemorrhage.

Measured neonatal outcomes included the incidence of LBW, prematurity, intrauterine growth restriction (IUGR), Apgar score at 1 min, neonatal intensive care unit admission and fetal demise.

Preeclampsia was defined as persistently elevated blood pressure (systolic $\geq$ 140 mmHg and diastolic pressure $\geq$ 90 mmHg on more than 2 occasions) with proteinuria. Anemia was taken as a value of hemoglobin <11 g% in peripheral blood. Gestational diabetes screening was conducted at 24–28 weeks of gestation with 50 g of glucose, blood sugar being taken after 1 h of glucose intake. If the blood sugar value was $\geq$140 mg%; then 100 g GTT (glucose tolerance test), using National Diabetes Data Group cutoff values, was carried out for diagnosis of gestational diabetes.

Intrauterine growth restriction was defined as birth weight less than tenth percentile for gestational age. LBW was defined as weight equal to or <2,500 g. Preterm delivery was defined as delivery before 37 completed weeks. Low Apgar score was considered if Apgar score at 1 min was <7.

Statistical analysis

Data were analyzed in five groups. Group I (controls) were euthyroid women, as defined by their normal TSH. Group II were women with overt (clinical) hypothyroidism defined as high TSH with low-free T4. Subclinical hypothyroidism (group III) also known as mild hypothyroidism was defined as TSH that is elevated in the presence of normal blood levels of thyroid hormone. Overt hyperthyroidism (group IV) group had an elevation in free T4 with an undetectable serum TSH. Subclinical hyperthyroidism (group V) was defined by a low serum TSH concentration in concert with normal thyroid hormone levels.

Analyses were performed using the statistical package of Epi-info statistical program by the center for disease control—epidemiology program office, Atlanta, Georgia and

Table 1 Maternal demographic characteristics

Group	Age (years)	Parity	Weight (kg)
I Control ($n = 552$)	25.9 ± 4	0.7 ± 0.9	54.3 ± 9.7
II (Clinical hypothyroidism) ($n = 29$)	29.6 ± 5.1*	0.6 ± 0.8	61.5 ± 11.3*
III (Subclinical hypothyroidism) ($n = 41$)	27.2 ± 4.1	0.98 ± 0.8	54.2 ± 9.4
IV (Clinical hyperthyroidism) ($n = 5$)	26.4 ± 4.6	1.2 ± 1.3	56.2 ± 14.3
V (Sub clinical hyperthyroidism) ($n = 6$)	25.2 ± 3.1	0.5 ± 0.8	46.8 ± 9

Values are expressed as mean ± SD

* $P < 0.05$ as compared to control

World Health Organization Global program on AIDS, Geneva, Switzerland.

The effects of thyroid dysfunctions were analyzed by comparing the frequencies of various outcomes in the above-mentioned groups. Continuous data were presented as mean ± SD and analyzed using unpaired, two-tailed student's *t* test. Proportional data were compared using Fisher's exact or Chi-square test where appropriate. The results from the logistic regression are expressed as relative risk (RR) and the corresponding 95% confidence interval and '*P*' values. $P < 0.05$ was considered statistically significant.

Results

Out of 633 women studied over a 3-year time span, 29 (4.58%) were overtly hypothyroid (group II), 41 (6.47%) were subclinical hypothyroid (group III), 5 (0.78%) were overt hyperthyroid (group IV) and 6 (0.94%) were subclinical hyperthyroid (group V). Rests of 552 women (87.2%) were euthyroid and acted as control (group I).

One hundred women were lost to follow-up and, therefore, their delivery outcome could not be recorded. Among pregnant women lost to follow-up, 84 women were from control group, 2 from overt hypothyroid group, 10 from subclinical hypothyroid group and 2 from overt hyperthyroid and subclinical hyperthyroid group each.

Maternal demographic characteristics are shown in Table 1. There was no difference in baseline demographics of pregnant women from the two clinical centers (data not shown). Maternal age and weight were high in pregnant women with overt hypothyroidism.

Table 2 illustrates the obstetrical variables assessed in antenatal period. The overt hypothyroid women were more

Table 2 Maternal medical and obstetrical variables assessed in antenatal period

S.No	Variables	Group I ($n = 552$)	Group II ($n = 29$)			Group III ($n = 41$)			Group IV ($n = 5$)			Group V ($n = 6$)		
		No. (%)	No. (%)	RR (CI)	*P* value	No. (%)	RR (CI)	*P* value	No. (%)	RR (CI)	*P* value	No. (%)	RR (CI)	*P* value
1	Anemia (Hb < 11 g%)	46 (8.3)	2 (6.9)	0.8 (0.2–3.3)	n.s.	6 (14.6)	1.8 (0.8–4.0)	n.s.	0	–	–	1 (16.7)	2.17 (0.26–18.2)	n.s.
2	Pregnancy-induced hypertension	43 (7.8)	6 (20.7)	3.6 (1.5–8.7)	0.04	4 (9.8)	1.3 (0.4–3.4)	n.s.	0	–	–	0	–	–
3	Gestational diabetes	18 (3.3)	1 (3.4)	1.1 (0.15–7.36)	n.s.	0	–	–	1 (20)	7.1 (0.8–60.35)	0.04	0	–	–
4	Intra uterine growth restriction	22 (4)	4 (13.8)	3.5 (1.1–11)	0.01	1 (2.4)	1.4 (0.3–5.3)	n.s.	0	–	–	0	–	–
5	Intra uterine demise	7 (1.4)	3 (13)	7.6 (2.7–21.6)	0.0004	1 (2.5)	6.9 (1.6–28.7)	n.s.	–	–		–	–	–

RR relative risk, *CI* 95% confidence interval

prone to have pregnancy-induced hypertension ($P = 0.04$), IUGR ($P = 0.01$) and intrauterine fetal demise ($P = 0.0004$). One maternal death occurred in this group and it was a case of severe anemia with myxedema coma. Patient had been non-compliant with the treatment. There were no maternal deaths in any of the other groups. The percentage of anemia was more in subclinical hypothyroid, but it was statistically insignificant (Table 2).

The overall rate of cesarean section was high in all groups and cesarean section for fetal distress was carried out in significantly higher number of women having subclinical hypothyroidism ($P = 0.04$).

Maternal thyroid dysfunction, especially hypothyroidism is found to be associated with bad obstetric history. In this study, no significant association was noted (data not shown).

The overt hyperthyroid women had significant presence of gestational diabetes ($P = 0.04$) and neonatal complications ($P = 0.03$) in the form of birth asphyxia needing admission to NICU, jaundice, hypoglycemia, neonatal morbidity and mortality (Table 3). The mean birth weight in control group was $2{,}848.5 \pm 463$ g, whereas in groups II, III, IV and V it was $2{,}654.8 \pm 722.8$, $2{,}605 \pm 699.6$, $2{,}866.6 \pm 230.9$ and $2{,}700 \pm 435.8$ g, respectively. The difference among groups was non-significant.

In limited cases, cord TSH and neonatal day-3 TSH screening was performed and no significant association was found between them and maternal TSH. TPO-Ab was positive in 17.2% ($n = 5$) of overt hypothyroid women.

Discussion

Our study presents the first data on overt as well as subclinical thyroid dysfunction among pregnant women from North Indian subcontinent. The most important finding in this study is the high prevalence of subclinical hypothyroidism (6.47%) among pregnant women. The relevance of this finding is substantiated by the adverse perinatal outcome. Most of the studies on thyroid dysfunctions among pregnant women are from our western counterpart. Few studies have been done among South Asian pregnant women reporting increased risk of thyroid dysfunction [8]. It was, therefore, important to conduct the present study because the findings of other studies may not apply to an Indian population.

As seen in previous studies, untreated or uncontrolled overt hypothyroidism during pregnancy may increase the incidence of maternal anemia, preeclampsia, spontaneous abortion, LBW, fetal death or still birth [3, 5]. In this study also the incidence of preeclampsia ($P = 0.04$), IUGR ($P = 0.01$), fetal demise ($P = 0.0004$) was significantly high in overt hypothyroid group. The maternal age of clinical

Table 3 Perinatal outcome: delivery and neonatal variables

S. No	Variables	Group I ($n = 468$)	Group II ($n = 27$)			Group III ($n = 31$)			Group IV ($n = 3$)			Group V ($n = 4$)		
		No. (%)	No. (%)	RR (CI)	*P* value	No. (%)	RR (CI)	*P* value	No. (%)	RR CI	*P* value	No. (%)	RR (CI)	*P* value
1	Preterm delivery	22 (5.4)	1 (4.7)	0.8 (0.1–6.3)	n.s.	3 (10.3)	1.9 (0.6–5.8)	n.s.	0	–	–	0	–	–
2	Cesarean for fetal distress	47 (11.5)	4 (19)	1.7 (0.6–4.9)	n.s.	7 (24)	2.8 (1.2–6.6)	0.04	0	–	–	0	–	–
3	Overall cesarean rate	149 (36.6)	11 (52.3)	1.8 (0.8–4.2)	n.s.	13 (44.8)	1.4 (0.6–2.7)	n.s.	2 (66.6)	3.4 (0.3–37.2)	n.s.	2 (50)	1.7 (0.2–12)	n.s.
4	Apgar score < 7 at 1 min	22 (5.3)	3 (11.1)	2.1 (0.7–6.5)	n.s.	4 (12.9)	2.4 (0.9–6.4)	n.s.	0	–	–	0	–	–
5	Neonatal complication	24 (5.1)	3 (11.1)	2.2 (0.7–6.7)	n.s.	4 (12.9)	2.4 (0.9–6.6)	n.s.	1 (33.3)	8.9 (0.8–95.1)	0.03	0	–	–

RR relative risk, *CI* 95% confidence interval

hypothyroid group was high which may be due to the difficulty associated with fertility. Similarly increased weight in this group could be because of the disease per se. TPO-Ab was positive in 17.2% of overt hypothyroid women. Since TPO antibody was done only in selective cases, further studies are needed to document relation of TPO-Ab positive pregnant women with perinatal outcome in context to Indian population.

Subclinical hypothyroidism is predominantly seen in women and progression from subclinical to overt hypothyroidism occurs in 3–20% of persons with thyroid autoimmunity [9–10]. In the past studies, it has been shown that these women have higher incidence of preterm delivery, IUGR, placental abruption and perinatal and neonatal morbidity and mortality [11–13]. The overall rate of cesarean section was high in all groups; reason being these were tertiary care teaching hospitals where referrals are sent. Cesarean section as an indication for fetal distress was significantly done among women of subclinical hypothyroid group ($P = 0.04$). This reinforces the importance of detecting subclinical thyroid disorders in pregnancy and to be aware of its maternal and fetal complications.

Although hyperthyroidism in pregnancy is uncommon, effects on both mother and child are critical. Therefore, prompt diagnosis and treatment are of paramount importance in preventing maternal and fetal morbidity and mortality. In this study, gestational diabetes was significantly present in clinical hyperthyroid group. Similarly, neonatal complications in overt hyperthyroidism group were significantly high ($P = 0.03$). The same findings were also observed in past studies [7, 14]. Subclinical hyperthyroidism as characterized by a low-serum TSH concentration in concert with normal thyroid hormone levels is also associated with poor obstetric outcome [14, 15]. However, in this study, no significant finding was seen as the sample size was small and disease is comparatively infrequent.

To accept the weaknesses of our study, we did only TSH test initially and then checked FT4 or TPO-Ab when the TSH was abnormal. There is a possibility that this strategy would have missed patient with isolated hypothyroxinemia (low FT4 and normal TSH) and women who are antibody positive and euthyroid. A weakness of our analysis is small sample size with infrequency of disease, such as hyperthyroidism; therefore, the confidence intervals around our risk estimates are relatively wide especially for outcomes, such as gestational diabetes, fetal demise and neonatal complications. Although no significant association was found between maternal TSH and cord TSH; however, cord blood TSH were done in very limited cases. Follow-up beyond newborn period was not possible because after discharge most infants either did not come for follow-up or they were seen in Pediatric clinic.

At present, there is no available recommendation for detecting or screening thyroid dysfunction among pregnant women in India. Recent consensus guidelines do not advocate universal thyroid function screening during pregnancy, but recommend testing for high-risk pregnant women with a personal history of thyroid or other autoimmune disorder or with a family history of thyroid disorders [16].

Our study shows a high prevalence of thyroid dysfunction, especially overt and subclinical hypothyroidism among Indian pregnant women with associated adverse perinatal outcome. Based on the results of the present study, we, therefore, suggest for a decrease threshold for screening and detection of thyroid dysfunction among Indian pregnant women attending routine antenatal clinic and to be potentially aware of associated maternal and fetal complications.

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Conflict of interest statement None.

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