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A STUDY ON SUBCLINICAL AND OVERT HYPOTHYROIDISM IN PREGNANCY AND ITS PREGNANCY OUTCOMES IN A TERTIARY CARE CENTRE

Obstetrics & Gynaecology

Veena K. R. Bhagavan* Department of Obstetrics and Gynaecology, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India *Corresponding Author

Varsha K. R Department of Obstetrics and Gynaecology, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

Ganesh H.K. Department of Obstetrics and Gynaecology, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

Anitha S Department of Obstetrics and Gynaecology, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

Kanishka Agarwal Department of Obstetrics and Gynaecology, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

ABSTRACT

Introduction and Aim: One of the most common disorder in pregnancy has been thyroid disorders. Thyroid disorders complicating pregnancy in first trimester can result in obstetric complication like miscarriage, pregnancy induced hypertension, preterm labour, abruptio placenta and also fetal complication like prematurity, low birth weight, still birth, perinatal death, increase in neonatal intensive care admission, respiratory distress syndrome also affects development of brain leading to mental retardation and cretinism. **Methodology:** A Prospective analytical and comparative study during antenatal check-up first visit TSH and FT4 was done. Subjects were divided into subclinical hyperthyroidism, euthyroid and overt thyroidism .31 subjects in each category and followed up till delivery. Statistics analysis was done with ANOVA and Chi square test. **Results:** Study implied that euthyroid pregnant women continued their pregnancy till term, whereas in subclinical and overt hypothyroidism the IQR was 32.75-39 gestational weeks and 34-39 weeks respectively and this was found to be statistically significant. It also shows that the incidence of intrauterine death was highest in overt hypothyroidism group. **Conclusion:** In conclusion, this study portrays that the adverse feto-maternal outcomes is seen with majority of overt hypothyroidism patients and also in subclinical hypothyroidism as compared to euthyroid group. Hence , it becomes even more necessary and significant to treat altered thyroid levels in pregnant women, for betterment of both the fetus and the mother.

KEYWORDS

Subclinical hypothyroidism, Overt hypothyroidism, Thyroid stimulating hormone, Maternal and Fetal outcome.

INTRODUCTION

Thyroid disorder in pregnant women influence fetal and maternal outcome of pregnancy and has effect even after the pregnancy . (1). TSH and HCG have same α-units ,HCG has intrinsic thyrotropic activity, and high serum hCG levels leads to thyroid stimulation(1). In 80 percent of women TSH levels declines in first trimester (1). Thyroid hormones, thyroxine (T4), and triiodothyronine (T3),production increases by 50% and iodine requirement also increases by 50% to meet maternal and fetal needs.(1) Thyroid hormones are bound to transport protein like Thyroid Binding Globulin (TBG),Transthyretin and albumin. Only a fraction (approximately 0.2%) of the thyroid hormone (free T4) is unbound and active(2).At target site T3 and T4 dissociate from the binding protein to enter the cell .In the cell T3 and T4 bind to nuclear alpha or beta receptors leading to activation of transcription and activation of certain gene and produce cell specific response. Liver degrade thyroid hormone and excreted in the bile(2). Thyroid receptors have high affinity for T3,T4 is relatively inactive.T4 is converted into active T3 by enzyme deiodinase(2).These physiological process occur in healthy women .If there is the thyroid dysfunction because of underlying pathology Thyroid disease will affect women significantly before during and after pregnancy. serum.TSH elevated during pregnancy should be defined using pregnancy and population specific reference ranges. serum TSH (usually >10 mIU/L) is overt hyperthyroidism associated with decreased thyroxine.Subclinical hypothyroidism is increase in serum TSH with normal concentration of Serum Thyroxine and triiodothyronine(1).Thyroid hormone is needed for neuronal migration, myelination, synaptic transmission and plasticity during fetal and early postnatal life.Not only overt hypothyroidism but also subclinical thyroid dysfunction will affect pregnancy and fetal life adversely.maternal adverse outcomes include miscarriage, pregnancy-induced hypertension, Pre-eclampsia, as well as placental abruption, anaemia, postpartum haemorrhage and fetal mortality incidence also increased(1). Adverse neonatal outcomes, which include preterm birth, low birth weight, increased admission to neonatal intensive care and increased perinatal morbidity and mortality also increased (2).Hypothyroidism can be easily detected and treated so that adverse outcomes to the mother and fetus can be minimised(3).Thyroid hormone replacement therapy to pregnant with overt and subclinical hypothyroidism decrease the risk of neurodevelopmental deficits and other adverse outcomes.This study emphasizes on subclinical and overt hypothyroidism and its pregnancy outcomes.

MATERIALS AND METHODS

Hospital based prospective analytical and comparative study was done in Department of Obstetrics and Gynaecology at A.J. Institute of medical Sciences and Research Centre, Kuntikana, Mangaluru, Karnataka. Pregnant women who attended OBG department and met inclusion criteria were considered for the study. The study period was from January 2021 to August 2022.

Eligibility criteria

Inclusion criteria

All pregnant women undergoing antenatal check-up in AJ Institute of Medical Sciences, Mangalore.

Exclusion criteria

1. Pre-existing thyroid disorder
2. Pre-existing chronic disorders like hypertension, diabetes
3. Pregnant women with autoimmune disorders
4. Pregnant women with known bad obstetric history
5. Pregnant women who are likely to be delivered at another hospital.

Sampling procedure

Based on the study conducted by Vinodhini *et al.,* (6), in order to expect a difference of 33% in outcome between the groups assuming 95% confidence interval, 80% power, sample size estimated for the study was 28 individuals each in the groups. Further, assuming 10% loss to follow-up , 31 individuals in each group. TSH Hence a total of 93 individuals were included in the study.

METHODOLOGY

Study done on pregnant women coming for antetnatal checkup. Detailed history taking and clinical examination done with emphasis on the family of thyroid disorder and obstetric history, past history, maternal age. Institutional ethical committee permission taken. After taking written consent subjects were recruited for the study. During

first antenatal check-up subjects were advised undergo thyroid function test i.e., TSH and FT4.TSH was measured by CLIA (chemiluminescence's immunoassay).

The Group 1 subclinical hypothyroidism with increased TSH but normal FT4 .The reference range considered TSH : >4 mIU/L

The Group 2 with TSH higher than 10 mIU/L irrespective of FT4 levels were categorized as overt hypothyroidism The Group 3 with TSH -< 4 mIU/L formed euthyroid group.

Women diagnosed with abnormal hormone values were advised for simultaneous treatment and follow-up. In such women, TSH was repeated every 6-8 weeks.

The subjects were closely monitored during the entire period of gestation and the pregnancy outcomes were analysed. The pregnant women were categorized based on age, *gravida* status, obstetrical complications, dosage of levothyroxine needed for treatment, mode and outcome of delivery, based on trimester wise abortions, the incidence of GDM, the haemoglobin levels.

The pregnant women were categorized based on the BMI as normal and BMI greater than or equal to 23kg/m^2 according to Asia-pacific classification (8)

The new-borns were categorized based on birth weight. Low birth weight new-borns were the ones whose weight were less than 2500 grams at birth for term neonates and whose weight less that 10th percentile of gestation-weight based chart according to Indian paediatrics association (9). The new-borns were also categorized based on APGAR score and also based on NICU admissions.

Statistical analysis

Kruskal-wallis H test was used to find the significant difference in outcomes such as pre-eclampsia, preterm delivery between groups. ANOVA test was used to find the significant difference in Hb levels, birth weight between the groups. Chi-square test was used to find the significant difference between other variables of interest between groups.

RESULTS

The Study shows the maximum number of pregnant women in subclinical hypothyroidism belonged to the age group of 26-30 years(35.5%) followed by 29% in the age group of 21-25 years, 25.8% in the age group of 31-35 years and 9.7% in >35 years age group. The maximum number of pregnant women in overt hypothyroidism belonged to the age group of 26-30 years(35.5%) followed by 22.6% in the age groups of 21-25 and 31-35 years and 19.3% in >35 years age group. The maximum number of pregnant women in euthyroid group belonged to the age group of 26-30 years(38.7%) followed by 32.3% in the age group of 21-25 years, 25.8% in the age group of 31-35 years and 3.2% in >35 years age group. The age distribution was similar among the groups; P value:0.61.

In our study the majority of the Study Participants among all the three groups belonged to primigravida followed by second gravida in both subclinical and overt hypothyroidism group whereas in euthyroid it was third gravida which was the second commonest. There was no statistical significance among the three groups based on the gravida status; P value : 0.57 .

The incidence of GDM among the three groups was not statistically significant.

There was no statistical difference seen with respect to the birth weight among the three groups.

This study showed that pregnancy was continued till third trimester in 90.3% of pregnant women in subclinical and overt group, whereas 100% in euthyroid group. There were three first trimester losses in both subclinical and overt hypothyroidism group. There was no statistical difference among the groups; P value: 0.13

This study showed that the number of live births, abortions and IUD. The number of live births were more in euthyroid as compared to subclinical and overt hypothyroidism. IUD was found to be 12.9% in overt hypothyroidism, whereas in subclinical and euthyroid status, there was no IUD noted.

There was no statistical difference noted with respect the haemoglobin levels among the groups.

This study shows that there is no statistical significant difference among the three groups with respect to the admission of newborns to NICU; P value 0.30 .

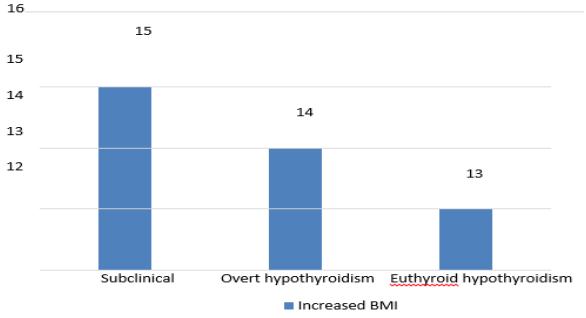

Fig. 1: Distribution of study participants with increased BMI

Fig. 1 shows that though there were more women with increased BMI noted in subclinical hypothyroidism as compared to overt and euthyroid, there is no statistical significance noted; P value: 0.88

Table 1: Distribution as per the median requirement of dosage of levothyroxine among subclinical and overt hypothyroidism groups

Levothyroxine dosage	Subclinical hypothyroidism	Overt hypothyroidism
Median	50	300
Kruskal Wallis H test: Kruskal Wallis H score: 38.087; p value: <0.001* (significant)		

Table 1 depicts the requirement of dosage of levothyroxine in both the subclinical and overt hypothyroidism groups. In subclinical hypothyroidism , the median dosage was 50 mcg/day , whereas in overt group the median dosage is 300 mcg/day. P value:< 0.001.

Table 2: Obstetric complications of study participants

Variable & its categories	Thyroid status							
	Subclinical hypothyroidism		Overt hypothyroidism		Euthyroid			Total
	N	%	N	%	N	%	N	%
	28	100.0	28	100.0	31	100.0	87	100.0
Preeclampsia								
Present	6	21.4	3	10.7	3	9.7	12	14.1
Absent	22	78.6	25	89.3	28	90.3	75	85.9
	Chi-square test: χ2: 2.038; df: 2; p value: 0.36							
Abruption								
Present	0	-	1	3.6	0	-	1	1.1
Absent	28	100.0	27	96.4	31	100.0	86	98.9
	Chi-square test: χ2: 2.132; df: 2; p value: 0.34							
Prematurity								
Present	3	10.7	5	17.9	3	9.7	11	12.6
Absent	25	89.3	23	82.1	28	90.3	76	87.4
	Chi-square test: χ2: 1.030; df: 2; p value: 0.59							
FGR								
Present	3	10.7	6	21.4	5	16.1	14	16.1
Absent	25	89.3	22	78.6	26	83.9	73	83.9
	Chi-square test: χ2: 1.190; df: 2; p value: 0.55							

In Table. 2 there was no statistical significance with respect to the incidence of preeclampsia, abruption, prematurity and FGR among the three groups. The incidence of preeclampsia was highest in subclinical hypothyroidism as compared to the other two groups. One Study Participant in overt hypothyroidism had abruption. The incidence of

FGR was highest in overt hypothyroidism as compared to subclinical and euthyroid .

Table 3: Distribution of Study Participants as per the median period of gestation

POG (weeks)	Subclinical hypothyroidism	Overt hypothyroidism	Euthyroid
Median	38.00	37.50	39.00
IQR	32.75 – 39.00	34.00 – 39.00	38.00 – 39.25
Kruskal Wallis H test: Kruskal Wallis H score: 6.977; p value: 0.03* (significant)			

Table 3 shows the distribution of Study Participants as per median period of gestation. In subclinical median was 38 weeks (IQR 32.75-39 weeks), in overt median 37.50 (IQR 34-39 weeks) and in euthyroid median was 39 weeks(IQR 38-39.25 weeks) and this was statistically significant; P value= 0.03

Table 4: Mode of delivery and outcome of Study Participants

Mode of delivery	Thyroid status							
	Subclinical hypothyroidism		Overt hypothyroidism		Euthyroid		Total	
	N	%	N	%	N	%	N	%
Normal	10	32.3	13	41.9	20	64.5	43	46.2
El LSCS@	7	22.6	2	6.5	1	3.2	10	10.8
Em LSCS@	11	35.5	9	29.0	10	32.3	30	32.3
Abortion@	3	9.7	3	9.7	0	-	6	6.5
IUD	0	-	4	12.9	0	-	4	4.3
Total	31	100.0	31	100.0	31	100.0	93	100.0
Chi-square test: $\chi 2$: 21.074; df: 8; p value: 0.007* (Significant)								

@In table 4: Elective LSCS, Emergency LSCS, Spontaneous abortion.There was 3 first trimester losses in both subclinical and overt hypothyroidism and 4 IUDs in overt hypothyroidism which was statistically significant; P value= 0.007. The number of pregnant women undergoing elective LSCS is 7 in subclinical, 2 in overt and 1 in euthyroid. The number of pregnant women undergoing emergency LSCS is 11 in subclinical, 9 in overt and 10 in euthyroid. The number of women undergoing normal delivery is 10 in subclinical, 13 in overt and 20 in euthyroid.

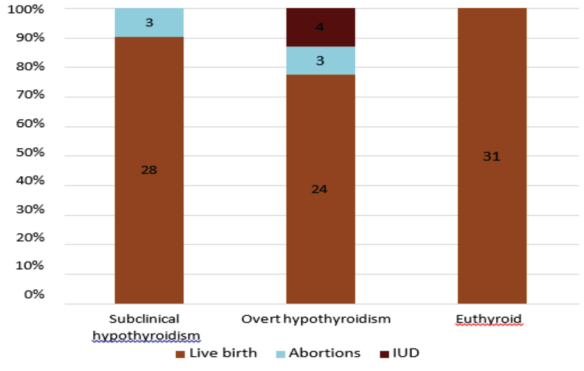

Figure 2: Distribution as per fetal outcome

Figure 2 shows the number of live births, abortions and IUD. The number of live births were more in euthyroid as compared to subclinical and overt hypothyroidism. IUD was found to be 12.9% in overt hypothyroidism, whereas in subclinical and euthyroid status, there was no IUD noted.

Table 5: APGAR score categories of newborns

Variable & its categories	Thyroid status							Total
	Subclinical hypothyroidism		Overt hypothyroidism		Euthyroid			
	N	%	N	%	N	%	N	%
	28	100.0	24	100.0	31	100.0	83	100.0
APGAR at the end of 1 minute after birth								
Normal	20	71.4	16	66.7	24	77.4	60	72.3
Low	8	28.6	8	33.3	7	22.6	23	27.7
	Chi-square test: $\chi 2$: 0.849; df: 2; p value: 0.65							
APGAR at the end of 5 minutes after birth								
Normal	28	100.0	23	95.8	31	100.0	82	98.8
Low	0	-	1	4.2	0	-	1	1.2
	Chi-square test: $\chi 2$: 2.488; df: 2; p value: 0.29							

Table 5 : depicts that there was no statistical difference noted with respect to the APGAR score at 1 and 5 minutes among the three groups

DISCUSSION

Thyroid disorders are one of the common endocrine disorders in the reproductive age group even subclinical maternal thyroid deficiency has been linked to poor pregnancy outcomes and may be helped by T4 replacement(7). It can be challenging for hypothyroid women to meticulously maintain adequate thyroid hormone levels during pregnancy due to fluctuations in T4 metabolism during this time. Despite having an apparent optimum thyroid status, fluctuations in thyroxine metabolism that happen during pregnancy may worsen the transfer of thyroxine from the mother to the fetus and cause deleterious effect on the pregnancy and the developing fetus. Several research have been published analysing the maternal and fetal outcomes in hypothyroid pregnant women. Among these, a few studies have contrasted the pregnancy outcomes of women with hypothyroidism with those with euthyroidism. Some people have drawn comparisons between overt and subclinical hypothyroidism during pregnancy. Studies comparing pregnant euthyroid women to those with subclinical hypothyroidism have also been conducted. In the current study ,out of 93 pregnant women, 31 were selected with subclinical hypothyroidism, 31 with overt hypothyroidism and 31 with euthyroid and fetomaternal outcomes were analysed. Age In the current study, majority of the women with subclinical hypothyroidism (35.5%), overt hypothyroidism (35.5%) and euthyroid (38.7%) were aged between 26-30 years of age. In a study by Vinodhini et al (6), majority of the subclinical group subjects were in 21-25 years age group (49.18%) and in overt group,majority were in 21-25 years age group (59.46%). Similarly in a study by Sreelatha et a(l8), maximum number of pregnant women in the age group 25-30 years had thyroid disorder (49%). Also in another study by Gupta et al 9, majority of the participants in the overt group belonged to 25-30 years and in the subclinical hypothyroidism group, majority belong ed to 25-30 years Gravida status In the current study, 54.8% of the women with subclinical hypothyroidism were primigravida, 45.2% of the women with overt hypothyroidism were primigravida and 41.9% of the euthyroid women were primigravida. Vinodhini *et al.,* (6), stated that most of the subclinical group subjects in her study were primigravida (44.26%) and in overt group , majority were equally distributed in primigravida and second gravida (40.54%). Sreelatha et al (8) stated that in their study 49% of primigravida and 51% multigravida women had thyroid disorder. BMI In the current study, though there were more number of women with increased BMI noted in subclinical hypothyroidism as compared to overt and euthyroid, but there is no statistical significance noted; P value: 0.88. In a study conducted by Cheng et al (10) , stated that high BMI during early pregnancy may be an indicator of maternal thyroid dysfunction; for Asian women whose BMI > 23 kg/m^2(8) and who are within 8 weeks of pregnancy, Requirement of levothyroxine dosage In the current study, majority of women in the subclinical hypothyroidism group was started on the levothyroxine dosage of 50 mcg/day , whereas in overt group the dosage was 300 mcg/day ,P value: 0.001, which means that the 50 mcg/day was appropriate dose of levothyroxine to effectively maintain the TSH levels under normal reference range and to prevent any complications from occurring. This was similar to a study conducted by Maraka *et al.,* (11), where 843 women with subclinical hypothyroidism was treated with an average dose of 50 mcg/day and this treatment was associated with lower risk of pregnancy loss. Anaemia In this study, 50% of the pregnant women with subclinical hypothyroidism had anemia, 42.9% with overt hypothyroidism and 45.2% of the women with euthyroidism had anemia. But in contrast to the current study, Vinodhini *et al.,*'s (6) study stated that only 9% of subclinical group and 13 % in overt group had anemia. This might be due to the Heme-dependent enzyme thyroid peroxidase impaired by iron shortage, which lowers the production of thyroid hormones and lower levels of fT3 and fT4 in the blood. Iron replacement therapy might treat this hypothyroidism. GDM In the current study, 3.3% of the pregnant women with subclinical hypothyroidism had diabetes mellitus. In Vinodhini *et al.,*'s (6) study, 11.8% of the pregnant women with subclinical hypothyroidism and 8.1% of the overt group had gestational diabetes. Goldman et al also stated a significant increase in the risk of GDM in overt hypothyroidism. Similar results were

reported in studies conducted by Ajmani *et al.,* (12) and Pokhanna *et al.,* (8).

The occurrence of preeclampsia in this study was comparatively higher among women with subclinical hypothyroidism when compared to other studies but there was no statistically significant association of preeclampsia with thyroid status of the patients. Vinodhini et al (6) stated that there was a statistically significant association of preeclampsia (p value < 0.05)with subclinical hypothyroidism. The prevalence of preeclampsia in our study was almost similar to the study conducted by Ajmani et al (22.3%).(12).One case of placental Abruption had occurred among women with overt hypothyroidism in this study but there was no statistically significant association of abruption with thyroid status of the patients. In Vinodhini et al's 6 study the prevalence was little higher with 10.8% and there was significant difference in the development of abruption among the two groups in her study. The maximum prevalence was reported in Pokhanna 14 et al's study with a prevalence of 22.2%. Comparatively, the occurrence of abruption was higher among women with overt hypothyroidism. This study demonstrated an increased incidence of prematurity of 17.9% among women with overt hypothyroidism and there was no statistically significant association of prematurity with thyroid status of the patients. But in contrast, Vinodhini et al (6) and Gupta et al 9 reported around 36.5% of prematurity in their study. In these two studies, there was statistically significant association of prematurity with thyroid status of the patients (p value < 0.05). This may be due to the fact that the myometrium has thyroid hormone receptors, which is one potential scientific reason that has been put up. It has been proven that the uterus of primates contains TSH and receptors for thyrotropin-releasing hormone. The myometrium's hCG receptors are also able to bind with TSH. While focusing on the neonatal outcome, FGR has been reported to be around 21.4% among women with overt hypothyroidism in this study and there was no statistically significant association of FGR with thyroid status of the patients. Vinodhini et al(6) and Gupta et al (9) also reported a similar prevalence of 27%. The occurrence of FGR was also comparatively higher among pregnant women with overt hypothyroidism.

Gestational age

In this study, 90.3% of the women with subclinical hypothyroidism continued till third trimester, 90.3% of the women with overt hypothyroidism and 100% of the euthyroid women continued till third trimester which is between 28 to 36 weeks of gestation. The median gestational age of the women with subclinical hypothyroidism was 38 weeks, median gestational age of the women with overt hypothyroidism was 37.5 weeks and median gestational age of the women with euthyroidism was 39 weeks. In a study by Vinodhini et al(6), most of the subclinical group subjects were around 28 weeks of gestation (31.15%) and most of the overt group subjects were 29 weeks of gestation (29.73%).

Mode of delivery

In this study, among the women with subclinical hypothyroidism 32.3% of the women had normal delivery, 22.6% were delivered through elective LSCS and 35.5% through emergency LSCS. Among women with overt hypothyroidism, 41.9% delivered through normal delivery, 6.5% through elective LSCS and 29% through Emergency LSCS. In this study there was a statistically significant association between the thyroid status of the patient and mode of delivery. Vinodhini et al [6] stated that 44.26% of subclinical group subjects had LSCS and 35.14% of overt group subjects had LSCS and there was no statistically significant association. Gupta et al (9)and Ajmani et al (12) also stated that LSCS was high among women with overt hypothyroidism.

Fetal outcome

In this study, among the women with subclinical hypothyroidism 90.3% had live birth and 9.7% had abortion. Among the women with overt hypothyroidism, 77.4% had live birth, 9.7% had abortion and 12.9% had IUD. The complications were more among women with overt hypothyroidism. These findings were similar to studies conducted by Vinodhini et al (6) Sarala devi et (15) al and Pokhanna(14) etal.

Birth weight

In this study, 14.3% of the women with subclinical hypothyroidism had low birth weight, 29.2% of the women with overt hypothyroidism had low birth weight and 19.4% of the women with euthyroidism had low birth weight and there was no statistically significant association between thyroid status and birth weight of the baby in our study. But in contrast, Vinodhini et al [6] stated that the incidence of LBW babies were 41% in the overt hypothyroidism and 21% in the subclinical hypothyroidism group and there was statistically significant association between thyroid status and birth weight of the baby. Overall, the prevalence of maternal and fetal outcomes in our study is comparable to that of other studies. In our study, the overt hypothyroidism group has a higher rate of complications than the subclinical hypothyroidism group. Because of the physiological changes that occur during pregnancy, if these thyroid problems are not identified or missed, there may be adverse consequences on the fetomaternal outcome. To avoid miscarriages, thyroid testing is required at the time of first visit. Since the fetus needs thyroxine for lung maturation, growth, and brain development, it is important to use an adequate replacement therapy to keep TSH within the appropriate reference limits for each trimester. Thyroid abnormalities should be treated promptly and effectively to ensure a healthy pregnancy with few complications for the mother and the fetus.

CONCLUSION

In conclusion, this study portrays that the adverse feto-maternal outcomes is seen with majority of overt hypothyroidism patients and also in subclinical hypothyroidism as compared to euthyroid group. Hence it becomes even more necessary and significant to treat deranged thyroid levels in pregnant women, for the betterment of both the fetus and the mother.

Connflict Of Interest

The authors declare no conflicts of interest.

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