Original Research Article

Indian Journal of Obstetrics and Gynecology
Volume 8 Number 2, April – June 2020
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.8220.3

Association of Preeclampsia and Thyroid Dysfunction in Pregnant Women and Perinatal Outcome

Annapoorna Yalla[1], Jhansi Y[2], Sahithi A[3], Ganapathi Swamy C[4]

How to cite this article:
Annapoorna Yalla, Jhansi Y, Sahithi A, et al. Association of Preeclampsia and Thyroid Dysfunction in Pregnant Women and Perinatal Outcome. Indian J Obstet Gynecol. 2020;8(2):23–28.

[1]Assistant Professor, [2,3]Senior Resident, [4]Assistant professor, Department of Obstetrics and Gynecology/Biostatistics, GSL Medical College and Hospital, Rajahmundry, Andhra Pradesh 533296, India.

Corresponding Author: Annapoorna Yalla, Assistant Professor, Department of Obstetrics and Gynecology/Biostatistics, GSL Medical College and Hospital, Rajahmundry, Andhra Pradesh 533296, India.

E-mail: drsannapoorna@gmail.com

Received on 18.05.2020; **Accepted on** 30.06.2020

Abstract

Introduction: In preeclampsia, there is failure of estrogen production due to placental dysfunction resulting in lowering of TBG, TT3, TT4 along with growth retardation of the foetus. It has been shown that individuals with subclinical hypothyroidism have impaired endothelium derived vasodilatation from diminished nitric oxide secretion that is restored after thyroxine (T4) replacement. The present study is proposed to evaluate the association of preeclampsia and thyroid dysfunction in pregnant women and perinatal outcome.

Methods: The present study was carried out on pregnant women with preeclampsia admitted to or attending the Outpatient Department of Obstetrics and Gynecology GSL medical college and hospital, between June 1st 2018 to May 31st 2019. Similar number of age & parity-matched normotensive pregnant women served as controls. Battery of investigations focusing on thyroid hormones were performed and both groups were compared in terms of thyroid status, perinatal outcome and complications.

Results: Incidence of hypothyroidism is high but mostly subclinical.Women with preeclampsia had higher TT3, TT4 levels as compared to non pregnant women. TSH levels were higher significantly higher in preeclamptic women than normotensive pregnant women. A significant negative correlation was observed between birth weight and TSH levels serum albumin and TSH levels in preeclamptic women.

Conclusion: These findings indicate that there is state of hypothyroxinemia in normal pregnancy and in preeclampsia. Identification of changes in thyroid hormones in preeclampsia might be of help in preventing the occurrence of preeclampsia.

Keywords: Preeclampsia; Hypothyroidism; Thyroid hormones; Pregnant women.

Introduction

Endocrinological changes are very complex in pregnancy with a key hole understanding of many biochemical alterations. Thyroid hormone in particular has not been understood well until the recent decade. There is an increased thyroid demand and increased iodine uptake and synthesis of thyroid hormones during pregnancy. Estrogen induces a rise in serum thyroid binding globulin (TBG) and the placenta releases several thyroid stimulatory factors in excess e.g., human chorionic gonadotropin (hcg).[1]

Thyroid hormones have a number of actions on cardiovascular physiology and blood pressure regulation, which are mediated by genomic mechanisms that cause ventricular remodeling or by direct effects. In most cases, cardiovascular aberrations follow long-term exposure to excessive or decreased hormone levels.[2–4]

Preeclampsia is a condition whose understanding still is not complete, but we have few evidences. In preeclampsia, there is failure of estrogen production due to placental dysfunction resulting in lowering of TBG, TT3, TT4 (total thyroxine, total triiodo thyroxine) along with growth retardation of the fetus[5]. Increasing evidence suggests that oxidative stress and altered endothelial cell function may have a role in preeclampsia.[6–8]

Hypothyroidism has been recognized as a cause of secondary hypertensionIt has been shown that individuals with subclinical hypothyroidism (normal TT3, TT4 and raised TSH) have impaired endothelium-derived vasodilatation from diminished nitric oxide secretion that is restored after thyroxine (T4) replacement.[9] Experimental studies have indicated that release of nitric oxide (NO) is altered in hypothyroidism and the resulting endothelial cell dysfunction might be a pathogenetic mechanism for preeclampsia in hypothyroidism.[10] There is further evidence of vascular-related sequelae, specifically in autoimmune thyroid disorders have been associated with an increased risk for placental abruption.[11–14]

Actual association of hypothyroidism with preeclampsia is not proven but case reports of a preeclampsia like syndrome are observed repeatedly time and again.[15–17] A recent review article has come to a consensus overt and subclinical hypothyroidism are associated with maternal and perinatal morbidity including preeclampsia.[18]

In a study that included a small cohort of women, including only women screened before 20 weeks of gestation, there was no relationship between subclinical hypothyroidism and pregnancy-associated hypertension.[12] In another study, a possible protective relationship between subclinical hyperthyroidism and pregnancy-associated hypertension was noted.[19] Thyroid assay is not a routine part of antenatal care in low resource settings, except in high risk women. We incited this study to see the possibility of thyroid dysfunction in women with preeclampsia focusing on hypothyroidism.

Methods and Methodology

The present study was carried out on pregnant women (208) with preeclampsia admitted to the Inpatient Department of Obstetrics and Gynecology GSL medical college and hospital, between June 1st 2018 to May 31st 2019. Similar number (206) of age & parity-matched normotensive pregnant women were taken as controls.

Inclusion criteria

- Blood pressure of ≥140/90 mmHg on at least two occasions, six hours apart and/or proteinuria.

Exclusion criteria

- 1. History of chronic hypertension
- 2. Renal disease
- 3. Metabolic disorder
- 4. Medication known to affect thyroid function.

On inclusion into the study after consenting, a detailed history was taken and thorough clinical examination was performed. Women with preeclampsia were grouped into mild variety and severe variety. Mild preeclampsia was diagnosed in hypertensive women (>140/90) who also had 1+ proteinuria determined by urine dipstick.

Severe preeclampsia was classified in hypertensive women with any of the following:

- 2+ or more proteinuria by dipstick
- Blood pressure higher than 160/110 mm hg,
- Persistent headache,
- Visual disturbances,
- Right upper quadrant or epigastric pain,
- Serum creatinine 1.2 mg/ml or more,
- Serum aspartate transaminase levels more than twice the upper limit of normal,
- Thrombocytopenia (platelets less than 100,000/ml).
- Intrauterine growth retardation (IUGR)

Study samples were taken before starting treatment and serum separated for assay for thyroid hormones(T3, T4, TSH, TT3, TT4) by radioimmunoassay (RIA)(VIDAS, bio Merieux, S.A) with the following reference values.

- T3: 0.92–2.33 nmol/L
- T4: 60–120 nmol/L
- TSH: 0.25–5 μIU/ml
- FT3: 4.0–8.3 pmol/L
- FT4: 10.6–19.4 pmol/L

All women were screened with the following antenatal tests according to our departmental protocol.

Blood grouping and Rh typing, Complete blood picture, Urine for microscopy and protein, Random blood sugar HIV, HbsAg, VDRL, Ultrasound for fetal growth and placenta.

In addition, women with severe preeclampsia were subjected to the following investigations

- Liver function test (Total bilirubin, Direct bilirubin, Alanine transaminase, Aspartate transaminase, Alkaline phosphatase)
- Serum uric acid
- Serum creatinine
- Clotting time, bleeding time
- Fundoscopy
- Ultrasound for renal parenchymal disease or renal doppler
- Fetal doppler velocimetry as deemed necessary

Women with hypothyroid or hyperthyroid were treated according to the protocols. Antihypertensives were administered to women with hypertension and followed closely with regular maternal and fetal surveillance. Preeclampsia patients delivered either by spontaneous vaginal delivery or cesarean section. Decision for operative delivery was taken on the basis of obstetric indications. All the new born were compared with APGAR score, birth weight, thyroid screening and milestone achievement up to 6 wks or later. The data so obtained was analyzed statistically and student's *t*-test and regression analysis were carried out. (SSPS 20.0 software)

Results

The demographic characteristics between both groups were similar as shown in the (Table 1) making both groups comparable.

Severe preeclampsia was seen in 127 women of which 42 (33%) had proteinuria, 35 (28%) had systolic blood pressure >160 mm of Hg, 14 (11%) had imminent signs of eclampsia, 10 (8%) had eclamptic seizures, abnormal fundoscopy in 1 (.5%) and 25 (20%) had IUGR

Hematological parameters were similar except for serum albumin was significantly below the reference range in the control group when compared to the test group (63.7% *vs* 36.3%). Serum uric acid was consistently raised in the test group versus the control group (85% *vs* 15%). Average fetal weight of the fetus by ultrasound was 2165 gm in test group versus 2768 gm in control group before delivery, whereas average amniotic fluid index by ultrasound was 9.6 in test group versus 12.4 in control group. Average gestational age at delivery was 258 days in the test group versus 266 days in control group. Average gestational age of detection of preeclampsia was 212 days.

Table 1: Demographic parameters.

Demographic characteristic	Test group	Control group	*P*-value
Mean age years	25	24	0.8
Mean BMI	27	26	0.6
Socio economic status	Low	low	–
Primiparous *n*(%)	132 (64%)	126 (61%)	–
Multiparous *n*(%)	76 (36%)	80 (39%)	–
Co morbidities *n*(%)	10	12	–
Clinical gestational age in days average	258	266	0.5
Average wt of fetus	2165 gm	2768 gm	–
Average AFI	9.6	12.4	–

Anemia (hemoglobin <11 gm/dl) was more common in test group (n = 145) when compared to control group (n = 115). Of the anemic women 65 had mild anemia 50 had moderate anemia and had 30 severe anemia in test group whereas 45 had mild anemia 52 had moderate anemia and 16 had severe anemia in control group. The thyroid parameters are as in the (Table 2).

Thyroid stimulating hormone (TSH) was normal in the euthyroid levels in 70 (33%) of the women in the test group and 120 (59%) women in the control group. TSH was found to be more than the reference levels in 130 (63%) of the women in the test group and 80 (38%) women in the control group. Hypothyroidism was seen only in 8 (4%) of the women in the test group and 6 (3%) women in the control group. Infact in majority of women TT3 and TT4 were found to be increased. TT3 was more than reference levels in 105 (50%) of the women in the test group and 110 (53%)

women in the control group. TT4 was increased in 116 (55.5%) of the women in the test group and 126 (62.5%) women in the control group. TSH less than reference level was seen in 8 (4%) of the women in the test group and 6 (3%) women in the control group. The rest had normal TT3 and TT4 in both the groups.

Some women did not approach term delivery and had a intrauterine death or still birth accounting to 6 women each from test and control group. 102 (51%) of the women in the test group and 130 (65%) women in the control group had normal vaginal delivery either induced or spontaneous onset. 16(8%) of the women in the test group and 12 (6%) women in the control group had assisted vaginal delivery with forceps and 10 (5%) of the women in the test group and 16 (8%) women in the control group had vacuum assisted delivery for various fetal and maternal indications. 74 (37%) of the women in the test group and 42 (21%) women in the control group had caesarian delivery for various indications.

Table 2: Thyroid hormone levels.

Parameter	Test group	Control group
Euthyroid TSH (0.25–5 mIU/ml)	70 (33%)	120 (59%)
Hypothyroid TSH (>5 mIU/ml)	130 (63%)	80 (38%)
Hyperthyroid TSH < 0.1	8 (4%)	6 (3%)
TT3(0.92–2.33 nmol/L)	95 (46%)	90 (44%)
T3 (>2.33 nmol/L)	105 (50%)	110 (53%)
T3 (<0.92 nmol/L)	8 (4%)	6 (3%)
TT4(60–120 nmol/L)	86 (43%)	74 (37%)
TT4 (>120 nmol/L)	116 (55.5%)	126 (62.5%)
TT4 (<120 nmol/L)	4 (1.5%)	2 (0.5%)

Most of the babies born to mothers in both groups had a good APGAR score. Birth weights of the babies were as follows (Table 3).

There were 58 NICU admissions in the test group and 12 admissions from the control group. The most common causes of admissions being prematurity, low birth weight, birth asphyxia, respiratory distress, sepsis. There were 26 neonatal deaths in the test group and 4 in the control group, most common cause being respiratory distress, sepsis and necrotizing enterocolitis. There was one neonatal cardiac anomaly.

All the neonates were tested for thyroid hormones and all the babies were found to have normal values. After loss to follow up till date 6 babies from the test group and 4 from the control group were having delayed milestones and the reasons are currently unknown. 115 babies from the test group and 126 babies from the control group have reached the appropriate milestones to date. All the women were tested again at 6 weeks for thyroid hormones and medications adjusted accordingly.

Table 3: Birth weight.

Birth weight	Test group	Control group
Extremely low birth weight (<1000 gms)	3 (1.5%)	1 (0.5%)
Very low birth weight (1000–1500 gms)	36 (17.5%)	10 (5%)
Low birth weight (2000–2500 gms)	86 (42.5%)	35 (17.5%)
Normal birth weight (>2500 gms)	77 (38.5%)	154 (77%)

Discussion

The incidence of preeclampsia is about 7.8% in our institute. It being a tertiary referral unit, the incidence of preeclampsia is a bit higher than the reference levels 5.4% in other studies.[20] In India incidence of hypothyroidism is higher (13.3%) mostly being subclinical hypothyroidism.[21] The incidence in our study is much higher in both the groups as we considered a higher cut off value (5IU)[22] when compared to the cited study (4.5 IU).

Thyroid stimulating hormone TSH is found to be significantly high ($p < 0.05$) in the test group compared to the control group.This reinforces our

theory reduced estrogen causing reducing TBG and T3, T4 values. In a similar study conducted by Sardana D et al.,[23] normotensive non pregnant women were compared with normotensive pregnant women and preeclamptic women. TSH was significantly raised in the preeclamptic group, which suggest the role of estrogen in the thyroid hormone dynamics. T3 levels were normal in both the groups for most of the subjects, while 8% had higher values in the control group though not statistically significant ($p = 0.08$). T4 levels were mostly normal in both the groups, while a slightly higher value was seen in the control group ($p = 0.09$).

Serum albumin was found to be stastically lower in test group when compared to the control group ($p < 0.004$). This could be due to the vasculopathy in the test group caused due to preeclampsia. Serum uric values also were higher in the test group ($p < 0.002$).

Though the etiopathogenesis of preeclampsia is complex, thyroid dysfunction seems to be a predictor for the severity of the preeclampsia as observed by the previous study.[23] Though our study did not establish the above difference between mild and severe cases, it is only logical to have severe thyroid dysfunction in more severe cases.

As expected, women with preeclampsia had neonates lower birth weights than that of the control group. ($p < 0.002$) and also more NICU admissions and perinatal mortality, but the milestones are similar in both the groups indicating no role of subclinical hypothyroidism in neurodevelopmental delay. Moreover there is no way of knowing the perinatal morbidity is caused by preeclampsia or hypothyroidism. May be another study where overt hypothyroid women and preeclamptic women may be compared to know the actual morbidity. Most of the neonates had normal thyroid function, again an attribute to the complexity of the pathogenesis

Conclusion

Preeclampsia is an important cause for morbidity to the mother and the baby. Subclinical hypothyroidism is associated with preeclampsia. Though the pathogenesis is entirely unclear, some underlying factor like estrogen maybe the causative agent. Though it is very early to use hypothyroidism as a predictor for severity of preeclampsia, its simplicity cannot be overrated as correction is simple and feasible. More randomized studies should be initiated in this regard as the understanding of the disease is still primordial.

References

1. Brent GA. Maternal thyroid function: Interpretation of thyroid function tests in pregnancy. Clin Obstet Gynecology 1997;40:3–15.
2. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. Curr Hypertens Rep 2003;5:513–20.
3. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501–09.
4. Sheffield JS, Cunningham FG. Thyrotoxicosis and heart failure that complicate pregnancy. Am J ObstetGynecol 2004;190:211–7.
5. Kaye E, Sahin Y, Ozkececi Z, et al. Relation between birth weight and thyroid function in preeclampsia-eclampsia. Gynecol Obstet invest 1994;37:30–3.
6. Kharb S, Gulati N, Singh V, et al. Lipid peroxidation and vitamin E levels in preeclampsia. Gynecol Obstet Invest 1998;46:238–40.
7. Kharb S, Total free radical trapping antioxidant potential in preeclampsia. Int J Gynecol Obstet 2000;69:23–6.
8. Kumar CA, Das UN. Lipid peroxides, anti-oxidants and nitric oxide in patients with preeclampsia and essential hypertension. Med Sci Monitor 2000;6:901–7.
9. Taddei S, Caraccio N, Virdis A, et al. Impairedendothelium-dependent vasodilation in subclinical hypothyroidism: Beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab 2003;88:3731–7.
10. Abbassi-Ghanavati M, Casey BM, Spong CY, et al. Pregnancy outcomes in women with thyroid peroxidase antibodies. Obstet Gynecol 2010;116:381–6.
11. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;105:239–45.
12. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 2008;112:85–92.
13. Haddow JE, McClain MR, Palomaki GE, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and placental abruption. Obstet Gynecol 2011;117(2 Pt 1):287–92.
14. Mecacci E., Parretti R., Cioni, et al., "Thyroid autoimmunity and its association with non-organ-specific antibodies and subclinical alterations of thyroid function in women with a history of pregnancy loss or preeclampsia," Journal of Reproductive Immunology, 2000;46(1):39–50.

15. Alfadda and M., Tamilia. "Preeclampsia-like syndrome thatis associated with severe hypothyroidism in a 20-week pregnant woman," American Journal of Obstetrics and Gynecology 2004;191(5):1723–24.
16. Annalisa Inversettietal"severe Hypothyroidism Causing Pre-Eclampsia-Like Syndrome"Case Reports in Endocrinology 2012(6):58605.
17. S. Patel, S. Robinson, R. J. Bidgood, et al. "A pre-eclamptic-like syndrome associated with hypothyroidism during pregnancy," Quarterly Journal of Medicine 1991;79(289):435–41.
18. Martínez Metal Hypothyroidism during pregnancy and its association to perinatal and obstetric morbidity: A review. Endocrinol Diabetes Nutr 2018 Feb;65(2):107–13. doi: 10.1016/j.endinu.2017.11.009
19. Casey BM, Dashe JS, Wells CE, et al. Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 2006;107:337–41.
20. Manjusha Sajith, et al. International Journal of Pharma Sciences and Research (IJPSR) Apr 2004;5(04).
21. Dhanwal DK. Prevalence of hypothyroidism in pregnancy: An epidemiological study from 11 cities in 9 states of India: Indian journal of endocrinology and metabolism Year 2016;20(3)387–90.
22. Erik K Alexander. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum Thyroid Volume 27, Number 3, 2017[a] American Thyroid Association[a] Mary Ann Liebert, Inc. DOI: 10.1089/thy.2016.0457
23. Sardana. "Thyroid hormones in pregnancy and preeclampsia" J Turkish-German Gynecol Assoc 2009;10:168–71.