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Study on comparison of maternal and fetal outcome in hypothyroid pregnancies with and without hypertension: a controlled case study

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ABSTRACT

Background: Incidence of subclinical hypothyroidism is 2.3% of pregnancies and overt hypothyroidism being 0.2%.Further incidence of hypertension one of the complications of maternal hypothyroidism strongly correlates with the levels of serum thyroid stimulating hormone (TSH). This study is designed to study maternal and fetal outcome in hypothyroid normotensive pregnancies (group 1) and hypothyroid hypertensive pregnancies (group 2) and to study the severity of hypertension in relation to thyroid function levels.**Methodology**: The prospective study was conducted on antenatal mothers attending MGMH,Petlaburz,OsmaniaMedicalCollege,Hyderabad during the period November 2012 to May 2014.The study was based on the analyses of 50 pregnant mothers diagnosed to have hypothyroidism .These included cases diagnosed before as well as during pregnancy .Another 50 pregnant mothers diagnosed to have hypothyroidism and developed hypertension during the course of pregnancy. Follow up was done with serum TSH and free T4 levels throughout pregnancy and outcomes were studied. Trimester specific values for thyroid function tests are used. **Results**: Cases suffering from overt hypothyroidism were 50% in group2 compared to 30% in group1 (chi-square=5.997, p value=0.04986).GHTN was seen in 52% of group 2 patients of which 12% belong to overt hypothyroid group. On the other hand 42% suffered from preeclampsia of which 32% belong to overt group (chi-square=16.55,p value=0.00236). A change in dosage was required in 36% in group1 & 42% in group2. Complications - preterm (grp1 4% & grp2 10%), IUD (grp1 2% & grp2 10%), IUGR (grp1 6% & grp2 14%) and Abruption (grp1 2% & grp2 6%) were observed. **Conclusion**: Changes in the thyroid hormone levels might be correlated with occurrence and severity of pre-eclampsia.

Key words: GHTN (gestational hypertension), hypothyroid, overt,preeclampsia,subclinical

Introduction

Incidence of subclinical hypothyroidism (elevated serum thyroid stimulating hormone (TSH) and normal freeT4) is 2.3% of pregnancies and overt hypothyroidism (elevated TSH and reduced free T4) being 0.2% of pregnancies. Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy and has been associated with miscarriage, fetal loss ,preeclampsia ,preterm delivery ,placental abruption ,low birth weight ,fetal distress and reduced intellectual function of the offspring[1-4].

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Mechanism of association between hypothyroid and preeclampsia is not well understood but the proposed mechanisms are- due to modest decrease in thyroid hormones with concomitant increase in S.TSH in maternal serum correlated with severity of preeclampsia/eclampsia and high levels of endothelin, Nitric Oxide (NO) a vasodilator released from endothelial cells regulates secretion of thyroid hormones by modulating regional blood flow in an animal study[5], the faulty estrogen production due to placental dysfunction reduces concentration of thyroid binding globulin, T4&T3 in preeclampsia women[6].Up to 20% of biochemically hypothyroid women are asymptomatic. A high index of suspicion is required in women treated previously for hypothyroidism, those with previous head and neck irradiation, previous postpartum thyroiditis and those with goiter and on drug therapies with side effects on

thyroid gland[7].The likelihood that either maternal or fetal complication will arise depends on the severity of disease and adequacy of treatment. Gestational hypertension occurs more often in overtly hypothyroid women (36%) than in women with subclinical disease (25%) or the general population(8%)[8].A separate study reported a markedly increased use of caesarian section because of fetal distress among women who were severely hypothyroid(56%) at their initial antenatal visit compared with women who were mildly hypothyroid or euthyroid(3%)[9].Research has shown that the incidence of low birth weight neonates is markedly increased in cases of overt hypothyroid (22%) compared with subclinical disease (9%) and the general population (7%)[8].Thyroxin requirements increase by 50-100% in the first trimester and is sustained throughout pregnancy. The present study aims at the study of maternal and fetal outcome in hypothyroid normotensive patients and hypothyroid patients associated with hypertension, need for dose adjustment and to study the severity of hypertension in hypothyroid patients.

Methodology

This is a prospective cohort study conducted in a tertiary care referral center during the period November 2012 –May 2014 after obtaining clearance from institutional ethical committee of Osmania Medical College, Hyderabad. Pregnant women diagnosed to have hypothyroidism (known cases of hypothyroid or diagnosed during pregnancy) and developed hypertension (Gestational hypertension, preeclampsia & eclampsia) during the course of pregnancy have been selected as cases. Mothers suffering from hypothyroidism attending antenatal out-patients with blood pressure values in normal range and willing to participate in the study were selected as controls. These Included cases diagnosed before pregnancy as well as during pregnancy. A written informed consent was taken from both cases and controls. With 30% of pregnancies to have desired outcome in control group with 95% confidence interval and an allowable error of 20% and to estimate a relative risk of two, the estimated sample size is calculated at 42 in each group and a total of 50 per group were recruited and studied. A detailed history was taken regarding clinical symptoms of hypothyroidism, obstetric history, past medical history about drugs affecting thyroid, family history and personal history. A thorough general physical examination with reference to temperature, pulse rate(PR),blood pressure(BP),respiratory rate(RR) followed by systemic examination of Cardiovascular system(CVS), Central nervous system(CNS) , Respiratory System(RS) and local thyroid examination. All patients were sent for S.TSH testing. If S.TSH levels are deranged FT4&FT3 levels are checked. Trimester specific values for thyroid function test were taken [10]. Those with TSH>2.3micU/ml,FT3<1.9pg/ml andFT4<0.86ng/dl are classified as overt hypothyroid. Patients with TSH>2.3 micU/ml, FT3 and FT4 within reference ranges were classified as subclinical hypothyroid. If S.TSH, FT3, &FT4 are in normal range considered euthyroid. Diagnosis is based on symptoms, clinical signs and biochemistry levels. Cases of Chronic hypertension, Endocrine & medical disorder affecting thyroid, medications affecting thyroid and renal diseases are excluded. Levothyroxine is the standard mode of management given. Initial dose depends on the severity. If S.TSH is <10micIU/ml, L-throxine dosage starting with 0.10mg/d is sufficient. Therapy increased by 0.25 to 0.50mg/day every 2-4wkly intervals till euthyroid status is obtained. Main aim is to maintain thyroid function tests in normal range. Follow up was done with S.TSH&FT4 measurements. Frequency of testing during pregnancy varied depending on control. TFTs repeated every 3-4wks in first half of pregnancy and 6-8wkly in the second half of pregnancy if not under control. If thyroid status is under control repeated each trimester. Further all patients were seen by endocrinologist for dosage adjustment. Progression of thyroid disorder, hypertension and complications arising from them like preterm deliveries, intrauterine fetal death, intrauterine growth restriction, gestational diabetes mellitus and abruption were studied.

Descriptive statistics like frequencies and percentages were used to express baseline characteristics of study population. MS-excel were used for all statistical analysis.

Results & analysis

Table 1: Baseline characteristic of study population Age distribution, gravida, period of hypothyroid diagnosis

	Group I (cases) n (%)	Group II (Controls) n (%)	Total
Age group			
18-20 years	**05 (10)**	**06 (12)**	**11**
21-25 years	**28 (56)**	**33 (66)**	**61**
26-30 years	**16 (32)**	**11 (22)**	**27**
31-35 years	**01 (02)**	**00 (00)**	**01**
Gravidity			
Primi	**21 (42)**	**26 (52)**	**47**
second	**18 (36)**	**12 (24)**	**30**
Third	**06 (12)**	**08 (16)**	**14**
Fourth	**04 (08)**	**04 (08)**	**08**
Fifth	**00 (00)**	**00 (00)**	**00**
sixth	**01 (02)**	**00 (00)**	**01**
Period of diagnosis			
Pre pregnancy	**24 (48)**	**25 (50)**	**49**
During pregnancy	**26 (52)**	**25 (50)**	**51**

Group 1 –hypothyroid normotensive patients

Group2–hypothyroid hypertensive patients

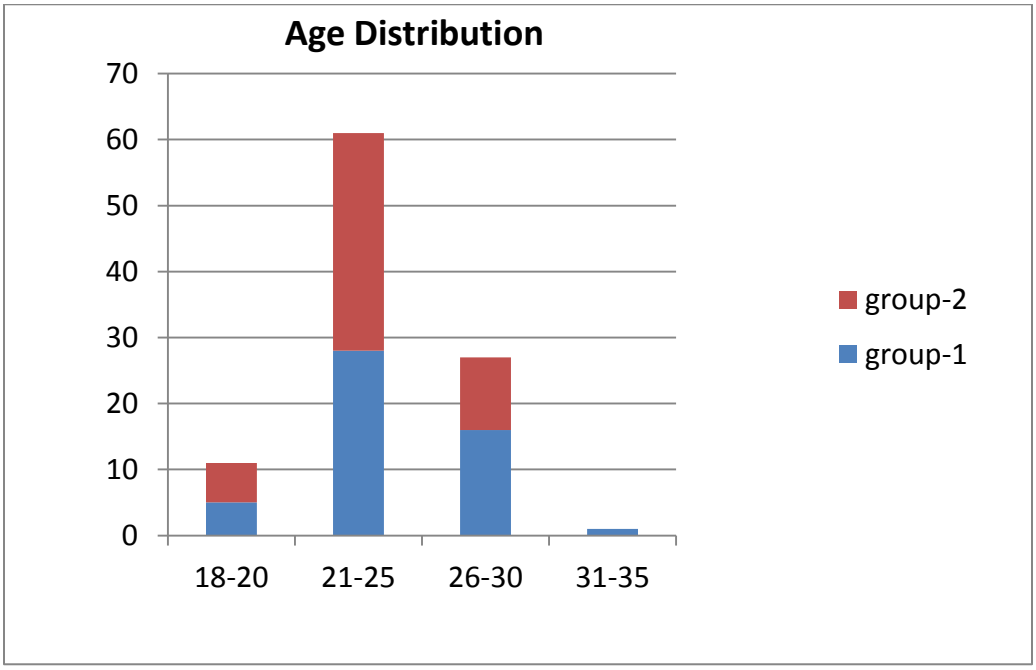

Fig 1: In the present study age distribution ranged from 18-35yrs.

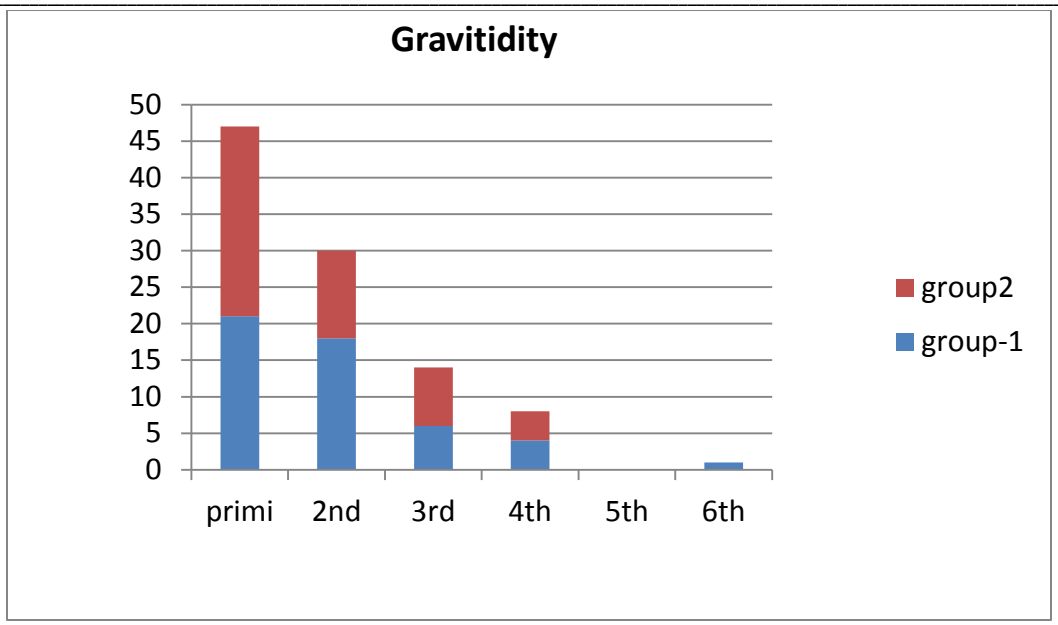

Fig 2:Majority of the patients in both the groups were primigravida (group1 -42% & group2 -52%) and constitute 47% of the total cases

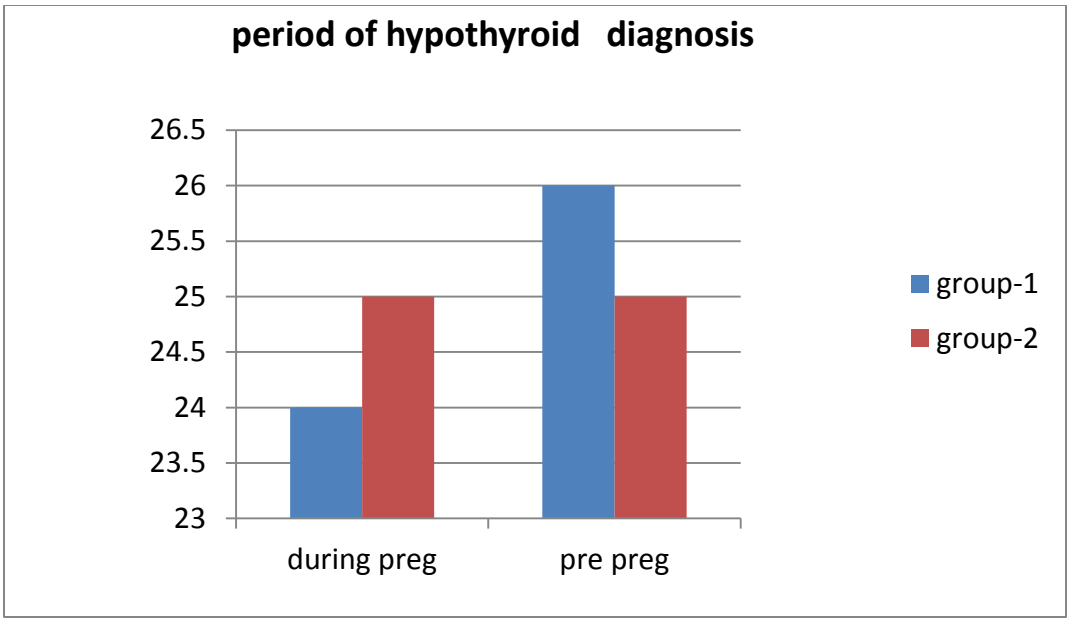

Fig 3 :49% of total cases were diagnosed during pregnancy for the first time

51% of cases were already known cases of hypothyroid diagnosed before pregnancy

Table 2:Hypothyroid status at the time of diagnosis

	Group 1		Group 2		Total	
Thyroid status	No	%	No	%	No	%
Euthyroid	12	24	13	26	25	25
Sub clinical	23	46	12	24	35	35
Overt	15	30	25	50	40	40
TOTAL	50	100	50	100	100	100

Chi square=5.997 ,P value=0.04986

Overall 40% of the patients belong to overt group,35% subclinical & 25% maintained euthyroid status.

In group 1 –majority about 46% of cases were subclinical, 30% overt & 24% euthyroid

In group2-50% of cases were overt ,26% euthyroid & 24% subclinical cases

Table 3:Distribution of hypertension in hypothroid patients(group 2)

Thyroid status	GHTN	%	PE	%	APE	%	TOTAL	%
Euthyroid	11	22	2	4	0	0	13	26
Subclinical	9	18	3	6	0	0	12	24
Overt	6	12	16	32	3	6	25	50
TOTAL	26	52	21	42	3	6	50	100

Chi square=16.55 ,Pvalue=0.002365

GHTN-gestational hypertension,PE-preeclampsia,APE-antepartum eclampsia

Incidence of GHTN is 52% (22%-euthyroid,18%subclinical,12%overt hypothyroid) PE is 42%(4%euthyroid,6%subclinical,32% overt hypothyroid) & APE is 6% (overt hypothyroidism) 32% of the preeclampsia patients were suffering from overt hypothyroidism

Dosage change during pregnancy

Table 4:Group 1

Period of diagnosis	change in dose	%	No change	%
Pre preg	13	26	12	24
preg	5	10	17	34
TOTAL	18	36	29	58

Treatment not taken by 3(6%) patients

Dosage change is seen in 36% patients at any time during pregnancy.

No change in 58% patients.

Table 5:Group2

Period of diagnosis	Change in dose	%	No change	%
Pre preg	12	24	13	26
Preg	9	18	16	32
TOTAL	21	42	29	58

Change in dosage is seen in 42% patients of which 24% were already known cases hypothyroid diagnosed before pregnancy.No change in 58% patients.

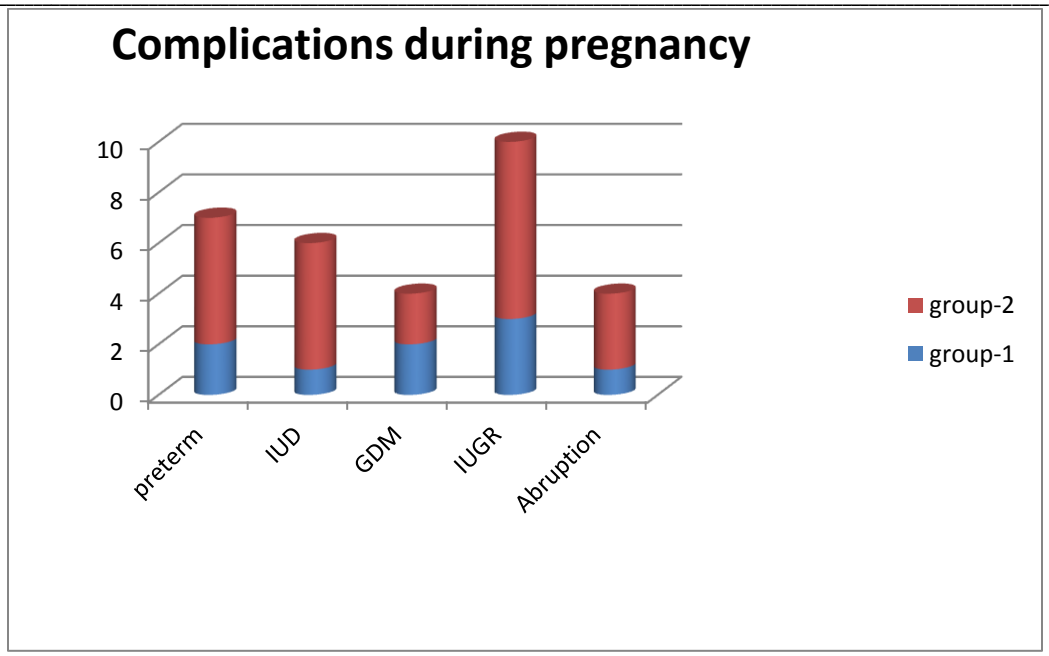

Fig 4 :IUD- intra uterine death ,GDM- gestational diabetes mellitus ,IUGR- intra uterine growth restriction

Group 1-preterm 4%,IUD 2%,GDM 4%,IUGR 6% & Abruption 2% .

Group 2-preterm 10%,IUD 10%,GDM 4%,IUGR 14% & Abruption 6%.

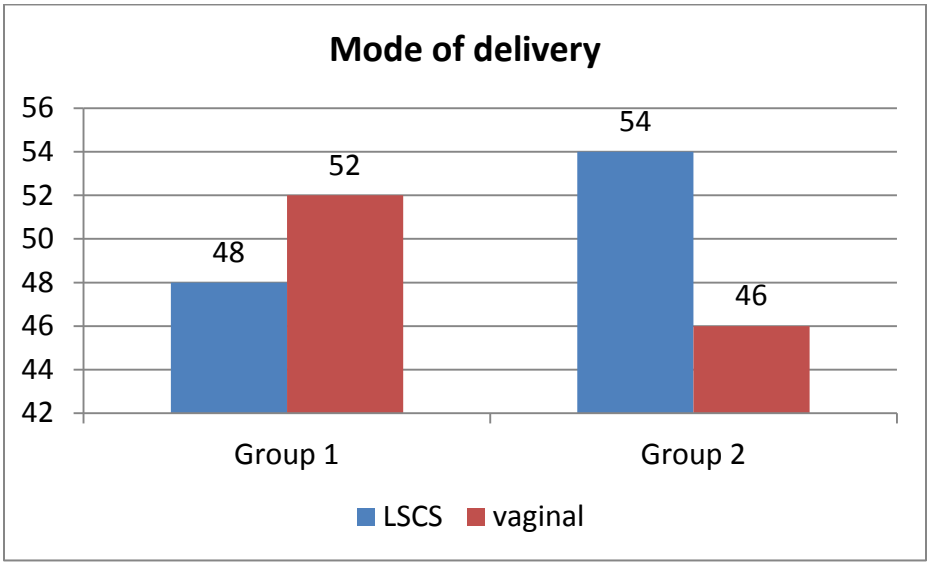

Fig 5 :Group1– total LSCS-24(48%) :Emergency -12(24%)& Elective -12(24%)

Group2- total LSCS-27(54%):Emergency-17(34%) & Elective -9(18%) Em.hysterotomy-1(2%) for abruption patient

Discussion

Thyroid dysfunction has an adverse effect on maternal and fetal wellbeing. Uncontrolled hypothyroidism and subtle hypothyroxinemia can cause adverse effect on obstetric and fetal outcome & also neuro-intellectual development in the offspring. In the present study maternal and fetal outcomes in hypothyroid normotensive patients (group1) and hypothyroid patients with associated hypertension (group2) were studied. In the present study 61% of the total patients were in the age group of 21-25yrs and 47% of the total patients were primigravida. No significant differences were seen in age and gravidity in both the groups. Cases suffering from overt hypothyroidism were 50% in group 2 compared to 30% in group1 (chi-square=5.997, p value=0.04986). Gestational hypertension (GHTN) was seen in 52% of group2 patients of which 12% belong to overt hypothyroid group. On the other hand 42% belong to preeclampsia of which 32% belong to overt group (chi-square=16.55, p value=0.00236).Although pregnancy is associated with mild hyperthyroxinemia, preeclampsia women have higher incidence of hypothyroidism[6].A study by Nadia et al[11]has shown a strong relationship between preeclampsia and hypothyroidism as 56% of screened preeclampsia patients had hypothyroidism. On the other hand preeclampsia is observed in 16.7% of subclinical and 43.7% of overt hypothyroid cases[12].BasbunG[15] studied that moderate decrease in thyroid hormones with concomitant increase in S.TSH levels correlate with severity of preeclampsia with a significant increase in endothelin levels

.S.TSH(1.55+/0.89microIU/mLversus2.96+/1.07micro IU/mL,P<.05)andendothelin(2.31+/0.61pg/mLversus6. 11+/1.41pg/mL,P<.001). Kumar.A[13]had showed that approximately 40% of preeclampsia women had S.TSH>5miu/ml compared to 12.2% in control. Leung et al[8] studied that 36% of overt and 25% of subclinical cases who remained hypothyroid at delivery developed hypertension. In this study 49% of hypothyroid cases were diagnosed during pregnancy & 51% were already known cases of hypothyroid diagnosed before pregnancy. Further a change in dosage requirement is seen in 36% in group1& 42% in group2.A retrospective study by Mandel SJ[14]had showed an increase in thyroxin requirement in 9 of 12 patients. Another study has showed an increase in thyroid requirement in 60% of patients at any time during pregnancy[15].Most of the cases in the present study had their visit in the 2nd trimester when already changes in thyroid physiology have taken place and the need for thyroid dose change is decreased. Complications seen in the present study were preterm (grp1 4% & grp2 10%), IUD (grp1 2% & grp2 10%), IUGR (grp1 6% & grp2 14%) and Abruption (grp1 2% & grp 2 6), Gestational Diabetes Mellitus (grp1&2 4%). Not much difference in GDM is seen in both the groups. But a higher incidence of preterm, IUD, IUGR and abruption is seen in group2.This is secondary to the severity of preeclampsia associated with raised thyrotropin levels similar to a study by Kumar.A [13]which showed approximately 40% of preeclampsia women had S.TSH>5miu/ml compared to 12.2% in control. IUGR& abruption complications were similar to a study by Goeletal et al[16] and IUD rates were comparable to a study by Davis[12] in overt hypothyroid patients. Tudela[18]studied that risk of developing GDM increases with increased thyrotropin levels. A negative correlation observed between birth weight and S.TSH in preeclampsia($r=-0.296$, $p<0.001$) M.Abolovich[19] studied that abortion, preterm & term deliveries in patients who are euthyroid on levothyroxine at the time of conception were 4%, 11%, and 84.9% respectively. Another study had showed that risk of preterm increase by two fold and risk of abruption by three times in subclinical hypothyroid patients[20].Ashoor[21]studied impaired thyroid function may predispose to miscarriage and fetal death. Wassurtrum [9] studied that 56% of pregnancies which initially presented with severe hypothyroidism resulted in caesarian section for fetal distress compared to 3% in mild hypothyroid/euthyroid patients. Study by R.Tudosa et al[22]showed early administration of treatment and maintenance of euthyroid status minimizes the risk of maternal and fetal complications. Exact mechanism whereby preterm labour, placental abruption and other pregnancy related complications occur is not known but one hypothesis being faulty early placentation.

Conclusion & summary

Thyroid hormone is essential for normal placental function and fetal brain development which in first trimester is dependent entirely on maternal thyroid hormone. Thyroid dysfunction has an adverse effect on maternal and fetal outcome. Of the total number of cases 61% were in the age group of 21-25 and 47% were primigravida. In group1 46% were suffering from subclinical and 30% from overt hypothyroidism whereas in group2 50% were suffering from overt and 24% from subclinical hypothyroidism. Of the 50% of the overt group with hypertension 32% were associated with preeclampsia. Changes in the thyroid hormone levels might be correlated with occurrence and severity of preeclampsia[13]. Further identification of thyroid

hormone in pregnancy might be of help in predicting preeclampsia[23].Need for thyroid dosage adjustment was 36% in group1 and 42% in group2.Thyroxine dosage often needs to be increased by 30%-50% by 4-6 weeks[Endocrine society, 2007].But most of the patients in our study had their first visit in second trimester when already changes in thyroid physiology has taken place. Complications in group2 (preterm-10%, IUD-10%, GDM-4%, LBW-14%, abruption-6%) were slightly higher than in group1 (preterm-4%, IUD-2%, GDM-4%, LBW-6%, abruption 2%) due to the severity of preeclampsia associated in group2. Early intervention with levo thyroxin showed no adverse obstetric and perinatal outcome[22].Hence preconception and early pregnancy counseling regarding importance of thyroid control is recommended. Currently the need for universal thyroid screening is controversial. Targeted screening can detect only two thirds of the cases[24] and also universal screening is found to be more cost effective than not screening[25].As early diagnosis and thyroxin replacement can prevent the adverse maternal and perinatal complications, thyroid function tests should be included in the line of routine investigations done on antenatal mothers.

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