A study of thyroid status in women with preeclampsia

Thesis

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بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم"

صدق الله العظيم

(سورة البقرة)

Abstract

Thyroid disorders are amongst the commonest endocrine disorders in women in child – bearing age and therefore they are encountered commonly in pregnancy. Disorders of thyroid hormones production and their treatment can affect fertility, maternal wellbeing, fetal growth and development. The aim of this work is to assess thyroid function in women with severe hypertensive disorders in pregnancy.

Key Words :

Blood pressure - Extracellular fluid – preeclampsia .

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ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
DIT	Diiodotyrosine
ECF	Extracellular fluid
HSA	Human serum albumin
hCG	Human chorionic gonadotropin
I	Iodine
MIT	Monoiodatyrosine
NHBPEP	National High Blood Pressure Education Program
NK	Natural killer
NIS	Sodium iodide symporter
PTU	propylthiouracil
rT_3	Reverse t3
SCH	Subclinical hypothyroidism
T3	Triiodothyyronine
T4	Thyroxine
TBA	TSH-receptor blocking antibodies
TBII	TSH-binding inhibitory immunoglobulins
TBG	Thyroxine-binding globulin
TH	Thyroid hormone
TRH	Thyroptophin-releasing hormone
TSH	Thyroid stimulating hormone
TSI	Thyroid-stimulating immunoglobulins
TSH	Thyroid-stimulating hormone
TRAbs	TSH receptor antibodies
TTR	Transthyretin

Introduction

Over the past several years it has been proved that maternal thyroid disorder influence the outcome of mother and fetus, during and also after pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism. It is associated with fetal loss, placental abruptions, pre-eclampsia, preterm delivery and reduced intellectual function in the offspring. In pregnancy, overt hypothyroidism is seen in 0.2% and sub clinical hypothyroidism in 2.3%. Fetal loss, fetal growth restriction, pre-eclampsia and preterm delivery are the usual complications of overt hyperthyroidism (low TSH and high T3, T4) seen in 2 of 1000 pregnancies whereas mild or subclinical hyperthyroidism (suppressed TSH alone) is seen in 1.7% of pregnancies and not associated with adverse outcomes.

Autoimmune positive euthyroid pregnancy shows doubling of incidence of miscarriage and preterm delivery. Worldwide more than 20 million people develop neurological sequel due to intra uterine, iodine deprivation. Other problems of thyroid disorders in pregnancy are post-partum thyroiditis, thyroid nodules and cancer, hyper emesis gravidarum.

Sufficient provision of thyroid hormone in the first trimester of pregnancy is essential for normal fetal brain development. There is growing evidence, however, suggesting that maternal thyroid hormone levels remain important until term. In the debate on benefits of screening for hypothyroidism in pregnancy, the question on the optimal thyroid hormone level remains unanswered, because reports on thyroid function in normal pregnancy are scarce.

Preeclamptic patients are at particular risk. Several articles describe an association between preeclampsia and maternal thyroid dysfunction and low birth weight; some authors even suggested maternal thyroid function abnormalities to be a causal factor.

The aim of this work is to assess thyroid function in women with severe hypertensive disorders in pregnancy.

Preeclampsia

Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4-6 weeks postpartum. It is clinically defined by hypertension and proteinuria, with or without pathologic edema. Preeclampsia is part of a spectrum of hypertensive disorders that complicate pregnancy. These include chronic hypertension, preeclampsia superimposed on chronic hypertension, gestational hypertension, preeclampsia, and eclampsia. Although each of these disorders can appear in isolation, they are thought of as progressive manifestations of a single process and are believed to share a common etiology. (1)

The diagnostic criteria for preeclampsia focus on measurement of elevated blood pressure and proteinuria that develop after 20 weeks' gestation. This must be differentiated from gestational hypertension, which is more common and may present with symptoms similar to preeclampsia, including epigastric discomfort or thrombocytopenia, but is not characterized by proteinuria. Additionally, patients with preexisting chronic hypertension may present with superimposed preeclampsia presenting as new-onset proteinuria after 20 weeks' gestation. (1)

Consensus is lacking among the various national and international organizations about the values that define the disorder, but a reasonable limit in a woman who was normotensive prior to 20 weeks' gestation is a systolic blood pressure (BP) greater than 140 mm Hg and a diastolic BP greater than 90 mm Hg on 2 successive measurements 4-6 hours apart. Preeclampsia in a patient with preexisting essential hypertension is

diagnosed if systolic BP has increased by 30 mm Hg or if diastolic BP has increased by 15 mm Hg. (2)

Proteinuria is defined as 300 mg or more of protein in a 24-hour urine sample. Serial confirmations 6 hours apart increase the predictive value.(2)

Diagnostic criteria for severe preeclampsia include at least one of the following:

Systolic BP greater than 160 mm Hg or diastolic BP greater than 110 mm Hg on 2 occasions 6 hours apart with the patient at bed rest. Proteinuria greater than 5000 mg in a 24-hour collection or more than 3+ on 2 random urine samples collected at least 4 hours apart. Oliguria with less than 500 mL per 24 hours. Persistent maternal headache or visual disturbance. Pulmonary edema or cyanosis. Concerning abdominal pain. Impaired liver function test findings. Thrombocytopenia. Oligohydramnios, decreased fetal growth, or placental abruption **(Working group of the National High Blood pressure Education program 2000)**

Pathophysiology

The mechanism by which preeclampsia occurs is not certain, and a number of maternal, paternal, and fetal factors have been implicated in its development. The factors currently considered to be the most important include abnormal placental implantation; maternal immunological intolerance; cardiovascular and inflammatory changes; and genetic, nutritional, and environmental factors. (3)

Placental implantation with abnormal trophoblastic invasion of uterine vessels is a major cause of hypertension associated with the preeclampsia syndrome. Normally, uterine invasion by endovascular trophoblasts cause extensive remodeling of uterine spiral arteries, resulting in enlarged vessel diameter. In preeclampsia, there is only shallow invasion, and the deeper uterine arterioles do not widen appropriately. (4)

Studies have shown that the degree of incomplete trophoblastic invasion of the spiral arteries is directly correlated with the severity of subsequent maternal hypertension. Subsequently, the resulting placental hypoperfusion leads by an unclear pathway to the release of systemic vasoactive compounds that cause an exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability, and platelet dysfunction, all of which contribute to organ dysfunction and the various clinical features of the disease. (4)

Immunological factors have long been considered to be key players in preeclampsia. One important component is a poorly understood dysregulation of maternal tolerance to paternally derived placental and fetal antigens. This maternal-fetal immune maladaptation is characterized by defective cooperation between uterine natural killer (NK) cells and fetal HLA-C, and results in histological changes similar to those seen in acute graft rejection. The endothelial cell dysfunction that is characteristic of preeclampsia may be partially due to an extreme activation of leukocytes in the maternal circulation, as evidenced by an upregulation of type 1 helper T cells. (5)

Genetics have long been understood to play an important role, and preeclampsia has been shown to involve multiple genes. Importantly, the risk of preeclampsia is positively correlated between close relatives; a recent study showed that 20-40% of daughters and 11-37% of sisters of preeclamptic women also develop preeclampsia. Twin studies have also shown a high correlation, approaching 40%. Over a hundred maternal and paternal genes have been studied for their association with the syndrome, including those known to play a role in vascular diseases, blood pressure regulation, diabetes, and immunological functions. Because preeclampsia is genetically and phenotypically a complex disease, it is unlikely that any one gene will be shown to play a dominant role in its development. (5)

Placentation in Preeclampsia

The shallow placentation noted in preeclampsia is a result of the inability of trophoblasts to invade the decidual vessels. In normal pregnancies, a subset of cytotrophoblasts called invasive cytotrophoblasts migrate through the implantation site and invade decidua tunica media of maternal spiral arteries and replace its endothelium in a process called pseudovascularization. As a result of these changes, these vessels undergo transformation from small muscular arterioles to large capacitance, low-resistance vessels. This allows increased blood flow to the maternal-fetal interface. Remodeling of these arterioles probably begins in the first trimester and ends by 18-20 weeks' gestation. However, the exact gestational age at which the invasion stops is unknown. (6)

In preeclampsia, this invasion of the decidual arterioles is incomplete. The invasive cytotrophoblasts fail to replace tunica media, resulting in mostly intact arterioles that are capable of vasoconstriction.