

ASSOCIATION OF DUAL ENDOCRINOPATHY WITH SEVERITY OF PREECLAMPSIA - A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Introduction: Hypertensive disorders complicate 5-10 percent of all pregnancies and contributes greatly to maternal and fetal morbidity and mortality. Women with gestational diabetes are at increased risk of preeclampsia and worsens the fetal prognosis. Thyroid hormones seem to be important in placentation and regulation of early pregnancy, partly explaining the association between hypothyroidism and preeclampsia. Incidence of both hypothyroidism and gestational diabetes was found significantly higher in women with Preeclampsia Induced Hypertension. There are few studies worldwide to establish the association between Preeclampsia, gestational diabetes mellitus and hypothyroidism in pregnancy. **Objective:** The objective of this study was to determine the association of dual endocrinopathy in pregnancy with severity of preeclampsia. **Study Design:** Prospective Observational Cross-sectional Study **Material and Methods:** 400 patients who met inclusion criteria and consented for the study were recruited in the study from November 2015 to October 2016 in the Department of Obstetrics and Gynaecology , SMGS Hospital, Govt Med College Jammu. All patients underwent relevant blood and urine tests. They were grouped into 2 groups – mild and severe preeclampsia. The association of two groups with dual endocrinopathy (hypothyroidism and gestational diabetes mellitus) was studied. **Statistical analysis:** Chi-square test was employed to determine association of dual endocrinopathy with severity of preeclampsia. P-value less than 0.05 was considered statistically significant. **Results:** In this study, majority of patients i.e. 70.50% (282 out of 400) were in the mild preeclampsia group and only 29.50% (118 out of 400) were in the severe preeclampsia group. According to present study, 14.4 % of severe preeclampsia patients had dual endocrinopathy while only 7.8 % of mild preeclampsia patients had dual endocrinopathy. This association was calculated using Chi-Square Test and was statistically significant (P value = 0.042). **Conclusion:** We found that there exists

significant association of dual endocrinopathy with severity of preeclampsia. Therefore the current study emphasise that early identification of dual endocrinopathy in patients of preeclampsia ,so timely treatment might decrease the morbidity associated with preeclampsia.

Keywords – Dual endocrinopathy, severity of preeclampsia, hypothyroidism, gestational diabetes mellitus.

INTRODUCTION

Hypertensive disorders complicate 5-10 percent of all pregnancies and contributes greatly to maternal and fetal morbidity and mortality. The preeclampsia syndrome is the most dangerous one (1). The etiology of preeclampsia is still obscure, despite many attempts to identify possible causes. Current theories suggest that clinical features of this syndrome are caused by systemic endothelial dysfunction resulting from abnormal placental development (2). The oxidative stress, inflammation, and vascular dysfunction have been implicated in the etiology of preeclampsia. At the placental level, failed adaptation of the uterine spiral arteries may cause hypoxia and repeated ischemia-reperfusion injury (3).

Insulin resistance has also been hypothesized to contribute to the pathophysiology of preeclampsia. Women who develop preeclampsia are more insulin resistant as compared to normotensive women. This effect is partially explained by the fact that many risk factors for preeclampsia are also associated with insulin resistance like obesity, advanced maternal age, non-white race, chronic hypertension and diabetes (4, 5).

In recent decades , the prevalence of diabetes is on rise (6). The reasons for the rise are mainly changes in lifestyle, dietary habits, older age at first conception, polycystic ovarian disease, obesity, metabolic syndrome, increased awareness and changing testing methodology for the condition. African American, Native American, Asian, and Hispanic women are at higher risk for gestational diabetes compared with white women (7). Women with gestational diabetes are at increased risk of preeclampsia and worsens the fetal prognosis (8). Fetal risks include spontaneous abortions, preterm delivery, malformations, fetal growth restriction, fetal demise, hydramnios, respiratory distress syndrome, hypoglycaemia, hypocalcemia, hyperbilirubinemia, polycythemia, hypertrophic cardiomyopathy, long term cognitive disorders including autism spectrum disorders or developmental disorders and inheritance of diabetes.

Hypothyroidism is the second most common endocrinopathy during pregnancy. The prevalence of hypothyroidism is about 2.5%, with clinical hypothyroidism accounting for 0.2–0.3%, and subclinical hypothyroidism for 2–3% (9,10). The pathophysiology correlating hypothyroidism and preeclampsia is not clear. Thyroid hormones seem to be important in placentation and regulation of early pregnancy, partly explaining the association between hypothyroidism and preeclampsia (11). It was postulated that the effect of preeclampsia on thyroid function during pregnancy is mediated by antiangiogenic factor soluble fms like tyrosine kinase (sFlt-1) which is elevated in patients with preeclampsia (12). During pregnancy there is increased demand for thyroid hormone. High maternal free T4 concentrations are associated with a higher risk of preeclampsia (13). Women who develop preeclampsia are more like to have decreased thyroid function (14). It is associated with adverse health outcomes for both mother and child, including increased risk of miscarriage,

gestational hypertension, preterm delivery, placental abruption, low birth weight and fetal death (15). Association of maternal thyroid insufficiency has been reported with delayed neuropsychological development in neonate and child (16).

Incidence of both hypothyroidism and gestational diabetes was found significantly higher in women with Preeclampsia Induced Hypertension (17).

As there are few studies worldwide to establish the association between preeclampsia, gestational diabetes mellitus and hypothyroidism in pregnancy. Therefore, the present study was conducted to determine the association of dual endocrinopathy in pregnancy with severity of preeclampsia.

METHODS

Study design

This was a prospective observational cross sectional study conducted in a tertiary care centre over a period of 1 year from November 2015 to December 2016 at SMGS hospital, Government Medical College, Jammu. Ethical approval was taken.

Study population

Singleton pregnant women at 24 weeks or more who delivered at SMGS Hospital, Jammu

INCLUSION CRITERIA

1. Age 18 - 40 years
2. Patient with two Blood Pressure readings of atleast 140 mmHg systolic and/or 90 mmHg diastolic, atleast 6 hours apart after 20th week of gestation with proteinuria $\geq 1+$ by qualitative urine examination or $\geq 0.3\text{g/L}$ in a 24 - hour urine collection after 20 weeks of gestation.

EXCLUSION CRITERIA

1. Pregnancy with Gestational hypertension, Eclampsia, Chronic hypertension, Preeclampsia superimposed on chronic hypertension
2. All women with history of renal disease, metabolic disorders and other chronic illnesses during pregnancy
3. Multiple pregnancy
4. Molar gestation

METHODOLOGY

460 patients who met inclusion criteria and consented for the study were recruited in the study from November 2015 to October 2016 in the Department of Obstetrics and Gynaecology, SMGS Hospital, GMC Jammu. Informed consent from all patients was taken.

A proforma was prepared for each patient asking about her last menstrual period, obstetric history, past medical history, signs and symptoms on her first visit. Blood pressure was recorded in the right arm and sitting position after a 10-min interval of proper rest.

Women who were admitted to the labor/antenatal ward underwent basic investigations including blood group, CBC, RFTs, LFTs, Blood Sugar and special investigations including Urine for Albumin, 24 hour Urinary Protein, serum TSH and OGTT.

For the collection of 24 hr Urinary sample, the patients were instructed to void the first morning sample and then start collecting urine in a special container for the next 24 hours and

the next morning sample was also collected. Patients were advised to avoid dehydration and strenuous exercise.

Finally 400 patients remained in the study who could complete their sample collection properly. They were grouped into two groups – Group A: Mild preeclampsia & Group B: Severe preeclampsia. Then the respective association of 2 groups with dual endocrinopathy was studied.

Preeclampsia was defined as hypertension associated with proteinuria greater than 0.3g/L in a 24 hour urine collection or 1+ by qualitative urine examination, after 20 weeks of gestation. It was classified as mild and severe preeclampsia. Mild preeclampsia was defined as when systolic BP remains below 160 mmHg and diastolic BP remains below 110 mm Hg. Severe preeclampsia was defined as any one of the following including blood pressure \geq 160 mmHg or 110 mm Hg, recorded on atleast 2 occasions, at least 6 hour apart, proteinuria \geq 5g in 24 hours, oliguria \leq 500 ml in 24 hour, visual disturbances, epigastric pain, nausea and vomiting, pulmonary, impaired liver function, thrombocytopenia or fetal growth restriction (18).

Serum TSH levels were measured by chemiluminescence immunoassay (CLIA). The TSH CLIA is based on the principle of a solid phase enzyme linked immunosorbent assay. The following reference ranges of TSH were taken (19)

First trimester - 0.1 to 2.5 mIU/L

Second trimester - 0.2 to 3.0 mIU/L

Third trimester - 0.3 to 3.0 mIU/L

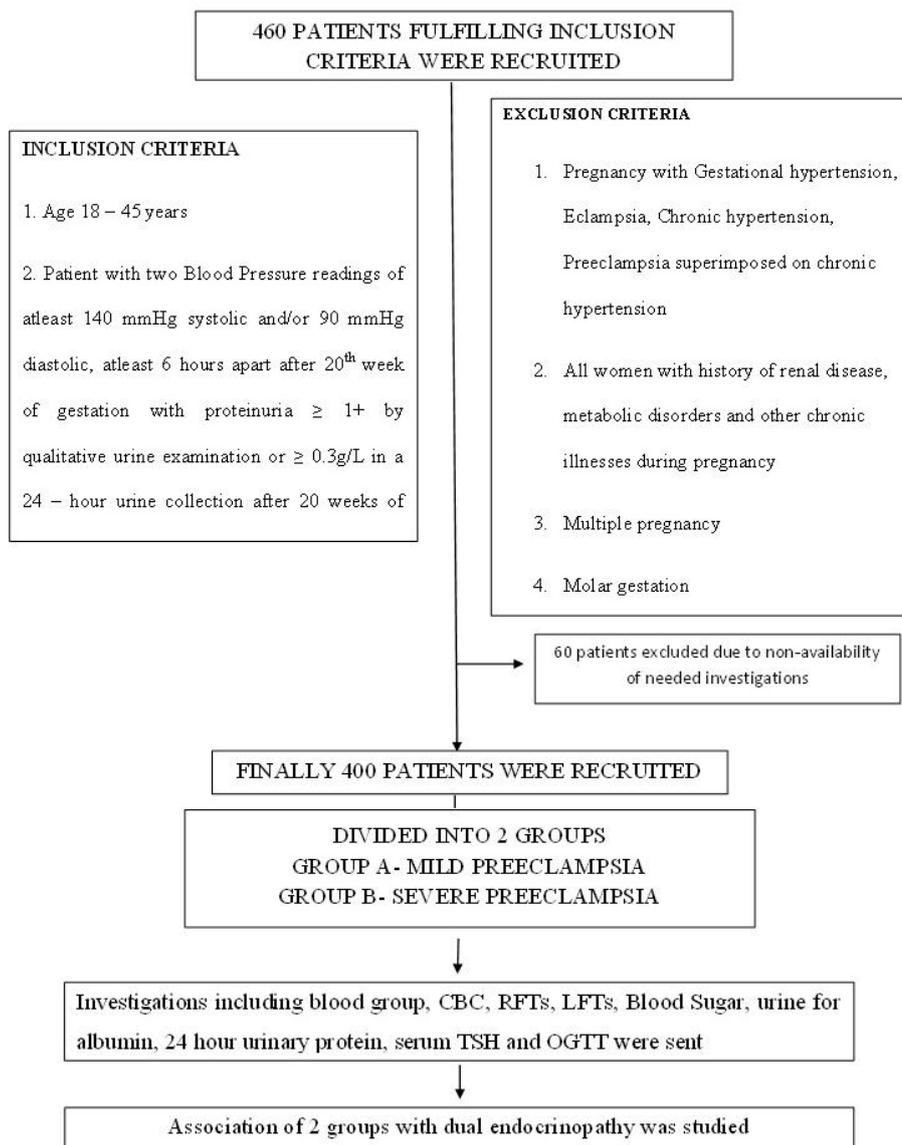
Gestational diabetes mellitus was defined as any degree of carbohydrate intolerance first detected during pregnancy (20). In all subjects, Oral Glucose Tolerance Test (OGTT) was done with 75 grams anhydrous glucose and plasma glucose was measured as fasting (after an overnight fast of atleast 8 hours), one and two hours. The diagnosis of Gestational Diabetes Mellitus was made when any of the following plasma glucose values were as follows:

Fasting blood glucose \geq 92 mg/dl

1 hr value \geq 180 mg/dl

2 hr value \geq 153 mg/dl

Statistical Methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean \pm SD and Categorical variables were expressed as percentages. Frequency distribution tables, and bar charts were used for data presentation. Chi-square test was employed to determine association of dual endocrinopathy with severity of preeclampsia. P-value less than 0.05 was considered statistically significant.

FLOWCHART OF METHODOLOGY**RESULTS**

Finally 400 patients remained in the study. Their blood and urine samples were sent for investigations as discussed above.

In this study, majority of patients i.e. 70.50% (282 out of 400) were in the mild preeclampsia group and only 29.50% (118 out of 400) were in the severe preeclampsia group.

According to this study, 9.75 % patients of preeclampsia had dual endocrinopathy (both hypothyroidism and gestational diabetes mellitus) which suggests a substantially higher prevalence of dual endocrinopathy in patients of preeclampsia.

Finally we found that there exists significant association of dual endocrinopathy with severity of preeclampsia. According to present study, 14.4 % of severe preeclampsia patients had dual endocrinopathy while only 7.8 % of mild preeclampsia patients had dual endocrinopathy. This association was calculated using Chi-Square Test and was statistically significant (P value = 0.042).

RESULTS

Table 1: Distribution of study patients as per severity of preeclampsia		
Severity	Number of Patients	Percentage
Group A-Mild Preeclampsia	282	70.50
Group B-Severe Preeclampsia	118	29.50
Total	400	100

In our study, maximum number of patients i.e. 70.50% (282 out of 400) were in the mild Preeclampsia group and only 29.50% (118 out of 400) were in the severe Preeclampsia group.

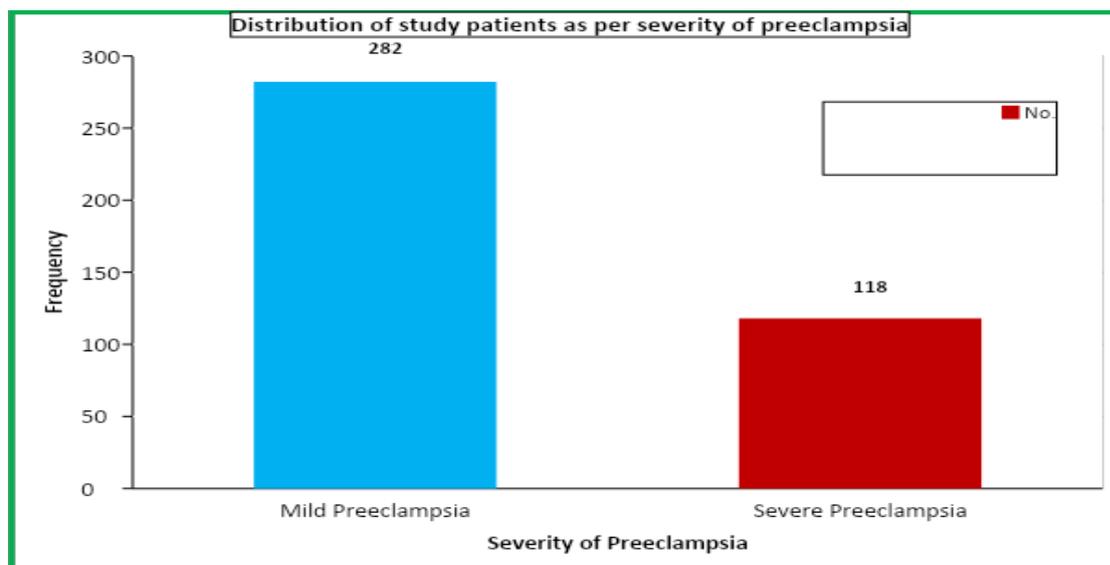


Figure 1:- Bar chart showing distribution of study patients as per severity of Preeclampsia

Table 2: Prevalence of Dual Endocrinopathy (Hypothyroidism and Gestational Diabetes Mellitus) in Preeclampsia patients		
Dual Endocrinopathy	Number of Patients	Percentage

Present	39	9.75
Absent	361	90.25
Total	400	100

According to above table, 9.75 % (39 out of 400) patients had Dual Endocrinopathy (both Hypothyroidism and Gestational Diabetes Mellitus) while 90.25% (361 out of 400) did not have Dual Endocrinopathy (both Hypothyroidism and Gestational Diabetes Mellitus).

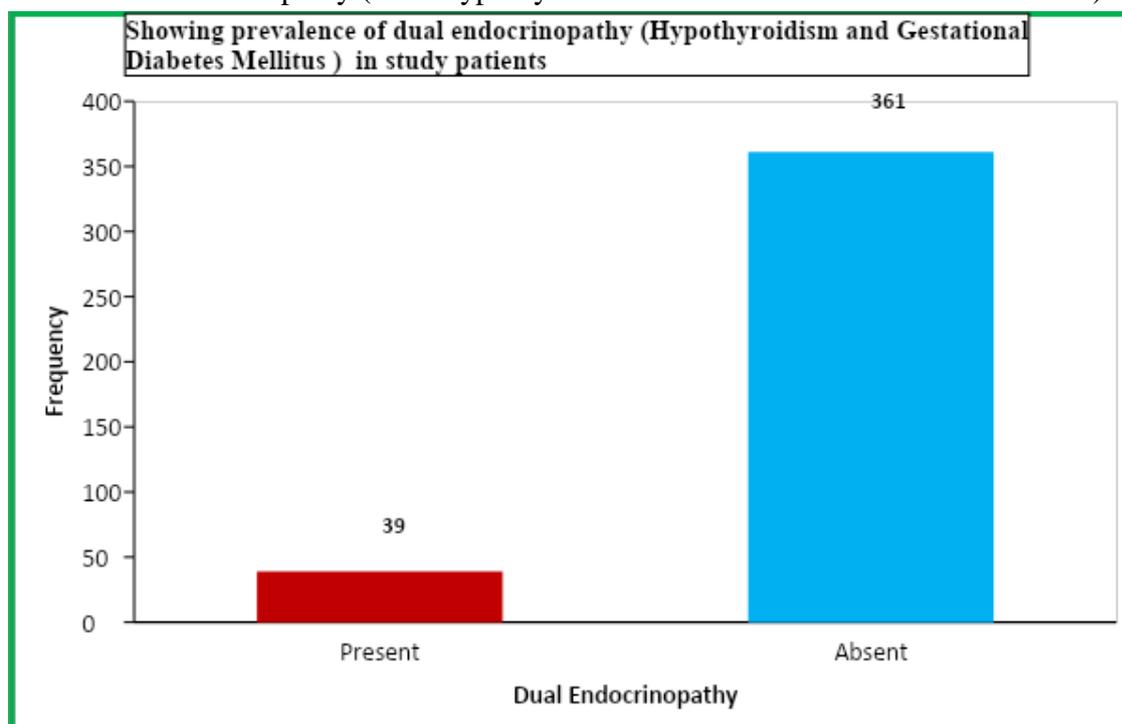


Figure 2 :- Bar chart showing prevalence of Dual Endocrinopathy (Hypothyroidism and Gestational Diabetes Mellitus) in study Patients

Table 3: Showing association of Dual Endocrinopathy with severity of preeclampsia				
Dual Endocrinopathy	Group A- Mild Preeclampsia		Group B-Severe Preeclampsia	
	Number	Percentage	Number	Percentage
Present	22	7.8	17	14.4

Absent	260	92.2	101	85.6
Total	282	100	118	100
Chi-Square = 4.13, P-value=0.042*				

*Statistically Significant association (P-value<0.05)

The above table, shows association of Dual Endocrinopathy with severity of preeclampsia. In our study, we found that 14.4% (17 out of 118) of Severe Preeclampsia had Dual Endocrinopathy and only 7.8 % (22 out of 282) of Mild Preeclampsia had Dual Endocrinopathy. In our study, association between Dual Endocrinopathy and Severity of Preeclampsia was calculated using Chi-Square test and it was significant. (p value = 0.042%)

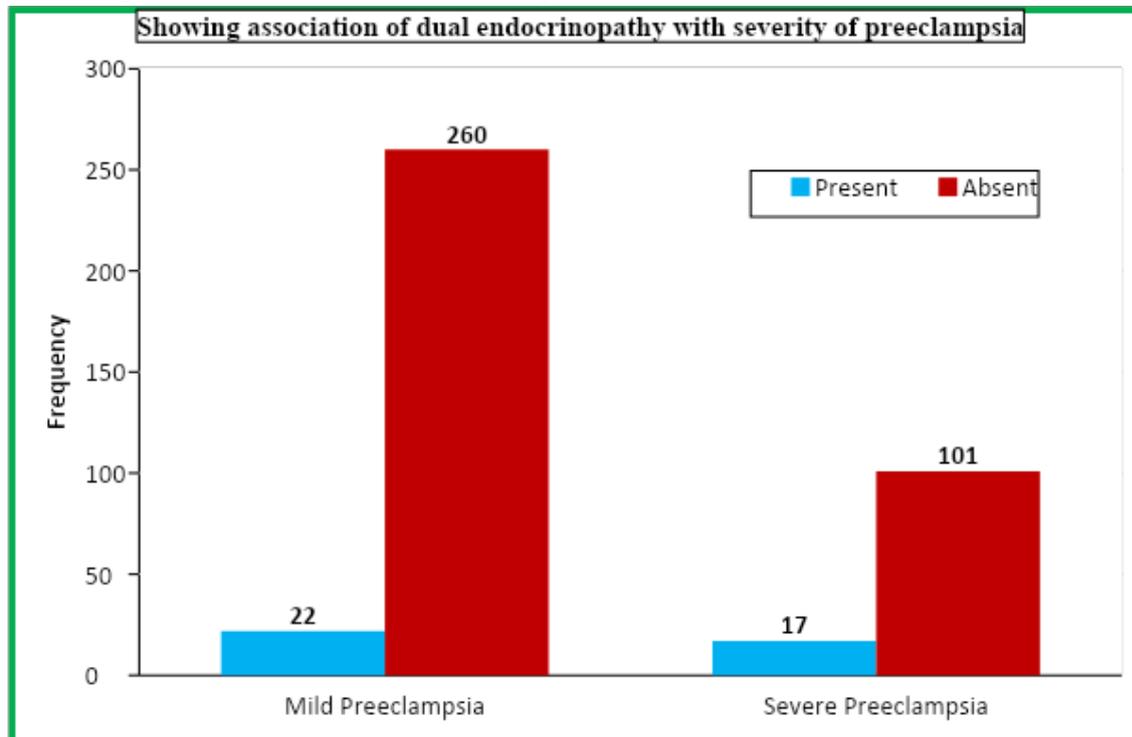


Figure 3:- Bar chart showing Showing association of Dual Endocrinopathy with severity of preeclampsia.

DISCUSSION

Diabetes and hypothyroidism are the two most common endocrinopathies during pregnancy. Both conditions have been previously shown to be associated with various pregnancy complications affecting both the mother and the neonate.

Preeclampsia syndrome is classified as mild and severe preeclampsia. In our study, majority of patients i.e. 70.50% were in the mild preeclampsia group and 29.50% were in the Severe Preeclampsia group (Table 1). According to a study conducted by Verma et al, 60% patients were in the mild preeclampsia group and 40 % in the severe preeclampsia group (17). It was

inconsistent with the study conducted by Gawde A et al in which 69% of the preeclampsia patients were in the severe preeclampsia group (21). The contrary results were may be because of different study design, demographic profile and different inclusion and exclusion criterias of the study population.

The mechanism of thyroid hormone changes in preeclampsia is not well understood although placental dysfunction, reduced conversion of T4 to T3, endothelial dysfunction, decreased plasma protein concentrations, are some suggested mechanisms. Increased serum concentration of soluble fms- like tyrosine kinase 1 during preeclampsia is associated with subclinical hypothyroidism during pregnancy (12). Hypothyroidism leads to increased diastolic hypertension, peripheral vascular resistance, and decreased tissue perfusion (22). Recently several studies also reported the significant association of thyroid hormones with the development and severity of preeclampsia (23). Serum TSH were increased in women with severe preeclampsia when compared to mild preeclampsia (24).

A possible underlying mechanism for association of GDM and preeclampsia is the effect of insulin resistance and glucose intolerance on the development of preeclampsia. Poor glycemic control as well as the presence of microvascular complications may increase the risk of preeclampsia and its co-morbidities (25).

In our study, 9.75 % patients of preeclampsia had dual endocrinopathy (Table 2). This result suggested that there is increased prevalence of dual endocrinopathy in the patients of preeclampsia. It was consistent with the study conducted by Tirosh et al, in which they found that 14% patients in hypothyroid and diabetic group (Type 1, 2 and GDM) developed preeclampsia (26). Some studies showed an increased risk of GDM, especially in women with hypothyroid disorders (27).

In our study, association of dual endocrinopathy with severity of preeclampsia was seen. 14.4 % (17 out of 118) patients of severe preeclampsia patients had dual endocrinopathy while only 7.8 % (22 out of 282) patients of mild preeclampsia patients had dual endocrinopathy. This association was found statistically significant (P value = 0.042). But we failed to cite any study in support of this observation as studies on association of Dual Endocrinopathy with severity of preeclampsia were lacking.

The strength of this study was that it was the first study of its kind which aimed to see association of severity of preeclampsia patients with dual endocrinopathy in India. Sample size was good (n=400).

The main limitation of the study was that no controls were taken in the study.

CONCLUSION

The current study concluded that Dual Endocrinopathy (both Hypothyroidism and Gestational Diabetes Mellitus) has significant association (p value =0.042) with severity of preeclampsia.

Therefore the current study emphasise that early identification of dual endocrinopathy in patients of preeclampsia and timely treatment might decrease the morbidity associated with preeclampsia. Our study is of a novel kind which has laid down a strong basis to look for dual endocrinopathy in patients of preeclampsia. Further larger studies are needed to validate the results.

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