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Association of Thyroid Status with Pregnancy Induced Hypertension and Impact of Levothyroxine Treatment.

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ABSTRACT

Background: Pregnancy induced hypertension is an important cause of maternal and fetal morbidity and mortality affecting 5-10% of pregnancies.PIH is more frequently associated with elevated TSH. Hypothyroidism is one of the causes of hypertension in nonpregnant state. Hypertension is completely reversible in 50% cases of hypothyroidism by levothyroxine therapy. Treating hypothyroidism in pregnancy may help to reduce PIH prevalence. Objectives- This is an observational study to find out association of PIH with hypothyroidism and to know result of levothyroxine treatment on PIH prevalence and its severity. **Methods:** 75 singleton pregnancies with PIH admitted to labour ward, evaluated with their TSH status in groupA. In Group B, 75 singleton pregnancies with subclinical or overt hypothyroidism treated with levothyroxine to maintain euthyroid state throughout pregnancy and observed for development of PIH. Overt hypothyroidism considered when TSH value ≥10 and subclinical hypothyroidism when TSH value between 3 and 10.. **Result:** Overt and subclinical hypothyroidism was present in 12% (9 out of 75) and 57.3%(43 out of 75) cases of PIH respectively. In group B, all hypothyroid pregnancies treated with levothyroxine throughout pregnancy, prevalence of PIH was 6.66% (5 out of 75) . Significant association of PIH and hypothyroidism demonstrated by Fisher's exact test ($p<0.001$). PIH prevalence significantly reduced in treatment group demonstrated by chi square test ($p<0.001$). **Conclusion:** Subclinical and overt hypothyroidism prevalence is significantly high among PIH patients. Treating subclinical and overt hypothyroidism in pregnancy, reduces prevalence of PIH and its severity.

Keywords: Hypothyroidism, Levothyroxine, Pregnancy Induced Hypertension.

INTRODUCTION

Pregnancy induced hypertension is new onset hypertension after 20 weeks of gestation with or without proteinuria.[1] They affect upto 5-10% of pregnancies and important factor of maternal and fetal morbidity and mortality.[1] This remains among top 3 causes of maternal morbidity and mortality globally.

Hypothyroidism has been listed as one of the causes of high blood pressure.[2] Pre-eclampsia is more frequently associated with elevated TSH.[3]One or more episodes of preeclampsia is associated with higher risk of reduced thyroid function subsequently.[3] The pathogenesis of hypothyroidism causing PIH may be due to altered nitric oxide release which results in endothelial cell dysfunction. Reduced nitric oxide causes vasoconstriction and arterial stiffness.[4] Hypothyroidism gives rise to diastolic hypertension, increased peripheral vascular resistance, hence decreased tissue perfusion due to vasoconstriction in systemic and renal vessels.[5]

Thyroid dysfunction is associated with proteinuria which results in increased excretion of thyroxine and thyroid binding globulins.[6]

Hypertension is completely reversible in 50% cases by thyroid hormone replacement therapy alone in hypothyroid patients.[7] Correction of hypothyroidism in pregnancy should maintain blood pressure within normal limit, may reduce prevalence of PIH and consequences of it.

In our study, we have evaluated thyroid status in PIH patients. Hypothyroid PIH patients can be considered as untreated candidates. Another group with subclinical or overt hypothyroidism detected in first trimester were treated adequately throughout pregnancy to maintain euthyroid state. Prevalence of PIH in this group was compared with the untreated groupto know whether treatment with levothyroxine in hypothyroid patients has any beneficial role in reducing PIH prevalence.

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MATERIALS AND METHODS

This is a comparative observational study between group A (untreated) & group B (treated group with

levothyroxine).This study was conducted in IMS & SUM Hospital under SOA university during period of January 2016 to December 2016.Ethical clearance was obtained from institutional ethics committee.

Group A comprises of 75 pregnant women with PIH admitted to labour room whose thyroid status was not known. All were singleton pregnancies at 28 - 40weeks of gestation. PIH was confirmed when BP recorded was 140/90 or more on 2 occasions 6 hours apart. For all cases urine analysis for proteins was done by dipstick method. Women without proteinuria were designated as gestational hypertension, those with proteinuria were included in PET group. Those with seizures were included in eclampsia group.

All pregnant women with known thyroid disease under treatment, systemic disorders like chronic hypertension, diabetes mellitus, autoimmune & collagen vascular diseases, medications affecting thyroid function are excluded from the study. For all recruited patients, informed consent was obtained. Serum TSH estimation was done.

Group B comprises of 75 women registered to our antenatal OPD with high TSH value done in first trimester. TSH value is routinely screened in all pregnant women in our institute. All these women with subclinical or overt hypothyroidism detected in first trimester. After obtaining informed consent, all were treated adequately with levothyroxine to maintain thyroid normalcy throughout the pregnancy. It was ensured by thyroid evaluation every 4 to 6 weeks. Pregnancies were followed till delivery for different maternal &fetal complications including PIH.

TSH estimation is done by electrochemoluminiscence method. TSH reference ranges are accepted as recommended by American Thyroid association.(First trimester -0.1-2.5mIU/L, Second Trimester-0.2-3mIU/L, Third trimester-0.3-3mIU/L).OH is considered when TSH value ≥10,subclinical hypothyroidism when TSH value between 3 &10,euthyroid state when TSH≤3 in 2nd and third trimester and ≤ 2.5 in first trimester according to guidelines of ATA.

Statistical Analysis

Statistical analysis is done with SPSS 20 version. Statistical significance was taken at 0.05 value. Datas analysed with unpaired t test, Yates corrected Chi-square and Fisher's-exact test.

RESULTS

Demographic data of both groups like age and parity were similar as mentioned below.

Data illustrated in [Table 1] depicts age distribution in both groups. Data analysed by unpaired t test (p value equals 0.1980 which is>0.05,hence not statistically significant)

Mean age of group A is 26.55±4.32 years

Mean age of group B is 27.36±4.19 years.

Data illustrated in [Table 2] depicts parity distribution in both groups. Data analysed byChi square test shows no significant difference between the two groups (p value 0.7382)

We have compared number of patients in each group with respect to age and parity. Age distribution was compared with unpaired t test.It revealed p=0.19 which is more than 0.05 which implies there is no significant difference. Parity in both groups compared with Chi square test. p value came out to be 0.7382 which is more than 0.05which implies there is no significant difference.

This suggests two groups are similar comparing their demographic variables.

[Table 3] depicts the gestational age at which the thyroid abnormality has been diagnosed. In group A, all patients recruited are all PIH patients attending to our labour room. For them, age of diagnosis of thyroid status is 34-40weeks. Gestational age at diagnosis of thyroid disorder in-group B is 10-12weeks (i.e. in their first antenatal visit)

[Table 4] depicts the type of hypertensive disorder in group A patients.In group B(treated group),5 women developed PIH .All cases were of mild variety. None of them developed any complications like eclampsia, HELLP syndrome.

[Table 5] depicts thyroid status of group A population i.e the PIH group. All patients are with unknown thyroid status which means they are untreated. Overt hypothyroidism is present in 9 out of 75(12%) cases which is quite significant. Subclinical hypothyroidism was present in 43(57.3%) patients.

[Table 6] depicts thyroid status of group B patients. Patients in group B who were picked up from routine screening in first trimester , were treated with L-thyroxine to maintain euthyroid state throughout pregnancy .Thyroid status was monitored every 4-6 weeks.Out of the 75 treated patients ,only 5 women developed PIH.4 were in subclinical hypothyroidism group and 1 woman in overt hypothyroidism group.

Now, association of hypothyroidism with PIH was tested. In group A(75=all PIH patients),52 out of 75 (69.3%)had either subclinical or overt hypothyroidism which is quite high compared to prevalence in normal population. Incidence of hypothyroidism in normal pregnant population is 5-15%.[8]

In group B,(75=all hypothyroid patients) ,treated adequately to make them euthyroid.In these euthyroid women,prevalence of PIH was 6.66%(5 out of 75) which is comparable to prevalence in normal population.[1]

[Table 7] depicts association of hypothyroidism with PIH. Comparing these 2 groups by Fisher's exact test p value is <0.001, which is significant. So, association of PIH and hypothyroidism is significant according to our study.

Now, prevalence of PIH was compared between untreated (group A) and treated (group B) patients. In group A, 52 patients are hypothyroid, untreated, all have PIH. In group B, 75 patients are hypothyroid, all are treated,only 5 women have developed PIH. Comparing by unpaired t test, p value is <0.001.So, according to our study, treatment of either subclinical or overt hypothyroidism, reduces prevalence of PIH.

The next question is, whether, treatment of subclinical hypothyroidism, reduces prevalence of PIH? Among group A patients, 43 women are with subclinical hypothyroidism, all have developed PIH. Among group B patients, out of 57 patients of subclinical hypothyroidism,4 patients developed PIH. Comparing both groups by chi square test, p value is <0.001 which is significant.

[Table 8] depicts perinatal outcome among both groups

In group B (treatedgroup), 5 neonates out of 75(6.67%) required NICU admission in comparison to group A (untreated PIH group) where 24(32%) required NICU admission.

In group B, no baby was stillborn whereas 11(14.7%) in group A.

Table 1: Age Distribution In Both Groups.

Age Distribution (Years)	Group A (No.Of Patients)	Group B (No.Of Patients)
16-20	4	4
21-25	30	22
26-30	30	32
31-35	9	15
>35	2	2
TOTAL	75	75

Table 2: Distribution Of Patients According To Parity.

Parity	Group A	Group B
Primigravida	47	44
Multigravida	28	31
Total	75	75

Table 3: Distribution Of Patients According To Gestational Age At Diagnosis (Group A)

Gestational age at diagnosis (in weeks)	<34	34-37	37-40
No of patients	4	26	45

Table 4: (Group A)

Type of hypertensive disorder	GH(gestational hypertension)	PET	Eclampsia
No of patients	12(16%)	49(65.3%)	14(18.7%)

Table 5: (Group A=75)

TSH value (in micro IU/ml)	<3(euthyroid)	3-10 (subclinical)	>10(overt)
No of patients	23(30.7%)	43(57.3%)	9(12%)

Table 6: (Group B=75)

Distribution of hypothyroid patients according to their thyroid status	Subclinical	Overt
No of patients(75)	57(76%)	18(24%)
Women developing PIH after treatment(5=6.66%)	4	1

Table 7: Perinatal Outcome

Group	Outcome 1(PIH)	Outcome 2(Hypothyroidism)
Group A	75	52
Group B	5	75

Table 8:

Perinatal outcome	Normal	ICU admission	Stillborn
Group A(No of patients=75)	40(53.3%)	24(32%)	11(14.7%)
Group B(No of patients=75)	70(93.3%)	5(6.67%)	0(0%)

DISCUSSION

Subclinical hypothyroidism is associated with adverse pregnancy outcomes, yet routine screening for thyroid disorders is a highly controversial. According to ACOG practice bulletin 2015,routine screening in pregnancy is not recommended.[9]Serum TSH estimation is the first line of screening in pregnancy.[9] Overt hypothyroidism should be adequately treated.[9]Selective screening is recommended in women with positive family history, pre-existing thyroid disease, goitre,type1 diabetes, preterm delivery, prior therapeutic head & neck irradiation.[10]

History of PIH is not considered in selective screening group. In our study in group A ,i.e.in PIH patients,9 out of 75 women (12%) had overt hypothyroidism. Had it been diagnosed in early pregnancy by routine screening, all would have been treated. In our study ,in group A(PIH patients) , prevalence of subclinical hypothyroidism is very high.43 out of 75 (57.3%) had subclinical hypothyroidism.

A cross sectional multicentre Indian study concluded prevalence of hypothyroidism in pregnancy is 13.13%,majority being subclinical.[11]

Prevalence of overt & subclinical hypothyroidism in pregnant population is 4.6% and 6.5% according to a study conducted on 633 Indian women. This study proved positive relationship of overt and subclinical hypothyroidism with PIH, intrauterine growth restriction and intrauterine fetal demise.[12]

Our study shows prevalence of overt and subclinical hypothyroidism in PIH population 12% and 57.3% respectively which is very high compared to normotensive pregnant population.

PIH prevalence was significantly high in overt and subclinical hypothyroid patients than the general population.36% overt and 25% subclinical hypothyroid women who remained hypothyroid at delivery(inadequately treated) developed gestational hypertension.[13] According to Ashoor et al., impaired thyroid function may predispose to late preeclampsia. In this study mean arterial pressure, uterine artery pulsatility index ,serum TSH was measured at 11-13 weeks of gestation in 102 singleton pregnancies those who developed PET subsequently and values compared with 4318 normal pregnancies.MAP and uterine artery PI was increased both in early(requiring delivery before 34 weeks) and late PET.TSH was significantly raised in cases of late preeclampsia.[14] Similar finding is observed in our study,71 out of 75(94.6%) cases in PIH group were late preeclampsia cases.12% of them having overt and 57.3% having SCH.

TSH levels are significantly higher in preeclampsia patients compared to normal pregnancy according to manjunath et al.[15] 57.3% cases of PIH in our study found to have subclinical hypothyroidism.

Similar result has been documented by other authors that subclinical hypothyroidism identified during pregnancy have increased risk of severe preeclampsia compared to euthyroid women.[16]

Consensus by two important endocrinologist societies (AACE & ATA) recommend TSH as the single best screening test for primary thyroid function. Decision to treat subclinical hypothyroidism should be tailored to individual patient.[17]

It will be logical to treat, if correction of hypothyroidism will reduce the prevalence of PIH or reduce the severity. In our study, group B are pregnant women having subclinical or overt hypothyroidism detected early in pregnancy in first trimester. All were treated adequately. Only 5 out of 75(6.7%) developed PIH .All were of mild variety without any severe complication of PIH. Comparison of treatment versus no treatment group by unpaired t test shows p value<0.001 which is significant. Among them, cases of overt hypothyroidism should be treated, it is uncontroversial.

Comparison of treated vs untreated cases of subclinical hypothyroidism by chi square test shows p value<0.001 .Treatment of SCH reduces prevalence of PIH significantly according to our study. According to study by Ashoor et al, hypothyroidism detected at 11-13 weeks predicts late preeclampsia.[14] In our study, treating such a pregnant population has reduced PIH prevalence comparable to general population.

Treatment of SCH in non-pregnant state reduces total cholesterol, non-HDL cholesterol, apolipoprotein B.[18] Levothyroxine treatment also reduces arterial stiffness and systolic blood pressure.[19]

Similar finding observed in a case report in a25 year old primigravida with hypertension detected at 22 weeks detected to have subclinical hypothyroidism. Treatment with levothyroxine alone normalised the blood pressure and pregnancy could be continued till term.[20]

Severe hypothyroidism can cause a pre-eclampsia like syndrome, particularly early onset. Treatment with levothyroxine reduces proteinuria and hypertension.[21] Similar observation found in our study. Treated group had low prevalence of PIH and mild variety.

Treatment of subclinical hypothyroidism in pregnancy is hugely controversial. Only candidates of SCH with TPO antibody positivity are to be treated considering the complications of pregnancy.[22] Very few studies have investigated whether treatment with levothyroxine can improve the pregnancy outcome.

Treatment of subclinical hypothyroidism reduces pregnancy loss significantly particularly with TSH levels between 4-10.At a TSH level between 4-10,there was no difference between treated and untreated group in relation to PIH development.[23]

Thyroid hormone treatment was associated with decreased pregnancy loss among women with subclinical hypothyroidism, especially with TSH concentration 4.1-10mIU/L. But associated with increased risk of preterm delivery, PIH and GDM.[24] But it was a retrospective observational study and use of administrative claims like potential for misclassification of treatment and confounders, lack of clinical details, selection biases related to health plan enrolment, diagnostic testing and treatment choice.

Women with treated hypothyroid disease had an increased risk for PIH(4.3% vs 2.6%,p=0.03) compared to women without thyroid disease.[25] A register based Swedish study without estimating treatment adequacy found increased risk of preeclampsia and diabetes compared to women in reference population.[26]

Neonatal outcome in untreated group(group A) analysed.24 out of 75 cases(32%) required neonatal ICU care and 11(14.7%) were still born. This perinatal outcome can be explained as result of PIH causing prematurity, LBW babies. According to a chinese single center cohort study, pregnant women with SCH had increased risk of gestational hypertension, LBW and IUGR babies.[27]

Impaired thyroid function may predispose to miscarriage and fetal death according to Ashoor et al.[28] Levothyroxin treatment is associated with decreased risk of low birth weight babies and low APGAR score among women with Subclinical Hypothyroidism.[29] Similar findings observed in our study. In untreated group 32% babies required ICU admission & 14.7% babies were stillborn.

In the treated group,5 out of 75(6.67%) required neonatal ICU admission, not a single baby was

stillborn. Normalisation of thyroid function may prevent gestational hypertension and its attendant complications i.e. premature delivery and poor perinatal outcome.[11] Similar finding observed in our study.

CONCLUSION

1. Routine screening is strongly recommended according to our study. We are missing a good number of overt and subclinical hypothyroid patients ,if this is not done.
2. Selective screening group does not include PIH patients. This group contains 12% cases of overt hypothyroidism in comparison to 0.2to 0.3% in normal pregnant population. Subclinical hypothyroidism prevalence is very high(57.3%) compared to normal pregnant population(6.5%).So, patients with history of PIH in previous pregnancy must be included in selective screening group. Cases of early onset of PIH should be evaluated with thyroid status. Treating from that point of time may improve outcome of pregnancy.
3. PIH is significantly associated with raised TSH, both subclinical and overt hypothyroidism.
4. Treatment of hypothyroidism(overt and subclinical) reduces prevalence of PIH. It reduces severity and complications of PIH.

Limitations

Both the groups are not exactly similar demographically .Group A candidates are already in third trimester and group B candidates are in first trimester. Though it would have been best to do a prospective randomised trial between treatment and no treatment group, such investigation is unethical after knowledge of possible adverse outcomes of subclinical and overt hypothyroidism in pregnancy quoted in various studies.

Anti TPO antibody was done in only few cases because of cost factor. According to ATA guidelines, pregnancies with subclinical hypothyroidism and high Anti TPO antibody should be treated.

Larger studies in future may throw light on this subject.

Abbreviations

AACE -American Association of Clinical Endocrinologists
ATA-American Thyroid Association
MAP- mean arterial pressure
PI- Pulsatility index
PIH-Pregnancy induced hypertension
PET- Pre eclamptic oxaemia
SCH-subclinical hypothyroidism
TPO – Thyroid Peroxidase

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