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Original Article

SUBCLINICAL HYPOTHYROIDISM IN PREGNANCY; IS THERE A NEED FOR PHARMACOLOGICAL INTERVENTION?

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ABSTRACT

Objective: To find the prevalence of subclinical hypothyroidism in the first trimester of pregnancy and to compare the maternal and perinatal outcome in them with euthyroid mothers.

Methods: The present study was a prospective observational case-control study done in a tertiary hospital over the period of one and half years. Pregnant women in the first trimester of pregnancy were tested for Thyroid Stimulating Hormone (TSH) levels and those who had TSH>2.5mIU/l, free T3 and free T4 estimation was carried out on the same sample. A total of 171 women could be followed up till delivery and their first-trimester thyroid profile was available for analysis. They were grouped into two groups, Group 1: all women with TSH level>2.5 mIU/l, considered to be hypothyroid (n=79), Group 2: women with euthyroid status with TSH levels 0.1 to 2.5 mIU/l (n=95). All the neonates delivered in the first group had cord blood TSH estimation.

Results: In the study period, there were 2632 deliveries. The number of pregnant women with first trimester TSH levels>2.5 mIU/l were 79, giving the prevalence rate of 3 % for subclinical hypothyroidism during pregnancy. The obstetric complications observed were gestational hypertension 3.8%, gestational diabetes 6.3%, placenta praevia1.3% and preterm delivery 7.6%. The perinatal complications included Intrauterine growth restriction (IUGR) 1.3%, Low Birth Weight (LBW) 3.8%, perinatal asphyxia 2.5% and neonatal hypothyroidism 1.3%. Only preterm delivery appeared to be significantly associated with subclinical hypothyroidism.

Conclusion: The observed complication rates were much similar, in fact, lesser with gestational diabetes, pregnancy hypertension, IUGR, LBW compared to global and Indian prevalence rates. This indicates that the cut-off for diagnosing subclinical hypothyroidism should be derived from TSH assays from the local geographic population and should guide the treating physician to establish appropriate TSH ranges where definite therapeutic intervention is required to improve the maternal and foetal outcome.

Keywords: Thyroid hormones, Subclinical hypothyroidism, Pregnancy complications, Levothyroxine

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INTRODUCTION

After diabetes, hypertension and anaemia, thyroid dysfunction constitutes for the majority of medical disorders in pregnancy. Among maternal thyroid disorders, hypothyroidism (2.5%) is more prevalent than hyperthyroidism (1 to 0.4%) [1]. There is a significant change in thyroid hormone metabolism in pregnancy. In a woman with poor thyroid reserve, thyroid deficient state occurs due to increased urinary loss of thyroxine due to increase in glomerular filtration rate (GFR) and placental transfer of thyroxin to the growing fetus. Hence, there is increased requirement for thyroid hormone during pregnancy (one and half times) and in the first trimester of pregnancy, fetus depends upon placentally transferred maternal thyroxin for its neuronal development, deficiency of which can result in mental retardation and cretinism [2]. Untreated mothers also can develop abortions, preeclampsia, abruptio placenta and preterm labour [3]. The effects on the baby include intrauterine growth restriction, intrauterine death, problems due to prematurity, increased admission rates to NICU [4]. Congenital hypothyroidism is known to occur more often in women with hypothyroidism in pregnancy and has a greater impact in the cognitive and scholastic performance of the child in future [5, 6].

There is no doubt that thyroxine replacement therapy for mothers with overt hypothyroidism (high TSH levels and low serum T4 concentration) improves maternal and foetal outcome. However same is controversial with subclinical hypothyroidism, where only TSH value is higher, but the thyroid hormones (T3 and T4) are within physiological range. Available evidence lacks potential benefits of thyroxine to reduce obstetric and neonatal complications in this special cohort of biochemical diagnosis of hypothyroidism without any symptoms of thyroid deficiency and supplementing them with thyroid medication simply may "medicalise" women with an intervention which should have been otherwise not necessary.

This prospective case-control study was carried out with an objective to find the prevalence rate of subclinical hypothyroidism in the first trimester of pregnancy and its implication on maternal–fetal–neonatal outcome in comparison to a cohort of pregnant women with normal thyroid status.

MATERIALS AND METHODS

The present study was a prospective observational case-control study done in the Department of Obstetrics and Gynaecology, Kasturba Medical Hospital which is a tertiary care center of Kasturba Medical College, Manipal serving more than 20 lakh population of surround districts. The study period extended between Jan 2015 to June 2016. Women with a singleton pregnancy who had first-trimester thyroid function tests were the target population. The duration of pregnancy was calculated from the date of last menstrual period (LMP) and cross verified with their first-trimester CRL values. Women with multifoetal gestation threatened and missed abortion, preexisting known medical disorders such as chronic hypertension, thyroid disorders were excluded from the study. All individuals signed informed consent prior to their enrollment in the study. The study complied with the Declaration of Helsinki and Departmental Scientific Committee gave permission to conduct the study after verifying local biomedical research regulations.

The venous blood of participating woman was collected in fasting status. The sample was sent to the main laboratory within 30 min of obtaining the sample. The serum was analysed for thyroid parameters (TSH initially and Free T3 and Free T4 if TSH was found

to be>2.5 mIU/l) using COBAS 6000 system. Similarly, cord blood TSH was estimated only when maternal TSH was in the higher range.

A total of 171 women could be followed up till delivery and their first-trimester thyroid profile was available for analysis. They were grouped into two groups, Group 1: all women with TSH level>2.5 mIU/l, considered to be hypothyroid (n=79), Group 2: women with euthyroid status with TSH levels 0.1 to 2.5 mIU/l (n=95). We used a cut-off value for TSH levels as 2.5 mIU/l to differentiate between hypo and euthyroid status according to the guidelines established by American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum [7].

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) for Windows (Version 16.0. Chicago, SPSS Inc.). Descriptive statistics included estimation of mean, standard deviation and range (minimum to maximum values). Histogram and normal curve feature of SPSS software is used to display data distribution graphically. Student T-test was used to test the statistical significance of different means and standard deviation of numerical data. Similarly, Chi square test was used for categorical data. A p value of<0.05 was considered to be significant. Obstetrical complications were visually presented by using graph feature of Microsoft excel.

Sample size estimation

A study reported in Indian Journal of Clinical Biochemistry showed that the first-trimester mean±standard deviation of measured TSH levels is 1.71±1.38mIU/l [8]. We decided that if the mean value exceeds 2.5 mIU/l (upper range for thyroid stimulating hormone in the first trimester) of sampled population, then it will be significantly different from the normal population. Accordingly, we estimated sample size to show the desired level of power of 90% and level of significance 0.05, by using the formula,

$$N = [(z\alpha+z\beta)\sigma/(\mu1-\mu2)]^2$$

Where zα = 1.96 (critical value that divides the central 95% of z distribution from 5% in the tails),zβ = 1.28 (critical value that separates the lower 10% of distribution from upper 90%),σ = standard deviation (1.38), μ1-μ2 = difference of two means (2.5-1.71 = 0.79).

Accordingly, it was estimated that 32 patients are required, and our present sample size of 79 patients is more than adequate to prove the hypothesis.

RESULTS

In the study period, there were 2632 deliveries. The number of pregnant women with first trimester TSH levels>2.5 mIU/l were 79 (Group I) giving the prevalence rate of 3 % for hypothyroidism during pregnancy. We used 2.5 mIU/l as a cut-off, as this is now universally accepted standard and approved by American Thyroid Association for thyroid disease [7].

Initially we performed only TSH levels in first trimmest of pregnancy and only when its level crossed the cut off, women were further subjected for free T3 and free T4 estimation (total T3 and total T4 were not considered as their level vary significantly in the first trimester because of physiological stimulation of thyroid glands by human chorionic gonadotrophin which is elevated in the first trimester of pregnancy). Hence in the level of free thyroxine in serum is a better predictor thyroid status rather than total thyroxine [9].

Table 1 shows complete thyroid profile of women diagnosed to have hypothyroidism in pregnancy.

Table 1: Thyroid profile of pregnant hypothyroid women (n=79)

Serum biochemistry	mean±SD	Minimum value	Maximum value
TSHmU/l	5.14±1.14	2.90	8.23
Free T3picomole/l	4.51±0.70	3.42	6.62
Free T4picomole/l	15.33±1.79	11.45	20.68

SD: Standard Deviation

Table 2 shows the demographic parameters. From this table, it can be inferred that hypothyroid pregnant women likely deliver earlier than euthyroid women and also their newborn will weigh lower compared to normal population.

Table 2: Maternal characteristics

Demographic parameter	Cases (n=79)	Controls (n=95)	P Value
Age in years (mean±SD)	27.5±3.6	28.3±3.2	0.12 (NS)
Primigravida	43	55	0.64 (NS)
Multigravida	36	40	
Gestational Age at delivery (weeks)	38.4±1.1	39.0±0.09	<0.001 (S)
Mean Birth Weight in Kg (mean±SD)	3.03±0.36	3.27±0.29	<0.0001 (HS)

SD: Standard Deviation, NS: Not Significant, S: Significant, HS: Highly Significant

Table 3 shows maternal outcomes such as gestational hypertension (blood pressure>140/90 mmHg in absence of proteinuria and any imminent symptoms of eclampsia and normal lab parameters), gestational diabetes (defined as any one value abnormal with standard WHO 75 grams oral glucose tolerance test), placental praevia (diagnosed by antenatal ultrasound) and preterm birth (delivery at gestational age less than 37 completed weeks) in cases and control. From table 3 and fig. 1, it can be seen that mothers with hypothyroidism had significantly higher rate of preterm delivery compared to euthyroid mothers.

Table 3: Pregnancy outcome

Obstetric complication	Cases (n=79)	Controls (n=95)	P Value
Gestational Hypertension	3 (3.8%)	4 (4.2%)	0.89
Gestational Diabetes	5 (6.3%)	2 (2.1%)	0.15
Placenta Praevia	1 (1.3%)	0 (0%)	0.27
Preterm Delivery	6 (7.6%)	1 (1.1%)	0.028

P value of<0.05 is considered significant

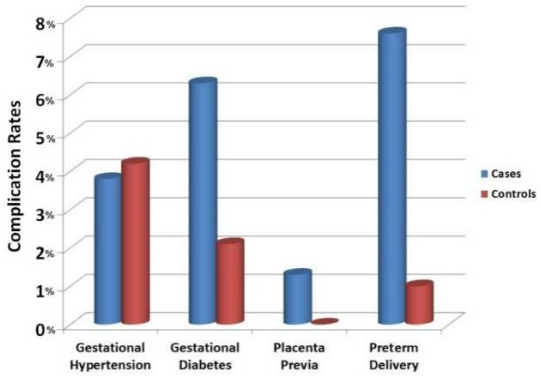

Fig. 1: Obstetric complication rates in cases and controls

Table 4 shows perinatal outcome in cases and controls. Intrauterine growth restriction was considered to be present when the expected fetal weight fell below 10th centile for the corresponding gestational age. We defined low birth weight as neonatal weight less than 2.5 kg. Perinatal hypoxia was said to exist when APGAR at 5 min was less than 3, need for assisted ventilation and admission to intensive neonatal care unit. There was one case of neonatal hypothyroidism in the hypothyroid group (cord blood TSH>20 mIU/l), however, the baby did not have serious complications and was discharged in time. Finally, the analysis showed that there was no significant difference between various perinatal outcomes in both the groups.

Table 5 shows the results of cord blood TSH levels in 79 hypothyroid mothers. There was one neonate whose cord blood TSH was>20 mIU/l. However neonatal T3 and T4 were within the normal range on the first and fourth day of life and baby was discharged with advice for regular follow up.

Table 4: Perinatal outcome

Perinatal complication	Cases (n=79)	Controls (n=95)	P Value
Intrauterine growth restriction	1 (1.3%)	2 (2.1%)	0.67
Low Birth Weight	3 (3.8%)	4 (4.2%)	0.89
Perinatal Asphyxia	2 (2.5%)	2 (2.1%)	0.85
Neonatal Hypothyroidism	1 (1.3%)	0 (0%)	0.23
P value of<0.05 is considered significant.			

Table 5: Descriptive statistics of cord blood TSH levels (mIU/l) in 79 newborn babies

Mean	7.98
Median	7.39
Std. Deviation	3.77
Range	1.28–21.0
Percentiles	
10th Centile	3.02
50th Centile	7.39
90th Centile	12.85

Fig. 2 shows the histogram of cord blood TSH indicating that a good number of newborns had TSH levels on either side of the mean. This means that if cut off value for neonatal TSH level is lowered, the number of babies to be screened for neonatal hypothyroidism increases.

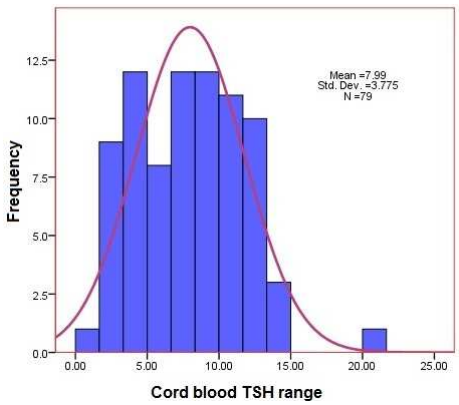

Fig. 2: Cord blood TSH levels in 79 newborns

DISCUSSION

There is a wide geographical variation of prevalence of hypothyroidism ranging between 0.3 to 0.5% in western countries, more so in developing countries like India. Even in India the prevalence rate varies across different states, as many of rural population suffer from dietary iodine deficiency, further aggravated by the presence of goitrogens in the diet, micronutrient deficiency such as selenium and others [10, 11]. Pre-existing thyroid hormone deficiency is further aggravated during pregnancy as thyroid hormone requirements are increased during gestation not only by the mother but also by the growing foetus. In addition, there is increased renal clearance of iodide [12]. Therefore, it is very important to screen expectant mothers for thyroid deficiency, though the routine investigations during the antenatal period does not include thyroid panel.

Estimation of TSH is the primary screening tool, but its levels are affected by HCG hormone (human Chorionic Gonadotrophin). Because of its alpha chain similarity with TSH, hCG has a weak stimulatory effect on the maternal thyroid gland, making it to enlarge physiologically and produce more thyroxine [13]. The net effect is suppression of TSH levels and hence a different cut off is required to make the diagnosis of hypothyroidism in pregnancy.

The reference ranges for thyroid hormone profile varies from laboratory to laboratory. If laboratory specific trimester ranges are not available, it is desirable to follow Regulation 14.2 of ATA (American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum) guidelines, which give the reference values for the euthyroid state during pregnancy (table 6) [7].

In our 79 cases, first trimester TSH level was higher than the recommended cut-off of 2.5 mIU/l, thereby substantiating the diagnosis of maternal hypothyroidism. As from table 1, when individual free T4 levels were looked into, none of them had low fT4 levels (cut-off 10.3 picomole/l) and this implies that all of our cases were belonging to the category of subclinical hypothyroidism. After consultation with thyroid physician, it was decided not to start them on any thyroxine replacement as their T3 and T4 levels were within

acceptable limits. However, all of them were advised to consume iodized salt for cooking. Even WHO recommends daily iodine intake of 250µg iodine for pregnant women, which is considerably higher than the recommended 150µg per day for general non-pregnant population [14]. Currently, the role of therapy with levothyroxine in subclinical hypothyroidism is controversial. According to Cochrane 2013 review, probably, the only indication to start thyroxine therapy is those cases of subclinical hypothyroidism with Anti-Thyroid Antibody positive status to improve health outcomes [15].

Table 6: Ranges of normal thyroid functions during pregnancy

Thyroid profile	First trimester	Second trimester	Third trimester
1. TSH	0.1 to 2.5 mIU/l	0.2 to 3.0 mIU/l	0.3 to 3.0 mIU/l
2. Free T4	0.8 to 1.2 ng/dl	0.6 to 1 ng/dl	0.5 to 0.8 ng/dl
Equivalent other Units	8 to 12 ng/l	6 to 10 ng/l	5 to 8 ng/l
	10.3 to 15.5 pm/l	7.7 to 12.9 pm/l	6.5 to 10.3 pm/l
3. Free T3	4.1 to 4.4 pg/ml	4 to 4.2 pg/ml	Not Reported
Equivalent other Units	4.1 to 4.4 ng/l	4 to 4.2 ng/l	Not Reported
	6.3 to 6.8 pm/l	6.2 to 6.5 pm/l	Not Reported
4. Total T4	6.5 to 10.1 mcg/dl	7.5 to 10.3 mcg/dl	6.3 to 9.7 mcg/dl
5. Total T3	97 to 149 ng/dl	117 to 169 ng/dl	123 to 162 ng/dl

mIU/l: micro international unit per liter, ng/dl: nanogram per deciliter, pm/l: picomole per liter, mcg/dl: microgram per deciliter

Table 7: Prevalence and maternal–foetal outcome in various Indian Studies

Author	Year of Study	Place of Study	Prevalence of Hypothyroidism	Obstetric and perinatal outcome	Reference
Ajmani SN *et al.*	2014	New Delhi	48 with hypothyroidism out of 400 women (12%)	Maternal: Anemia (12.5%), Preeclampsia (10%), Abruption (4.2%), GDM (2.1%), PPH (6.3%) Foetal: IUGR (41.7%), LBW (16.7%), Foetal Distress (10.4%)	[29]
Aggarwal N *et al.*	2014	Chandigarh	197 with hypothyroidism out of 1791 women (10.9%)	Maternal: PROM (4%), Hypertension (12%), GDM (2%), Preterm labour (16%), Abruption (1%) Foetal: SGA (16%), Jaundice (14%), RDS (1.5%)	[30]
Pavanaganga *et al.*	2015	Bangalore	168 with hypothyroidism out of 1663 women (10.1%)	Maternal: Pre-eclampsia (21.8%), GDM (6.4%), Preterm labor (7.1%) and anemia (5.8%) Foetal: IUGR (7.7%), SGA (14.7%), IUD (3.3%)	[31]
Singh A *et al.*	2015	Telangana	30 with hypothyroidism out of 400 women (7.5%)	Maternal: Miscarriage (6.7%), Anemia (10%), Preeclampsia (33.3%), Preterm labor (3.3%), PPH (3.3%) Foetal: IUGR (16.7%)	[32]
Kalpesh K *et al.*	2015	Ahmedabad	46 with hypothyroidism out of 350 women (13.1%)	Maternal: Preterm (26%), Anemia (21.7%), Preeclampsia (10.8%), Abruption (2.1%), GDM (8.6%), and PPH (10.8%) Foetal: IUGR (6.5%), LBW (34.7%), Stillbirth (2.1%)	[33]
Nirmala C *et al.*	2015	Trivandrum	78 cases and 78 controls	Maternal: Abortion (23.1%), Gestational Hypertension (35.9%), PPH (12.8%), Preterm Delivery (25.6%) Foetal: LBW (28.2%),	[34]
Sreelakshmi U *et al.*	2015	Bangalore	101 with hypothyroidism out of 4864 women (2.07%)	Maternal: Threatened abortion (44.6%), preterm delivery (24.8%) Foetal: IUGR (5%), IUD (15%)	[35]
Nath J *et al.*	2015	Moradabad	60 with hypothyroidism out of 1000 women (6%)	Maternal: Abortion (4.5%), Preeclampsia (7.8%), Abruption (2.3%), Preterm (2%), PPH (1.%) Foetal: Prematurity (2%), LBW (2/4%), IUGR (1.8%), Stillbirth (0.9%), neonatal Sepsis(1.5%)	[36]
Saraladevi *et al.*	2016	Warrangal	116 with hypothyroidism out of 1000 women (11.6%)	Maternal: Preeclampsia 9.37%, Preterm delivery 7.81%, Abortions 4.68%, Abruptio placenta 1.56% Foetal: IUGR 6.25%,Low birth weight 4.68%, Still birth 1.56%	[37]
Patwari M *et al.*	2016	Assam	75 cases and 75 controls	Significantly higher caesarean rates (48%), low birth weight (500 grams less), higher incidence of birth asphyxia (30.4%).	[38]
Chunchaiah S *et al.*	2016	Bangalore	81 with hypothyroidism out of 800 women (10.1%)	Maternal: Abortion (11.9%), Preeclampsia (13.6)%, GDM (8.5%), Anemia (8.4%), Preterm labour (5%) Foetal: IUGR (3.8%), Still birth (1.7%)	[39]
Patel RD *et al.*	2016	Ahmedabad	40 with hypothyroidism out of 500 women (8%)	Maternal: Abortion (7.5%), Preeclampsia (10%, GDM (8.5%) Foetal: IUGR (13%), Neonatal jaundice (60%)	[40]
Rajalakshmi MS *et al.*	2016	Imphal	10 with hypothyroidism out of 300 women (3.3%)	Maternal: Anemia (80%), Abortion (3.3%), Preeclampsia (5.5%), GDM (2.7%) Foetal: IUGR (0.7%)	[41]
Present Study	2016	Manipal	79 with hypothyroidism out of 2632women (3%)	Gestational Hypertension (3.8%), GDM (6.3%), Placenta praevia (1.3%), Preterm (7.6%) Foetal: IUGR (1.3%), LBW (3.8%), Perinatal Asphyxia (2.5%), Neonatal hypothyroidism (1.3%)	-

Table 7 shows obstetric and perinatal outcome from different studied conducted in India in different parts of the country. It can be seen that there are complications both with respect to mother and baby as a result of subclinical hypothyroidism and this warrants close monitoring of the pregnancy even with fT4 and fT3 in normal ranges.

Though in our study, the incidence of preterm labour was significantly more than controls (7.6% vs. 1.1%), it is not appreciably more than the general incidence of preterm labour (11.1%) [16]. The reported national incidences of hypertensive disorders of pregnancy (10.08%) [17], Gestational Diabetes (13.4%) [18], Anemia complicating pregnancy (50%) [19], placenta previa (1.01%) [20], IUGR (16.8%) [21], Low Birth Weight (20%) [22], Birth asphyxia (6%) [23], are relatively higher, compared to the statistics in maternal subclinical hypothyroidism, meaning that subclinical hypothyroidism with normal free T3 and T4 levels may not significantly contribute to the incidence of above-mentioned complications.

In non-pregnant women, a TSH range of 4 to 5 mIU/l is considered as an upper limit, however the majority of the studies including American Thyroid Association (2011) suggest that lower range is recommended for the pregnant population as already mentioned earlier. But there are studies who have found a much higher range of TSH levels in pregnancy without any undue effects on mother and baby. TSH data from cohorts of pregnant women without any preexisting thyroid disease have shown higher ranges, for example, upper limit of 4.87 mIU/l in China [24], 5.00 mIU/l in India,5.09 mIU/l [25] in US [26], and 5.5 mIU/l in UK [27].

Pushing down the limit to 2.5 mIU/l may apparently increase the incidence of gestational hypothyroidism as high as 28% causing undue worry to the obstetrician and apprehension to the patient [28]. There is a strong notion that one should not follow universal guidelines, instead, should depend upon customized ranges based on TSH levels of the local population.

To find the effect of thyroxine replacement for subclinical hypothyroidism in pregnancy, a recent Cochrane Review [15] in the year 2013, analysed the results of four randomised controlled trials critically and it was opined that data is too insufficient to make any recommendations intervention with thyroxine therapy in obstetric practice. Another well-designed study did not observe any significant differences in the study group (232 women who received thyroxine for high TSH and normal T3 and T4 values) and placebo group (264 women who did not receive thyroxine for the same thyroid profile) with regard to preterm delivery, birth weight and child's cognitive function at 3rd year of life [42], They opined that thyroxine intervention is unlikely to provide any measurable benefit if median TSH concentration falls below 3.8 mIU/l. Even in non-pregnant population, treatment with thyroxine has not provided any measurable benefits, such as improvement of lipidemic profile and systemic inflammatory markers and treatment should be started only if TSH concentration is above 10 mIU/l [43].

Currently National guidelines advocates screening for hypothyroidism for those women who belong to high-risk category (mothers residing iodine deficiency area, obesity, symptoms of thyroid dysfunction or presence of goiter, positive family history, bad obstetric history, previous recurrent miscarriages, preterm delivery, intrauterine demise, preeclampsia-eclampsia, abruptio placentae, treatment with amiodarone or lithium) [44]. The cut-offs are as same recommended by American Thyroid Association. The recommendation states that the pregnant woman should be started on levothyroxine 25 µg/day for TSH range of 2.5 to 10 mIU/l and 50 µg/day if initial TSH is>10mIU/l. Postpartum treatment will be continued at recommended doses for those with TSH>10mIU/l. For women with TSH between 2.5-10mIU/l, treatment should be discontinued after delivery. If this practice is strictly enforced, we are likely to come out with a large interventional data, and the controversy about thyroxine replacement in subclinical hypothyroidism may be authentically solved.

The present study drives home two important points; first using a cut-off of 2.5 mIU/l is unlikely to identify women at risk of obstetric and perinatal complication, second there is a need for Indian reference for trimester-specific range for TSH which is derived from large pregnant population with euthyroid status (normal free T3 and T4 levels) corrected for ethnic and regional differences.

CONCLUSION

The obstetric complications do occur in women with hypothyroidism, but whether they are just associations or random occurrences are yet to be explored. With improved prenatal counselling facilities, one should aim at early detection of maternal hypothyroidism and decide the need for thyroxine replacement according to the situation, which will greatly improve the obstetric and perinatal outcome. In complicated cases, a multidisciplinary team approach, comprising of obstetrician, physician, anaesthetist, paediatrician and endocrinologist, hopefully, will improve pregnancy outcome of those who are affected.

CONFLICT OF INTERESTS

Declared none

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