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Levothyroxine replacement in subclinical hypothyroidism during pregnancy and its effect on fetomaternal outcome

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Abstract
Background: We aimed to study improvement in feto-maternal outcome in pregnant women with subclinical hypothyroidism treated with levothyroxine therapy.
Methodology: This was prospective comparative study, on antenatal Women who had first trimester thyroid function tests at our Hospital. All female were categorized into three groups (Group A- TSH level>2.5-4 µIU/l receiving levothyroxine treatment; group B- TSH level between 4.1-10 µIU/l receiving levothyroxine treatment and Group C- women with TSH level >2.5-4 µIU/l not receiving levothyroxine treatment). Fetomaternal outcome was assessed between the groups.
Results: We observed no significant difference in maternal outcome between three groups but APGAR score was significantly lower in group B as compared to other two groups ($p<0.05$).
Conclusion: Levothyroxine replacement therapy is safe and effective in case of subclinical and overt hypothyroidism & in SCH pregnancy loss in mother & neonatal admission rate to NICU shows a significant decrease on levothyroxine administration.

Keywords: Levothyroxine, fetomaternal outcome, subclinical hypothyroidism, prospective, dose adjustment.

Introduction
Thyroid dysfunction is the second most commonly observed endocrinological disorder in pregnancy and the most common cause of hypothyroidism is primary abnormality in thyroid. However, in some cases, it is also caused by hypothalamic dysfunction. Thyroid hormone is crucial for normal development of placenta, neuronal Migration, synaptic transmission and myelination during the early stages of neurodevelopment. The American Endocrine Society (AES) define hypothyroidism during 1st trimester of pregnancy as a patient with a serum TSH level >10 mI U/L with or without a normal free T4 level and SCH as patient with a serum TSH level > 2.5 µIU/l with a normal free T4 level. The American Thyroid Association (ATA) defines SCH asTSH between 2.5 and 10 µIU/l with a normal FT4 concentration [1]. Subclinical hypothyroidism (SCH) is a mild form of hypothyroidism defined as an elevated thyroid stimulating hormone (TSH) concentration in addition with normal free thyroxine (FT4) levels and no symptoms of hypothyroidism, is a common finding in pregnancy, occurring in more than 25% of pregnant women (depending on the assay and reference ranges used) [2]. Presence of SCH in pregnancy expected to have adverse effects on the growth and development of the fetus. The adverse pregnancy outcomes include, miscarriage, pregnancy induced hypertension, and its severe form pre-eclampsia, as well as placental abruption, anaemia, post-partum hemorrhage, and increased fetal morbidity and mortality. These obstetric complication contribute overall increase in the frequency of adverse neonatal outcomes, which include preterm birth, low birth weight, increase admission to neonatal intensive care and increase perinatal morbidity and mortality [3]. Starting thyroxine treatment in the 1st trimester (preferably prenatally) may decrease the incidence of complications. Starting treatment after completion of 1st trimester will not eliminate already established fetal neuro developmental delay, as during the first trimester the fetus depends completely on maternal thyroid hormone for the normal brain development. Pregnancy modifies the clinical state of disease and alters the thyroid function tests. For this reason hypothyroid women treated with levothyroxine need to increase their daily levothyroxine doses during pregnancy.

As a result, despite a crunch of high-quality randomised controlled trials (RCTs) of levothyroxine replacement therapy, many health organisations have advised for levothyroxine replacement therapy for women with subclinical hypothyroidism diagnosed in pregnancy [4]. These are further supported by a basic belief that levothyroxine therapy is physiologic and benign. Emerging data challenge this belief due to the demonstration of increased risks associated even with levothyroxine replacement and/or elevated free T4 (even in the subclinical hypothyroid range) in pregnancy including: increased risks of pre-eclampsia, small for gestational age neonates, preterm delivery, gestational diabetes and, in fact, lower IQ [5].

Not much studies available to see if early thyroxine supplementation and adequate treatment reduces the incidence of complications in pregnant woman with hypothyroidism. The present study is an attempt to study the improvement in maternal and perinatal outcome in pregnant women with subclinical hypothyroidism treated with levothyroxine replacement therapy. In present study, we also aimed to compare the feto-maternal outcome in pregnant women having TSH value (2.5 to 4 MIU/l) with pregnant women having TSH value (4.1 to 10 MIU/l) both treated with levothyroxine & with pregnant women having TSH value (2.5 to 4 MIU/l) not treated with levothyroxine.

Materials and Methods

The present study was conducted as a prospective comparative study, on Women with a singleton pregnancy who had first trimester thyroid function tests at Department of Obstetrics and Gynaecology, MY Medical Hospital Indore during the study period of 1 year i.e. from 1st May 2018 to 30th April 2019. All the women with a singleton pregnancy with first trimester thyroid function tests and willing to participate in the study were included whereas women with multi-fetal gestation & known chronic disorders, such as diabetes, hypertension, TB, as well pregnant females with overt hypothyroidism were excluded from the study.

Study was divided into two stages:

- Stage1 of the study consisted of selection of pregnant females. 2 ml of Blood was collected in fasting state from the patients by venipuncture and was allowed to clot, and serum was separated by centrifugation at room temperature. The serum was stored at 2 to 8°C till its usage. The TSH was estimated by using CLIA (Chemiluminescent Immunosorbent Assay) method. The serum was analysed for thyroid parameters. Based upon their findings, females was classified into three groups.
- Group A: all women with TSH level>2.5 µIU/l but less than 4.0 mIU/ l recieveing levothyroxine treatment (n=50)
- Group B: all women with TSH level between 4.1µIU/l but less than 10µIU/l receiving levothyroxine treatment (n=50)
- Group C: all women with TSH level>2.5 µIU/l but less than 4.0 µIU/l not receiving levothyroxine treatment (n=50).

Subclinical hypothyroidism patients were treated with Levothyroxine in the dose of 1.20 µg/kg/day for subclinical hypothyroidism. Serum TSH estimation was repeated at 4-6weeks interval then at 3 monthly interval. TSH concentration was maintained less than 2.5MIU/L in the first trimester, less than 3MIU/L in the second and third trimester. All the patients were followed till the end of pregnancy.

- Stage 2 of the study consisted of comparing the maternal and perinatal outcome between three groups in mothers with subclinical hypothyroidism treated with thyroxine replacement between all the three groups.

Statistical Analysis

All the data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. PRISM and Microsoft office was used to prepare the graphs. Student t- test and ANOVA was used to compare the means. Tukey post Hoc analysis was performed to compare the significance between all the three groups using one way ANOVA. Chi Square test was used to compare the categorical data. $P< 0.05$ was considered as significant.

Results

A total of 150 antenatal females fulfilling the inclusion criteria were enrolled and categorized in three groups.

Table 1- Comparison of groups according to baseline variables

		Groups			Total	P value
		Group A	Group B	Group C		
Age (years)	<20	7 (14)	11 (22)	7 (14)	25 (16.7)	0.363
	21-25	22 (44)	21 (42)	22 (44)	65 (43.3)	
	26-30	20 (40)	13 (26)	20 (40)	53 (35.3)	
	31-35	1 (2)	3 (6)	1 (2)	5 (3.3)	
	>35	0 (0)	2 (4)	0 (0)	2 (1.3)	
SES	Lower	3 (6)	2 (4)	5 (10)	10 (6.7)	0.159
	Lower Middle	21 (42)	16 (32)	22 (44)	59 (39.3)	
	Upper Class	6 (12)	8 (16)	1 (2)	15 (10)	
	Upper Lower	18 (36)	17 (34)	14 (28)	49 (32.7)	
	Upper Middle	2 (4)	7 (14)	8 (16)	17 (11.3)	
Parity	P0	24 (48)	19 (38)	15 (30)	58 (38.7)	0.08
	P1	18 (36)	20 (40)	11 (22)	49 (32.7)	
	P2	5 (10)	5 (10)	14 (28)	24 (16)	
	P≥3	3 (6)	6 (12)	10 (20)	14 (9.3)	
Gestational age at presentation		8.88±2.1	8.44±1.9	8.12±1.97	-	0.157

Majority of the patients in Group A had age between 21-25 years (44%) followed by 26-30 years (40%), in Group B majority belonged to 21-25 years of age (42%). In group C, majority of the subjects belonged to age groups of 21-25 years (44%) followed by 26-30 years. In present study, two groups were comparable with respect to age, socioeconomic status,

parity and gestational age (p>0.05). (Table 1)

Table 2: Comparing TSH levels between groups

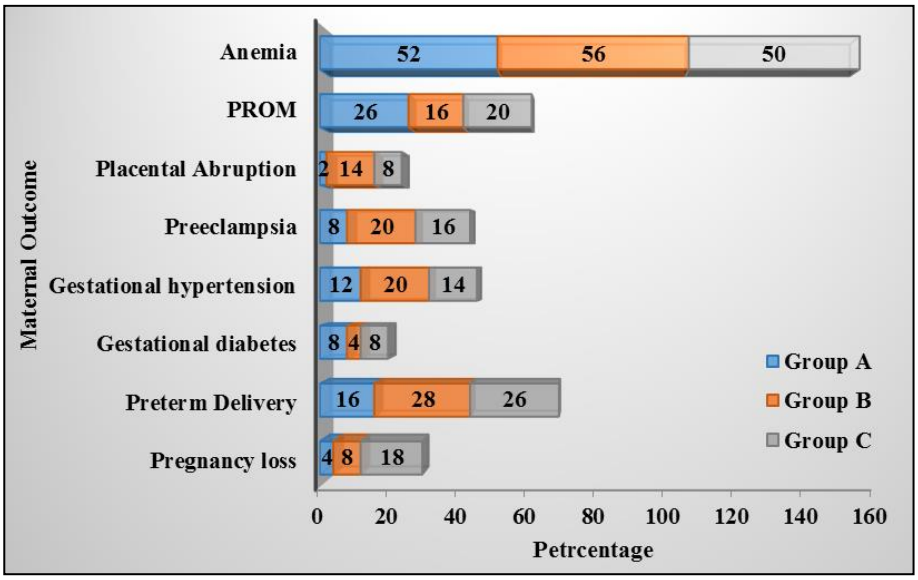
TSH		Mean	Std. Deviation	P value
At Presentation	Group A	3.4800	1.35662	A&B; p<0.001, A & C; p=0.426, B & C; P<0.001
	Group B	6.5640	1.75345	
	Group C	3.1540	.43948	
After 6 wks	Group A	2.5996	3.61437	A&B; p=0.818, A & C; p=0.076, B & C; P=0.016
	Group B	2.2860	2.04669	
	Group C	3.7360	1.71020	
At 3 month	Group A	1.4026	1.02030	A & B; p=0.963, A & C; p<0.001, B&C;P<0.001
	Group B	1.4724	.68910	
	Group C	4.4120	1.95413	

In present study, TSH level at the time of presentation was significantly lower in Group A (3.4800) as compared to Group B (6.5640) (p<0.001), similarly TSH level was significantly higher in Group B (6.5640) as compared to group C (3.1540) (p<0.001). At 6 weeks and 3 months follow up after treatment, TSH level were similar in both Group A and Group B (p>0.05). However, TSH was significantly higher in Untreated Group C as compared to Group A and Group B (p<0.05) (Table 2)

Table 3: Dose adjustment in group A and group B at various follow up

Follow up	Group	TSH level	Dose adjustment			Total	P value
			Decreased	Increased	Same		
6 weeks	A	High	0 (0)	6 (75)	2 (25)	8 (100)	0.001
		Normal	0 (0)	1 (2.4)	41 (97.6)	42 (100)	
	B	High	0 (0)	6 (60)	4 (40)	10 (100)	0.001
		Normal	1 (2.5)	0 (0)	39 (97.5)	40 (100)	
3 months	A	High	0 (0)	1 (50)	1 (50)	2 (100)	0.13
		Normal	0 (0)	6 (12.5)	42 (87.5)	48 (100)	
	B	High	0 (0)	1 (50)	1 (50)	2 (100)	0.03
		Low	0 (0)	1 (100)	0 (0)	1 (100)	
		Normal	1 (2.1)	4 (8.5)	42 (89.4)	47 (100)	
12 months	A	High	0 (0)	1 (50)	1 (50)	2 (100)	0.134
		Normal	0 (0)	6 (12.5)	42 (87.5)	48 (100)	
	B	Low	0 (0)	1 (100)	0 (0)	1 (100)	0.024
		Normal	1 (2)	5 (10.2)	43 (87.8)	49 (100)	

At 6 weeks of follow up, significant dose adjustment was required in both group A and group B (p<0.05). However at 3 and 6 months of follow up, significant dose adjustment was required in group B but not in group A (p<0.05). (Table 3)
No significant difference in mode of delivery was noted in our study between three groups (p>0.05).



Graph 1: Maternal Outcome between groups

Maternal anemia was most common finding in all the groups. In Group A, most common Maternal Outcome was PROM (26%) followed by preterm delivery (16%) and gestational hypertension (12%). In Group B, most common Maternal Outcome was Preterm Delivery (28%) followed by Gestational hypertension (20%) and Preeclampsia (20%) and in Group C most common Maternal Outcome was Preterm Delivery (26%) followed by PROM (20%) and Pregnancy loss (18%). However the distribution of maternal outcome in all the groups was similar as reveled by the insignificant p value of >0.05 in all the maternal outcome. (Figure 1)

Table 4: Neonatal outcome between groups

Neonatal outcome	Group A	Group B	Group C	P value
Premature rupture of membrane	8 (16)	7 (14)	3 (26)	0.256
Intrauterine growth restriction	8 (16)	10 (20)	11 (22)	0.741
Low APGAR score	2 (4)	12 (24)	2 (4)	0.001
Neonatal Death	4 (8)	5 (10)	5 (10)	0.924
Neonatal admission to nursery	9 (18)	14 (28)	8 (16)	0.284
Low birth weight	5 (10)	8 (16)	6 (12)	0.656
Still birth	3 (6)	6 (12)	5 (10)	0.576

Most common neonatal outcome in Group A and group B was Neonatal admission to nursery (18% and 28% respectively) whereas in group C, most common was Pre-mature rapture of membrane (26%). Low APGAR score was more common in Group B (24%) as compared to Group A (4%) and group C (4%) (P=0.001). Rest all neonatal outcome were statistically similar between all the three groups. (Table 4)

Discussions

Presence of SCH in pregnancy can be expected to have adverse effects on the growth and development of the fetus. The adverse pregnancy outcomes include, miscarriage, pregnancy induced hypertension, and its more severe form pre-eclampsia, as well as placental abruption, anaemia, post-partum hemorrhage, and increased fetal morbidity and mortality. In present study we tried to study the maternal and perinatal outcome in mothers with subclinical hypothyroidism treated with thyroxine replacement therapy [3].

In present study, majority of patients irrespective of the groups belonged to age range of 21 to 25 years. However the age distribution was similar in all the three groups (p>0.05). Similar age distribution was recorded by Singh *et al.* i.e. 50% patients of subclinical thyroid also belonged to 20-25 year [6]. Similarly Nidhi *et al.* reported the mean age of pregnant subjects was 26.7 year which is comparable to our result [7]. Singh *et al.* recorded that majority of women suffering from overt & subclinical hypothyroidism as well as hyperthyroidism are nulliparous in 72% cases as compared to 32% in euthyroid patient.[6] However, in present study three groups were comparable with respect to parity (p>0.05).

In present study, it was found that TSH level at the time of presentation was significantly lower in Group A and C as compared to Group B (p<0.001). At 6 weeks and 3 months follow up, after treatment TSH level were similar in both Group A and Group B but TSH was significantly higher in Untreated Group C as compared to Group A and Group B. Similar observations were made by Kim *et al.*, where a continuous decrease of median TSH concentration during the first trimester of pregnancy (median TSH concentration: 1.82 μIU/l for 3+0 to 6+6 weeks; 1.53 μIU/l for 7+0 to 7+6 weeks; and 1.05 μIU/l for 8+0 to 13+6 weeks) was observed [8]. Mandal *et al.* in similar study observed TSH value >2.5 μIU/ml (32.94%) with normal FT4 and they were diagnosed as SCH. TSH level >4.5 μIU/ml was estimated in 13.92% (71) of the subjects [9].

The present study documented no significant difference in maternal outcome among females of three groups (p>0.05). Similar maternal outcome in patients of hypothyroidism were recorded by Singh *et al.* in which the authors observed 37.5% miscarriage rate, 5% had placental abruption, 15% women experienced the preterm premature rupture of membranes [6]. However, Männistö *et al.* reported increased odds of preeclampsia (OR = 1.47, 99% CI = 1.20–1.81), superimposed preeclampsia (OR = 2.25, 99% CI = 1.53–3.29), gestational diabetes (OR = 1.57, 99% CI = 1.33–1.86), preterm birth (OR = 1.34, 99% CI = 1.17–1.53), induction (OR = 1.15, 99% CI = 1.04–1.28), cesarean section (prelabor, OR = 1.31, 99% CI = 1.11–1.54; after spontaneous labor OR = 1.38, 99% CI = 1.14–1.66), and ICU admission (OR = 2.08, 99% CI = 1.04–4.15) in overt hypothyroidism [10].

Maternal SCH in pregnancy was identified as a risk factor for fetal growth restriction [11]. However, we documented significantly higher cases of low APGAR score in group B as compared to other two groups (p<0.05). Wikner *et al.* reported that risk for preterm birth was marginally increased (OR 1.13, 95% CI 1.03-1.25) in cases with subclinical hypothyroidism [12]. Liu *et al.* observed that maternal SCH in pregnancy is a risk factor for fetal growth restriction with a combined relative risk (RR) value of 2.4 [95% confidence interval (CI): 1.56, 3.7]. Meta-analysis of 10 studies that provided numbers of preterm infants revealed a significant association between maternal SCH in pregnancy and premature delivery, with a combined RR of 1.96 (95% CI: 1.34, 2.88). There was a significant effect of maternal SCH in pregnancy on fetal distress in utero (p=0.003) [11] Männistö *et al.* reported that maternal hypothyroidism has previously been shown to increase risk for neonatal intensive care treatment [10]. Sannaboraiah *et al.* reported risk of NICU admission in 15% subthyroid females receiving levothyroxine whereas neonates of 27% cases with overt hypothyroidism required NICU admission [13].

In present study, on comparing the TSH level at 6 weeks of follow up, it was found that in Group A, 42 patients had normal TSH, In group B 40 patients and in Group C,24 patients had normal TSH levels. In Group A, in majority of the normal TSH level patients, no change (97.6%) in dose was done, however, 1 (2.4%) normal TSH patients required dose increment. In Group B, 97.5% of the Normal TSH patients does not require any dose increment, however in 2.5% dose was decreased (p<0.001). Rajput reported on weekly follow up observed that TFT remained within the normal range, but TSH increased (group I, daily 2.8 ± 1.4 μIU/l, weekly 3.9 ± 1.1 μIU/l, p=0.001; group II, weekly 4.6 ± 1.1μIU/l, daily 2.7±1.2μIU/l, p = <0.001) and T3/T4 decreased with weekly therapy as compared to daily therapy. No significant difference in HSS score was found between daily and weekly administration of LT4 [14].

After 3 month and 6 month of follow up, dose adjustment was required in significantly higher proportions of cases of group B (p<0.05). Tariq *et al.* documented that none of the patients who had abnormally low TSH or elevated FT3 or FT4 levels had hospitalizations, TSH levels improved significantly in majority of the subjects at 3 month follow up [15]. Our findings at 6 months were supported by findings of Singh *et al.* in which authors reported no significant difference in symptoms score between cases in post treatment phase with TSH <2.5 μIU/l and TSH ≥2.5 μIU/l, as patients with hypothyroidism on LT treatment could not differentiate in residual symptoms below-normal range serum TSH (<0.3 μIU/l), low-normal reference range serum TSH (0.3–1.99 μIU/l), and high-normal serum TSH (2.0–4.8 μIU/l) brought by slight changes in small LT4 dosage (20%) [16].

Present study has some limitations in terms of small size single centred and cross sectional characteristics of sample make is less alike to the population. Inclusion criteria is to wise to control the actual effects of replacement of LT4.

Conclusion

Pregnant women with SCH had increased risks of GHTN and PROM, and their neonates had increased risks of IUGR and LBW. These adverse outcomes show a wide decreasing trend on levothyroxine administration in overt hypothyroidism but in SCH as our study reveals effects are limited. However, pregnancy loss widely decreased on levothyroxine administration as maternal outcome remain unaffected. Thyroid function test should be employed in all the pregnant women to detect and avoid the negative maternal and neonatal outcomes. Levothyroxine replacement therapy is safe and effective in case of subclinical and overt hypothyroidism & in SCH pregnancy loss in mother & neonatal admission rate to NICU shows a significant decrease on levothyroxine administration.

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