ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Subclinical hypothyroidism with preeclampsia.

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ABSTRACT

Preeclampsia is a multi-systemic disorder, unique to pregnancy, that may complicate 5-10% of all pregnancies .It has a multi factorial theories regarding its etiology that is why it can affect many organs in the body including thyroid gland. Hypothyroidism Complicates 1% of pregnancies, most commonly due to iodine deficiency so it is more likely to occur in women in areas of endemic iodine deficiency or Hashimoto's thyroiditis in developed world. Subclinical hypothyroidism is an entity when thyroid function is only mildly affected, indicated by normal level of thyroxin and elevation of TSH. This cross-sectional study was carried out in AL-Zahra maternity and pediatric teaching hospital in AL-NAJAF city during the period between 1st of May, to 10th of October 2015.The patients were recruited from Labor room as a total of 128 patients (30 with no history of hypertension, 45severe preeclampsia, 53 mild preeclampsia). For each patient proper history was taken regarding age, gestational age, parity, previous history of thyroid disorder, current history of hypertension and past medical history. The participants were divided into 3 groups with (no, mild, and severe) PE. There was no statistically significant difference among groups regarding age ,gestational age ($P>0.001$)while the difference was significant difference among them in relation to Systolic BP, Diastolic BP, BMI, Platelet, SGOT, SGPT, B. urea, S. uric acid and S. Creatinine ($P<0.001$). Highly significant difference in weight of neonate and APGAR score was observed among women with high TSH than women with normal TSH (P value< 0.001).The level of TSH is increasing significantly with increasing maternal age and with increasing severity of PE ($P<0.001$). The 3 groups showed no statistically significant difference in the level of free T4. It was observed that there was strong association between high TSH level and development of PE (100% association). Cases with severe PE were found to be associated with subclinical hypothyroidism(elevated TSH level) rather than mild cases.

Keywords: Pregnancy; Preeclampsia; Severe preeclampsia; Subclinical hypothyroidism.

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ISSN: 0975-8585

ISSN: 0975-8585

INTRODUCTION:

Preeclampsia(PE) is a multisystem disorder specific to pregnancy. Its etiology is unknown but explained by many theories. According to the criteria of international society of the study of hypertension in pregnancy ,the preferred definition of preeclampsia is a diagnosis of pregnancy induced hypertension(diastolic blood pressure>90mmHg)occurring after 20weeks of gestation with proteinurea>300 mg protein per day [1]. It affects about 5-10%of all pregnancies over the world with the onset of symptoms usually in the late second or third trimester and it may also occur up to six weeks postpartum.[2] Of the affected cases 3-5% is associated with highest maternal and fetal morbidity and mortality of its complications (liver, renal, DIC, pulmonary and neuorological abnormalities) .[3] Many theories have been implicated in the etiology of PE including: Endothelial cell injury;Immune rejection of the placenta; Compromised placental perfusion; Altered vascular reactivity; and Imbalance between prostacycline and thrombxane. Additionally genetic factors and diet may play a role in its etiology.[4] It is known that preeclampsia is principally related to poor trophoblastic invasion in the myometrium and this led to loss of normal physiological vasodilatation and production of placental reactive oxidative substances.As the vascular endothelium is present in all organ systems ,this explains the wide spread aspects of syndrome.Women with PE often have elevated thyrotropin (TSH) levels toward the end of pregnancy and women with history of one or more episodes of PE have been shown to carry higher risk of developing reduced thyroid function which may result from the effects of exposure to anti angiogenic factors during pregnancy, complicated by preeclampsia . at early pregnancy thyroid dysfunction has also been associated with the development of preeclampsia and gestational hypertension[5]. The changes in T-cells subsets that may be seen in preeclampsia. Cells can take part in the pathophysiology of preeclampsia by producing auto-antibodies against adreno-receptors and auto-antibodies that bind the AT1-R[6]. Preeclampsia can be categorized as mild and severe. In mild preeclampsia, hypertension and proteinurea (>300mg) are present but not to these extreme levels of severe preeclampsia and patient has no evidence of other organinvolvement [7]. Risk factors can be classified as maternal, placental/fetal, medical risk factors and Paternal-specific factors.[8] Many tests are suggested for the diagnosis of preeclampsia like complete blood count (CBC),electrolytes creatinine, liver enzymes, bilirubin and a urine dip for protein. [9] Obstetric management of preeclampsia depends on a high index of suspicion, careful observation and early intervention[10]. In cases of mild preeclampsia the treatment is only expectant as the prenatal outcomes are similar to non-hypertensive women[11].The American College for Obstetric and Gynecology (ACOG) suggests monitoring according to the recommendations of the national high blood pressure education program working group(NHBPEPWG). [12]. Induction of labor (IOL) is recommended for women at 37 weeks' gestational age with a favorable and unfavourable cervix by prostaglandins [13]. A multicenter, randomized controlled study comparing IOL versus expectant monitoring in women with mild hypertension, IOL was shown to improve a maternal and neonatal outcomes and lower the rate of cesarean delivery[14]. In cases of severe preeclampsia, the main goals of therapy are to control BP and to prevent eclampsia, with the aim of vaginal delivery and cesarean section is reserved for cases of emergency or after failure of induction of labor [15].

Medications commonly used by obstetricians to treat hypertension associated with severe preeclampsia include hydralazine, labetalol, and nifedipine (or other calcium channel blockers) [16]. Seizure prophylaxis is routinely starting with magnesium sulfate and continues for at least 24 hours postpartum[17]. Vaginal delivery is preferable. IOL is considered in selected cases [18]. Corticosteroids should be considered to accelerate fetal lung maturity at 24–34 weeks,followed by delivery 48 hours later in those with gestational ages of 33–34 weeks[19]. Immediate delivery should be recommended also in cases of uteroplacental insufficiency combined with oligohydromnios [20].

Hyperthyroidism

Since normal pregnancy can lead to some clinical findings similar to thyroxin (T4) excess, mild thyrotoxicosis can be diagnosed with difficulty. Confirmation is by a markedly depressed thyrotropin (TSH) level and with an elevated serum free T_4 (fT_4) level. Autoimmune thyrotoxicosis(Grave's disease) can affect 2/1000 pregnancy and is caused by TSH receptor stimulating antibodies[21]. Poorly controlled disease can be complicated by miscarriage, preterm labor, IUGR and maternal thyrotoxic crisis.[21]

Hypothyroidism

Complicates about 1% of pregnancies. The most common cause is iodine deficiency especially in women in areas of endemic iodine deficiency or Hashimoto's thyroiditis in developed world[22]. It can present in form of Fatigability, constipation, cold intolerance, muscle cramps and weight gain. Edema , dry skin, hair loss and prolonged relaxation phase of deep tendon reflexes are other findings. Overt hypothyroidism is diagnosed by abnormally high serum thyrotropin level along with an abnormally low thyroxine level. Pregnancy with hypothyroidism can be complicated bycongenital abnormalities, hypertension, placental abruption, premature delivery, fetal growth restriction and postpartum haemorrhage. If thyroxine replacement therapy is adequate, hypothyroidism is not associated with an adverse pregnancy outcome for the mother or fetus.[23].

SUBCLIICAL HYPOTHYROIDISM

Describes a condition in which there is mild thyroid failure, explained by normal blood level of thyroxine, but the blood level of TSH is elevated.[24]. Many factors can be attributed to its occurance like drugs (radioactive iodine, lithium, anticancer drugs), recent pregnancy and child birth.[25]

Patient and methods

The study was performed at AL-Zahra maternity and pediatric teaching hospital in AL-NAJAF city .This cross- sectional study was done during the period between 1st of May, to 10thof October 2015.participants were recruited from Labor room as 30 with no history of hypertension,45 with severe preeclampsia, and 53with mild preeclampsia. For each patient, proper history was taken asking about maternal age , gestational age, parity , previous history of thyroid disorder , current history of hypertension and past medical history. Examination was performed by measuring blood pressure in sitting position ,body mass index(BMI) was calculated for each patient (body weight/m2) and blood sample collected from each patient and send for laboratory analysis in form of :-

- Complete blood picture (platelet count)
- Renal function test(blood urea ,serum creatinine , serum uric acid)
- liver function test(S.G.O.T,S.G .P.T)
- Thyroid test(free T4,TSH) by using ELISA with commercial kit.
- General urine examination(for protein urea)
    - Outcome of the neonate (weight, APGAR score)
- Diagnosis of subclinical hypothyroidism was made by finding of an increased TSH with normal or low free T4 provided there are no symptoms and signs of hypothyroidism.

Exclusion criteria

Patients who excluded from the study are those with: Twin pregnancy ,chronic hypertension ,diabetic mellitus, andrenal disease , in addition to all known cases of thyroid disorder.

Analysis of the results

By correlation of thyroid hormone analysis abnormality in relation with severity of preeclampsia.
Normal value of TSH (0.5-4.70µIU/mL) .
Normal value of Free T4(0.8 – 1.8ng /dL).

Statistical analysis

Statistical analysis was done by using statistical package for social sciences (SPSS) version. analysis of variance (ANOVA test) with low significant difference (LSD) was used for comparison between groups for numerical variables and chi-square test for categorical data. Risk measurement was calculated by measuring Odds ratio. P-value of < 0.05 was regarded as significant.

ISSN: 0975-8585

RESULTS

This study consist of 128 women, categorised into three groups: mild PE, severe PE and non PE group.

Table (1) demographic characteristics, renal function, and liver enzymes of studied 3 groups.

Variable	Non PE(A) N=30	Mild PE(B) N=50	Sever PE(C) N=48	P-value		
	Mean ±SD	Mean ±SD	Mean ±SD	A vs B	A vs C	B vs C
Age/years	26.16±6.25	25.78±6.65	27.78±9.00	0.824	0.359	0.192
Gestational age/weeks	39.63±1.35	39.28±1.89	37.54±1.98	0.412	0.1	0.1
Systolic BP mmHg	117.65±6.33	152.36±7.73	177.08±17	<0.001	<0.001	<0.001
Diastolic BP mmHg	72.75±5.76	94.90±3.27	120.52±14.15	<0.001	<0.001	<0.001
BMI kg/m2	27.96±2.28	28.92±1.72	30.37±2.25	0.048	<0.001	0.001
Platelet	205.73±44.37	208.87±32.52	155.83±35.21	0.712	<0.001	<0.001
SGOT mg/dl	14.73±2.242	15.96±2.175	24.79±6.457	0.222	<0.001	<0.001
SGPT mg/dl	6.40±2.567	10.34±3.360	19.68±7.879	0.002	<0.001	<0.001
B. urea mg/dl	30.13±3.53	31.88±4.34	38.06±8.01	0.2	<0.001	<0.001
S.uric acid mg/dl	5.22±0.595	5.36±0.990	8.52±1.865	0.642	<0.001	<0.001
S.creatinine mg/dl	0.86±0.047	0.88±0.129	1.24±0.314	0.784	<0.001	<0.001

In this table there is no statistically significant difference among groups regarding age ,gestational age (P>0.001)while the difference is significantly obvious among them regarding Systolic BP, Diastolic BP, BMI, Platelet, SGOT, SGPT, B. urea, S. uric acid and S. creatinine (P<0.001).

Table (2) newborn condition of the studied groups.

Variable	Non PE(A) N=30	Mild PE(B) N=50	Sever PE(C) N=48	P- value		
	Mean ±SD	Mean ±SD	Mean ±SD	A vs B	A vs C	B vs C
Newborn weight/Kg	3.36±0.371	3.20±0.329	2.49±0.516	0.1	<0.001	<0.001
APGAR score First minute	4.65±0.483	4.68±0.624	3.53±0.625	0.818	<0.001	<0.001
APGAR score Five minute	8.93±0.257	8.68±0.511	7.44±1.012	0.145	<0.001	<0.001

In table (2) the newborn weight is lower in group C than group A and B(P<0.001). APGAR score at first and five minutes is obviously lower in group C than in other 2 groups

Table(3) Comparison between TSH level and neonatal outcome.

	TSH		P-value
	High (N=39)	normal (N=89)	
Newborn weight/Kg	2.64±0.516	3.11±0.52	<0.001
APGAR score First minute	3.921±0.911	4.40±0.713	0.002
APGAR scoreFive minute	7.63±1.195	8.58±0.643	<0.001

Table (3) shows that the neonatal weight and APGAR score are lower among women with high TSH than women with normal TSH.

ISSN: 0975-8585

Table(4) association between age groups and TSH level.

		TSH		P –value
		High	Normal	
Age /years	<20	7	29	0.001
		17.9%	32.6%	
	20-25	6	21	
		15.4%	23.6%	
	26-30	4	22	
		10.3%	24.7%	
	31-35	10	9	
		25.6%	10.1%	
	>35	12	8	
		30.8%	9.0%	
Total		39	89	
		100.0%	100.0%	

This table demonsterates that there was significant association between age of women and level of TSH explained by increasing level of TSH with increasing age.

Table(5) level of TSH and free T4 in different groups.

Variable	Non PE(A) N=30	Mild PE(B) N=50	Sever PE(C) N=48	P value		
	Mean ±SD	Mean ±SD	Mean ±SD	A vs B	A vs C	B vs C
Free T4 ng/dl	1.18±0.31	1.24±0.541	1.04±1	0.817	0.961	0.537
TSH microU/ml	2.50±1.42	4.33±2.21	6.79±4.45	0.013	<0.001	<0.001

In table (5) all groups show no significant differeence in the level of free T4,while TSH shows significant difference which increases in relation to severity of PE.

Table(6) association between level of T4 and groups

		Groups		Odds ratio	95%CI	P value
		Cases	Controls			
Free T4	Low	28	1	11.6	1.5-89.3	0.004
		28.6%	3.3%			
	Normal	70	29			
		71.4%	96.7%			
Total		98	30			
		100.0%	100.0%			

Table (6) explains that women with low free T4 are 11.6 times more likely to develop PE.

Table(7) association between level of TSH and groups.

		Groups		P- value
		Cases	Controls	
TSH	High	39	0	<0.001
		39.8%	0.0%	
	Normal	59	30	
		60.2%	100.0%	
Total		98	30	
		100.0%	100.0%	

Table (7) shows highly significant association between TSH level and development of PE, it was noticed that 100% of women with high TSH had PE.

DISCUSSION

Preeclampsia in its severe course may be associated with some degree of thyroid dysfunction due to immune system dysfunction as part of its etiology. Subclinical hypothyroidism may be associated with under detected serious fetal complications. That's why attention should be kept for the possibility of hypothyroidism in severe cases of PE.

In our current study the body mass index (BMI) was studied and it was obvious that those women (BMI ≥ 30 Kg/M^2) were associated with more preeclampsia, and this was backed up by James M. Roberts(2011)[26] who found that obesity increased the risk of preeclampsia and cardiovascular disease, and can be explained by several mechanisms like total body fat distribution, insulin resistance , metabolic syndrome,inflammation ,oxidative stress ,angiogenic and anti-angiogenic factors and life style factors associated with obesity.

Severe preeclampsia was defined by finding abnormalities in Platelete count ,liver function test , and renal function test.

In our study there is significant difference in level of TSH in severe PE as compared with control and mild PE p value <.001 and this is in agreement with Leung AS (1993)[27]who found that eclampsia, preeclampsia, and pregnancy induced hypertension was significantly obvious in the overt and subclinical hypothyroid patients, than in the general population and our result agrees with those of Karen L (2012)[28]who demonstrated that there was a significant association between subclinical hypothyroidism (SCH) and severe preeclampsia (adjusted odds ratio 1.6, 95% confidence interval 1.1–2.4; P.03) this association may be due to autoimmune behavior of P.E that affect thyroid gland ,while Wang (2011)[29]observed no significant association between Subclinical hypothyroidism and some obstetrical complications including gestational hypertension, premature delivery, anemia, postpartum hemorrhage, low neonatal APGAR scores and low birth weight ,and MannistoT (2010)[30]found that thyroid dysfunction in early pregnancy did not increase risk of PE and the sample size or the nature of studied society may be responsible for this difference in result.

Our study demonstrated that women with subclinical hypothyroidism have significant lower birth weight as well as APGAR score in cases of severe PE(2.64± 0.516) as compared with normal TSH(3.11± 0.52) and APGAR score in 1 and 5 minute is significantly lower in subclinical hypothyroidism (3.921±0.911) versus (4.40±0.713) ,(7.63±1.195)versus (8.58±0.643) and this seems to go with the study of Forough Saki (2014)[31] who found that Subclinical hypothyroidism had a significant association with intrauterine growth restriction (IUGR)P = 0.028 as well as low APGAR score at first minute P = 0.022.

In our study we found that the difference is significant regarding the effect of age between normal women and those with SCH. (30.8%) whose age > 35 years and this is similar to study of Hollowell JG (2002) [32]who found that maternal age represented a significant risk factor for autoimmunologically- based hypothyroidism.

CONCLUSION AND RECOMMENDATIONS

Cases of severe PE were found to be significantly associated with subclinical hypothyroidism with significantly high serum T.S.H than in mild or normotensive groups Investigation for thyroid dysfunction in each patient with mild preeclampsia was recommended to decrease fetal complications and subsequent maternal morbidity. Larger study may be needed to justify routine use of thyroid function test in severe preeclampsia cases or for patients at risk of PE .

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