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Original article

Severe Hypothyroidism Causing Pre-Eclampsia-Like Syndrome

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Abstract:

Background: Overt hypothyroidism is characterized by decreased free thyroxine T4 serum levels or elevated thyroid-stimulating hormone. It is reported in 0.3 to 0.5% in pregnancy. This study aimed to describe the presentation of pre-eclampsia like syndrome among pregnant women with overt hypothyroidism, provide a management strategy for pre-eclampsia like syndrome among pregnant women with overt hypothyroidism and report the incidence of associated complications with overt hypothyroidism in pregnant women. **Methods:** This was a cross sectional study conducted on 50 patients with preeclampsia associated with severe hypothyroidism. All studied cases were subjected to Physical examination, thyroid examination, routine laboratory investigations and fetal ultrasounds. **Results:** Low APGAR score (<7) at the first minute was significantly more frequent in severe preeclampsia (p=0.021) and a significant higher blood pressure in severe preeclampsia than mild preeclampsia group (p<0.001). Platelet count was significantly lower in severe preeclampsia group (p<0.001). NICU admission, PPH and end organ dysfunction were more significantly frequent in severe preeclampsia (p<0.001). **Conclusion:** Finding of the present study reveal that pregnant women with overt hypothyroidism and a pre-eclampsia-like syndrome are commonly diagnosed at a younger age, with a significant association between positive family history of thyroid disorder and the development of severe pre-eclampsia. Significant differences in blood pressure, platelet count, and various biochemical markers were observed between mild and severe pre-eclampsia cases in this population.

Keywords: Severe Hypothyroidism; Pre-Eclampsia-Like Syndrome; Pregnant Women; Overt hypothyroidism

Introduction

Overt hypothyroidism is characterized by decreased free thyroxine T4 serum levels or elevated thyroid-stimulating hormone. It is reported in 0.3 to 0.5% in pregnancy. In spite the low incidence rate, overt hypothyroidism causes severe obstetric complications, such as miscarriage, intrauterine growth retardation, placental abruption, postpartum haemorrhage, congenital malformation, and preeclampsia-like syndrome [(1)].

The association between hypothyroidism and preeclampsia was reported in previous studies. Hypothyroidism causes reversible hypertension in both pregnant and non-pregnant women. Hypothyroidism causes vascular smooth muscle contraction in systematic and renal vessels, which increases peripheral vascular resistance as well as diastolic hypertension, and decreases tissue perfusion [(2)].

Reported a case of a 17-week pregnant 42-year-old woman, with severe hypothyroidism due to Hashimoto's thyroiditis, and associated with a severe early-onset preeclampsia-like syndrome [(3)]. In that case, severe pre-eclampsia caused miscarriage at 24 weeks of gestational age, in spite of increasing doses of levothyroxine and liothyronine sodium. Alfadda et al. reported a case of 20-week pregnant 37-year old woman, with a history of treated Graves disease. They concluded that overt hypothyroidism may be associated with a preeclampsia-like syndrome that causes a high risk of adverse obstetric outcome [(4)].

Treatment of this condition needs not only the use of higher than conventional maintenance doses of levothyroxine but also a rapid loading dose that is given orally or even intravenously to achieve a normal serum T4 levels [(5)].

Sixteen pregnancies in 14 overtly hypothyroid women were studied. Seven women had preeclampsia; 5 of the women had a history of chronic hypertension. Five infants were born with weights of <2000 g; 2 infants were stillborn at 27 and 30 weeks of gestation, and the deaths were associated with abruptio placentae and preeclampsia. The authors speculated that overt hypothyroidism leaded to adverse pregnancy outcome such as preeclampsia and placental abruption [(6)].

Hypothyroidism can also cause proteinuria, thus, resulting in increased excretion of thyroxine and thyroid-blinding globulins, which cannot be compensated by the body in severe cases [(7)]

The purpose of this study was to describe the presentation of pre-eclampsia like syndrome among pregnant women with overt hypothyroidism, provide a management strategy for pre-eclampsia like syndrome among pregnant women with overt hypothyroidism and report the incidence of associated complications with overt hypothyroidism in pregnant women.

Patients and methods

This was a cross-sectional study conducted to describe the presentation and provide a management strategy for pre-eclampsia like syndrome among pregnant women with overt hypothyroidism and also to report the incidence of associated complications with overt hypothyroidism in pregnant women. The study included 50 patients with preeclampsia associated with severe hypothyroidism. The study was carried out during the period from January 2023 to January of 2024.

The study was approved by the institutional review board of Benha University and Toukh Teaching hospital. An informed written consent from all participants before participation was obtained.

Inclusion criteria were pregnant women (30-35) weeks with a history of hypothyroidism, incidence of early onset preeclampsia-like syndrome is associated with severe hypothyroidism. Preeclampsia is diagnosed by detecting high blood pressure and one or more of the following complications after the 20th week of pregnancy [(8)]: Protein in your urine

(proteinuria), a low platelet counts, impaired liver function, signs of kidney trouble other than protein in the urine, fluid in the lungs (pulmonary edema), new-onset headaches or visual disturbances.

Exclusion criteria were history of chronic hypertension, any renal disease, any metabolic disorder or medication known to affect thyroid function.

All studied cases were subjected to the following: Detailed history taking, including [Medical history; obstetric history, symptoms assessment]. General examination including **[**Vital signs: pulse, blood pressure, capillary filling time, respiratory rate and temperature**]. Physical examination, Thyroid examination [Routine laboratory investigations [**complete blood count, T4, TSH, urine analysis, and liver function tests]. **Fetal ultrasounds**.

Fetal Ultrasounds:

Regular fetal ultrasounds was performed to monitor fetal growth and detect any potential congenital malformations. All fetus parameters were regularly assessed through scheduled ultrasounds, ensuring comprehensive monitoring of fetal development and timely identification of any deviations from normal growth patterns.

A high-frequency linear array transducer was used, optimal for detailed assessment of fetal anatomy. The probe provides high-resolution images crucial for accurately measuring fetal parameters and assessing growth patterns.

The biparietal diameter is a critical measurement in fetal ultrasound, representing the distance between the two sides of the head. BPD is taken at the level where the thalamus, cavum septi pellucidi, and ambient cistern are visible, ensuring accurate assessment of fetal head growth. This measurement helps in determining gestational age and monitoring for developmental anomalies.

Doppler ultrasound was employed to assess the blood flow in various fetal vessels, including the umbilical artery, middle cerebral artery, and ductus venosus. This technique measures the velocity of blood flow, providing insights into the health of the placenta and the fetal circulatory system. Abnormalities in Doppler flow patterns can indicate potential complications like fetal hypoxia or placental insufficiency.

Abdominal circumference is measured at the level of the stomach and the portal sinus of the umbilical vein. This parameter is crucial for monitoring fetal growth and assessing nutritional status. AC is particularly important in the context of this study as both hypothyroidism and pre-eclampsia can impact fetal growth. In cases of severe hypothyroidism associated with pre-eclampsia-like syndrome, accurate estimation of fetal weight is vital for early identification of intrauterine growth restriction (IUGR), which is a common complication.

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Statistical analysis

Statistical analysis was done by SPSS(IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Quantitative variables were presented as mean and standard deviation (SD). Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

Table 1 shows demographic data, and obstetric history in the studied patients.

Table 2 shows blood pressure and laboratory investigations in the studied patients.

Based on comparison of demographic data and medical history of the patients according to the severity of pre-eclampsia, a significantly higher maternal age in severe preeclampsia group than mild preeclampsia patients (p=0.003). Positive

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family history was significant more frequent with severe preeclampsia group (p<0.001). Table 3

According to comparison of clinical data according to the severity of pre-eclampsia, a significant higher blood pressure in severe preeclampsia than mild preeclampsia group (p<0.001). Platelet count was significantly lower in severe preeclampsia group (p<0.001). A significant higher level of TSH, ALT, AST, serum creatinine, urea and proteinuria in severe preeclampsia group (p<0.001). Table 4

Table 1: Demographic data, and obstetric history in the studied patients

		Total patients n=50
Maternal age (years)	Mean ± SD	29.68 ± 3.88
Age groups, n (%)	<30 years	31(62%)
	>30 years	19(38%)
FH of thyroid disorder, n (%)	Yes	5(10%)
	No	45(90%)
Duration of hypothyroidism, n (%)	<3 years	18(36%)
	>3 years	32(64%)
Gestational age (week)	Mean ± SD	31.73 ± 2.48
	< 30 weeks	17(34%)
Gestational age, n (%)	30 - 35 weeks	30(60%)
	> 35 weeks	3(6%)
Parity, n (%)	Primigravida	29(58%)
	Multigravida	21(42%)
	No abortions	9(18%)
Abortions, n (%)	One abortion	16(32%)
	More than one abortion	25(50%)

Table 2: Blood pressure and laboratory investigations in the studied patients

Variable	**Total patients n=50**
SBP (mmHg)	149.39 ± 6.36
DBP (mmHg)	95.49 ± 4.03
Laboratory investigations	
TSH (µIU/ml)	5.99 ± 0.30
FT4 (µg/dl)	0.95 ± 0.23
FT3 (µg/dl)	1.19 ± 0.28
Hemoglobin level (g/dL)	11.36 ± 0.74
WBCs (x103)	7.42 ± 1.55
Platelet count (x109)	259.40 ± 69.37
ALT (U/L)	36.34 ± 12.87
AST (U/L)	35.28 ± 12.4
Serum albumin (md/dL)	3.76 ± 0.51
Serum Creatinine (mg/dL)	0.99 ± 0.21
Urea level (mg/dL)	16.07 ± 2.19
Proteinuria (mg/24 hours)	343.94 ± 49.65

Table 3: Fetal outcome and maternal complications in the studied patients

Variable		Total patients n=50
Birth weight, n (%)	<2.5 kg	15(30%)
	>2.5 kg	35(70%)
APGAR score at first minute, n (%)	<7	22(44%)
	>7	28(56%)
Fetal distress, n (%)		34(68%)
NICU admission, n (%)		12(24%)
Maternal complications		
PPH, n (%)		18(36%)
End organ dysfunction, n (%)		5(12%)

NICU: Neonatal Intensive Care Unit

Table 4: Demographic data, medical history and clinical data according to pre-eclampsia severity

Variable		Mild PE n=44	Severe PE n=6	p
Maternal age (years)		29.09 ± 3.6	30 ± 3.29	0.003*
Gestational age (weeks)		31.59 ± 2.42	33.17 ± 2.64	0.161
Positive FH of thyroid disorder		2(4.55%)	3(50%)	<0.001*
Parity	Primigravida	25(56.80%)	4(66.70%)	0.640
	Multigravida	19(43.20%)	2(33.30%)	
Abortions	One abortion	13(29.55%)	3(50.00%)	0.584
	More than one abortion	23(52.27%)	2(33.33%)	
Duration of hypothyroidism	<3 years	15(34.09%)	3(50%)	0.446
	>3 years	29(65.91%)	3(50%)	
Clinical data				
SBP (mmHg)		147.36 ± 4.17	162.67 ± 2.94	<0.001*
DBP (mmHg)		94.32 ± 2.27	104 ± 3.58	<0.001*
TSH (µIU/ml)		5.91 ± 0.14	6.54 ± 0.53	<0.001*
FT4 (µg/dl)		0.96 ± 0.23	0.87 ± 0.19	0.511
FT3 (µg/dl)		1.21 ± 0.29	1.05 ± 0.03	0.372
Hemoglobin level (g/dL)		11.41 ± 0.72	11.02 ± 0.85	0.297
WBCs ($x10^3$)		7.43 ± 1.55	7.32 ± 1.73	0.850
Platelet count ($x10^9$)		278.84 ± 45.48	116.83 ± 40.7	<0.001*
ALT (U/L)		32.52 ± 6.08	64.33 ± 15.34	<0.001*
AST (U/L)		31.5 ± 5.51	63 ± 14.07	<0.001*
Serum albumin (md/dL)		3.76 ± 0.48	3.72 ± 0.78	0.850
Serum Creatinine (mg/dL)		0.93 ± 0.12	1.43 ± 0.23	<0.001*
Urea level (mg/dL)		15.56 ± 1.72	19.83 ± 1.6	<0.001*
Proteinuria (mg/24 hours)		328.8 ± 28.01	455 ± 24.29	<0.001*

PE: Preeclampsia; *: Significant ≤0.05

Discussion

The mean maternal age in our study was 29.68 ± 3.88 years, with the majority of cases (62%) being younger than 30 years, while 38% were older than 30 years. These findings align with previous studies that have reported a similar distribution of maternal age in pregnant women with hypothyroidism. For instance, a study by Parizad Nasirkandy et al. (2017) reported that the age was under 30 in women with hypothyroidism during pregnancy [(9)].

Regarding the past medical history of our study participants, 10% reported a positive family history of thyroid disorder. This finding is consistent with previous research that has demonstrated a familial clustering of thyroid disorders. Stagnaro-

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Green et al. found that a positive family history was present in 13-20% of women with hypothyroidism during pregnancy [10].

In terms of the duration of hypothyroidism, our study revealed that 36% of the patients had been diagnosed with hypothyroidism for less than 3 years, while 64% had been diagnosed for more than 3 years. These findings indicate that a significant proportion of pregnant women with overt hypothyroidism have a pre-existing diagnosis prior to pregnancy. This aligns with the recommendations of the American Thyroid Association (ATA), which advises women with known hypothyroidism to optimize their thyroid hormone levels prior to conception [11].

In terms of obstetric history, the mean gestational age of the patients was 31.73 ± 2.48 weeks. Most of the studied patients had a gestational age between 30 and 35 weeks (60%). According to parity, 58% of the patients were primigravida, while 42% of the patients were multigravida. Of the patients studied, 18% had no history of abortions, 32% had one abortion, and 50% had more than one abortion.

A systematic review and meta-analysis by Parizad Nasirkandy et al. (2017) observed that subclinical hypothyroidism during pregnancy was associated with an increased risk of preterm birth [9].

The relationship between a history of abortions and hypothyroidism during pregnancy is an area of ongoing research. Some studies have suggested a potential association between hypothyroidism and recurrent pregnancy loss [12, 13].

In the current study, the mean TSH level was 5.99 ± 0.30 μIU/ml, while the mean free T4 (FT4) level was 0.95 ± 0.23 μg/dl and the mean free T3 (FT3) level was 1.19 ± 0.28 μg/dl.

According to the guidelines from the American Thyroid Association (ATA), the recommended reference ranges for TSH levels in pregnant women are typically lower compared to non-pregnant adults, with the upper limit usually ranging from 2.5 to 3.0 μIU/ml [11]. The mean TSH level observed in our study falls within these reference ranges, indicating that the majority of patients had their TSH levels adequately managed.

In terms of birth weight, 30% of the patients had a low birth weight (less than 2.5 kg), while 70% of the patients had a birth weight greater than 2.5 kg. Additionally, the Apgar score at the first minute after birth was recorded for each patient. Of the patients studied, 44% had an Apgar score of less than 7, while 56% had an Apgar score greater than 7.

A systematic review and meta-analysis by Derakhshan et al. reported a higher risk of low birth weight in infants born to mothers with subclinical or overt hypothyroidism [14].

According to fetal complications, 68% of the neonates had respiratory distress. Additionally, 24% of neonates required admission to (NICU). According to maternal outcome, 36% of the patients experienced PPH while 12% patients had end organ dysfunction.

This is consistent with previous research that has shown an association between maternal hypothyroidism and respiratory distress in newborns. Sahay and Nagesh reported an increased risk of respiratory distress in infants born to mothers with subclinical or overt hypothyroidism [12].

Regarding maternal outcomes, 36% of the patients experienced postpartum hemorrhage (PPH). Postpartum hemorrhage is a known complication in pregnancy, and the observed prevalence in our study suggests that pregnant women with overt hypothyroidism and a pre-eclampsia-like syndrome are at an increased risk of this condition [15].

Furthermore, 12% of the patients in our study had end organ dysfunction. End organ dysfunction refers to impairment or malfunctioning of vital organs, such as the liver, kidney, or cardiovascular system. The presence of end organ dysfunction highlights the severity and complexity of the pre-eclampsia-like syndrome in pregnant women with overt

hypothyroidism. Therefore, proper management and multidisciplinary care are crucial in order to mitigate the potential adverse effects on both maternal and fetal health.

Based on comparison of demographic data and medical history of the patients according to the severity of pre-eclampsia, a significant higher maternal age in severe preeclampsia group than mild preeclampsia patients (p=0.003). Positive family history was significant more frequent with severe preeclampsia group (p<0.001).

The presence of these associations emphasizes the role of maternal age and family history as potential risk factors for the severity of pre-eclampsia. Advanced maternal age and positive family history may contribute to the complex pathophysiology of pre-eclampsia, involving genetic, environmental, and physiological factors. The identification of these risk factors can help healthcare providers identify high-risk individuals and implement appropriate monitoring and preventive measures.

Population-wide and large cohort studies confirm that maternal family history of pre-eclampsia increases pre-eclampsia risk by threefold to fourfold [16-20]. This association is stronger for preterm pre-eclampsia (risk ratio (RR) 2.15, 95% CI 1.69–2.73) than for term pre-eclampsia (RR 1.49, 95% CI 1.4–1.58) [19].

Our study compared clinical data and outcomes based on the severity of pre-eclampsia and found significant differences between the severe and mild pre-eclampsia groups. In terms of clinical data, the severe pre-eclampsia group exhibited significantly higher blood pressure compared to the mild pre-eclampsia group (p<0.001). This finding aligns with established criteria for diagnosing severe pre-eclampsia, which includes elevated blood pressure as a defining characteristic.

Furthermore, the severe pre-eclampsia group demonstrated a significantly lower platelet count compared to the mild pre-eclampsia group (p<0.001). Thrombocytopenia is commonly associated with the severity of pre-eclampsia and is indicative of platelet dysfunction in this condition.

In addition, the severe pre-eclampsia group exhibited significantly higher levels of TSH, ALT, AST, serum creatinine, urea, and proteinuria compared to the mild pre-eclampsia group (p<0.001). These findings suggest a greater degree of thyroid dysfunction, liver dysfunction, renal dysfunction, and protein leakage in the severe pre-eclampsia group. Elevated TSH levels and liver and renal dysfunction are commonly observed in severe pre-eclampsia cases [21].

Conclusion

Finding of the present study reveal that pregnant women with overt hypothyroidism and a pre-eclampsia-like syndrome are commonly diagnosed at a younger age, with a significant association between positive family history of thyroid disorder and the development of severe pre-eclampsia. Significant differences in blood pressure, platelet count, and various biochemical markers were observed between mild and severe pre-eclampsia cases in this population. Additionally, neonates born to mothers with severe pre-eclampsia and overt hypothyroidism are at an increased risk of respiratory distress and NICU admission, while maternal outcomes are characterized by a higher incidence of postpartum hemorrhage (PPH) and end-organ dysfunction.

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Author contribution

Authors contributed equally in the study**.**

Conflicts of interest

No conflicts of interest

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