

Original Research Article

The Pre-Eclampsia like Syndrome. A Rare Complication of Pregnancy Associated Hypothyroidism

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Abstract

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The pre-eclampsia like syndrome is a rare, severe complication during pregnancy weeks 16- 24 at multipara, elder women known or not to suffer of subclinical/overt hypothyroidism. It is characterized by persistent hypertension, under hypotensive therapy, progressive abdominal ascites, and bilateral pleural/pericardial effusions, severe proteinuria aggravated from day-to-day. The pathological mechanisms are partially different from those of gestational hypertension, being a diastolic disorder, with changes in plasma volume, and a very early endothelial dysfunction generating vasoconstriction in kidneys' vessels and systemic circulation, and systemic inflammatory response. The plasma volume changes are initiating the volume-dependent mechanism of reduced plasma renine activity on one side, and on the other the increase of proteinuria to high values like those from the nephrotic syndrome, with the increase of the excretion of thyroxine and thyroid-binding globulins, which sometimes can not be compensated, and aggravates the hypothyroidism High TSH levels are correlated to endothelin high levels. The diagnosis is a challenge to distinguish pre-eclampsia like syndrome from other forms of gestational hypertension. High doses levothyroxine are mandatory, and may help maternal life salvage, not the fetus, mothers having high risk for future cardiovascular events.

Keywords: Hypothyroidism, Pregnancy, Pre-eclampsia, Maternal-fetal complications

INTRODUCTION

The pre-eclampsia like syndrome is a very rare pathological condition discovered usually in elder pregnant women during the second trimester, around weeks 16- 24, in cases known or not with hypothyroidism (Patel et al., 1991). Pre-eclampsia like syndrome can be discussed besides early and late pre-eclampsia, which are more frequently associated to subclinical/ overt hypothyroidism.

It is still missing a consensus, or is still controversies about the necessity of a screening to depict asymptomatic hypothyroidism in pregnant women (Lazarus and Premawardhana, 2005), or in countries with mild iodine deficiency to have women preconception screening of thyroid status (Rashid and Rashid, 2007). It was appreciated the importance of large studies on the

changes of thyroid function during pregnancy, hypothyroidism inducing many adverse events on mothers, and off-springs (Glinoe, 1998; Vaidya et al., 2007; Negro et al., 2010; Cignini et al., 2012), but very recent published papers of some scientific societies have proposed universal assessment of thyroid function during the first trimester of pregnancy, and ideally before week 10 of gestational age, because thyroid disease is a quite prevalent condition, easily diagnosed, with an effective and safe treatment available (Hoermann and Midgley, 2012; Pop, 2014; Vila et al., 2014), and cost- efficient (Thung et al., 2009). It is proposed to measure TSH, and if abnormal to measure free or total T₄ (Vila et al., 2014; Soldin et al., 2013), because thyroid testing of only those pregnant women at increased risk for thyroid disease,

case finding, will miss 30-80% of women with thyroid disease (Milanesi and Brent, 2011), facts which are proved during - first, and second trimester (Yang et al., 2014), or in the third trimester (Qjan et al., 2013). Other controversy is about the treatment with levothyroxine for subclinical hypothyroidism, detected in the first trimester, current evidences being inadequate to do so, and an ongoing randomized placebo controlled trial of levothyroxine treatment for subclinical hypothyroidism during pregnancy with early pregnancy sampling and longitudinal follow-up, expected to be completed in 2015, will provide new information on the natural history of untreated subclinical hypothyroidism and indicate whether levothyroxine treatment is beneficial in reducing adverse outcomes (Mestman et al., 2013; Clinical Trials.gov, 2013).

Hypothyroidism during Pregnancy

During pregnancy it is discussed a large spectrum of hypothyroid states that includes subclinical and overt hypothyroidism, isolated thyroid peroxidase antibody positivity, isolated hypothyroxinemia, and these patterns, in some situations, may be related to iodine status, selenium status, or underlying thyroid disease (Qjan et al., 2013). Thyroid diseases affect up to 5% of all pregnancies. (Mannistö, 2013), hypothyroidism being the second endocrinopathy during pregnancy: 2-3% of pregnant women are suffering from hypothyroidism, from whom 0.2- 1% (Casey et al., 2005) or with a lower incidence as 0,3-0.5 % (Negro and Mestman, 2011) have overt hypothyroidism -low free thyroid hormones, high TSH, and 2-2.5% (Mannistö, 2013) or 1.5- 4% (Vaidya et al., 2007) have subclinical hypothyroidism -defined as normal FT4 levels with high TSH. Subclinical hypothyroidism was found to be the most frequent thyroid disease occurring in pregnancy (Vaidya et al., 2007; Mannistö, 2013; Mitchell et al., 2003; Casey and Leveno, 2006), with differences between populations/countries, and criteria of diagnosis, iodine intake, or study design (Vaidya et al., 2007).

Women with subclinical hypothyroidism identified during pregnancy have an increased risk for severe preeclampsia, and other cardiovascular unwanted events when compared with euthyroid women (Wilson et al., 2012), with the consideration that the role of subclinical hypothyroidism in the development of maternal and fetal complications is not univocal (El Baba and Azar, 2012).

Minimum 5-10% of women have antithyroid antibodies (the Hashimoto's thyroiditis), and high risk to develop some degree of thyroid insufficiency during pregnancy (24), and/or of maternal morbidity later in life Männistö et al., 2010; Gaberšček and Zaletel, 2011).

Uncontrolled hypothyroidism induces high rates of adverse events during pregnancy as miscarriage, preterm birth, congenital malformations, intrauterine fetal

growth restriction, perinatal morbidity, and mortality, and peculiarly gestational hypertension with a special clinical manifestation- pre-eclampsia like syndrome, which induces many diagnosis issues in comparison to proper gestational hypertension (Alfadda and Tamilia, 2004).

The incidence of pre-eclampsia in hypothyroid women is 11- 44%, special in overt hypothyroidism (Poppe and Glinoe, 2003), and is more severe in women with subclinical hypothyroidism in comparison to euthyroid cases (Wilson et al., 2012), and when hypothyroidism is untreated the risks of complications are higher (Negro and Mestman, 2011). Recent logistic regression analysis demonstrated that the cases with late pre-eclampsia have more frequently high TSH levels, and low free T4 (Ashoor et al., 2010), fact which was confirmed by two prospective population based cohort studies, the Northern Finland Birth Cohorts 1966 and 1986, and nulliparous women with late pre-eclampsia or gestational hypertension had a 1.8 increased risk of subsequent hypothyroidism (Mannistö et al., 2013).

Pathophysiology of pre-eclampsia like syndrome

Hypothyroidism is recognized as the second cause of hypertensive disorders, and when pregnancy associated the hypertension is not a surprise (Stabouli et al., 2010).

The pathogenic mechanisms are partially different to those involved in early and severe pre-eclampsia. In the years of 80's the syndrome of low T3 was reported as classic for pre-eclamptic patients (Lao et al., 1988). When one consider pre-eclampsia, it is discussed the deficient placental angiogenesis with placental ischemia, and endothelial cells dysfunction, with the imbalance between pro-angiogenic/vasodilator and anti-angiogenic/vasoconstrictor factors, in the favor of the last, because of impaired trophoblast differentiation and invasion, which are inducing the systemic, uterine, and placental vasospasm (Levine et al., 2004; Burton et al., 2009).

Gestational hypertensive disease also shows a correlation with concentrations of TSH, and endothelin, in parallel with the severity of hypertension (Leung et al., 1993; Buimer et al., 2005; Wolfberg et al., 2005), and an old opinion correlates thyroid hormone concentrations to the severity of pre-eclampsia (Lao et al., 1988). Pre-eclampsia and its sequelae are strongly connected to a systemic inflammatory response, which in hypothyroid population can be correlated to autoimmune thyroiditis (Von Dadelszen et al., 2005); it was demonstrated that the presence of antithyroid antibodies is connected to the development of pre-eclampsia (Mecacci et al., 2000) and of pre-eclampsia like syndrome (Inversetti et al., 2012).

The hypothyroid population is characterized by two very important aspects that explain the development of pre-eclampsia like syndrome: significant changes of plasma volume, and proteinuria (Gilles et al., 2008).

Table 1. Characteristics and Outcome of the recorded cases from Pub Med

Authors/ Country/Year	Number of cases/ maternal age	GA (wks) at onset	Hypothyroidism	Outcome	
				Fetus	Mother
Patel S, Robinson S, Bidgood RJ, Edmonds CJ/ UK, 1991	1/ 34 years	20	Overt hypothyroidism	Death	Saved with Levothyroxine
Alfadda A, Tamilia M/ Canada, 2004	1/37 years	20	Overt hypothyroidism	Death	Saved with Levothyroxine
Inversetti A, Candiani M, et al/ Italy, 2012	1/42 years	17	Hashimoto' s thyroiditis	Death at 23 wks+ 6 days	Saved with Levothyroxine, and liothyronine sodium

Legend: GA: gestational age; wks: weeks

The hypertension of hypothyroid cases is a diastolic disorder, with a different mechanism from gestational hypertension. The vascular dysfunction is an very early endothelial dysfunction, with onset around 16-17 weeks gestation, with important vasoconstriction in systemic, and kidneys' circulation, inducing peripheral vascular resistance, and diastolic hypertension, plus severe proteinuria, (Alfadda and Tamilia, 2004; Negro and Mestman, 2011).

The recorded cases from Pub Med (Table 1) with pre-eclampsia like-syndrome were women over 35 years of age, for whom the atherosclerosis and the metabolic impact characteristic for overt and subclinical hypothyroidism are for sure responsible of the diastolic disorder (Staub et al., 1992; Trbojević, 2003).

During pregnancy, and specially when the hypothyroid state is subclinical, and not depicted at the onset of pregnancy, or it is not sufficiently corrected by levothyroxine supplementation, the changes of plasma volume are initiating a volume-dependent mechanism of hypertension – the mechanism of reduced plasma renine activity (Stabouli et al., 2010) on one side, and on the other side the increase of proteinuria to high value like those from the nephrotic syndrome, with the increase of the excretion of thyroxin and thyroid-binding globulins, which sometimes can not be compensated, and aggravates the hypothyroidism (Chandurkar et al., 2008). Other pathological characteristic of pre-eclampsia like-syndrome is an impaired nitric oxide (NO) availability, and an alteration partially independent of dyslipidemia, which are reversed by levothyroxine supplementation (Taddei et al., 2003).

Clinics and diagnosis of pre-eclampsia like syndrome

In advanced age, multiparous pregnant women, known and treated or not for hypothyroidism, besides persistent hypertension under hypotensive therapy, there are described headaches, generalized edema, with progressive abdominal ascites and pleural/pericardial

bilateral effusion, severe proteinuria which is aggravated from day- to – day, up to aspects characteristic for nephrotic syndrome (Patel et al., 1991; Gilles et al., 2008).

The diagnosis in pre-eclampsia like syndrome is a challenge for distinguishing it from other forms of gestational hypertension

Laboratory findings: besides that characteristic for hypertension, there are TSH increasing levels from day – to – day, and levels of free triiodothyronine and free thyroxine that continue to decrease, presence or absence of antithyroid antibodies, being known that thyroid peroxidase antibodies (TPO-Abs) or thyroglobulin antibodies (TG-Ab), which act as a marker of silent autoimmune thyroiditis, have concentrations which decrease as pregnancy progresses, explaining false negative results regarding thyroid autoimmunity in late gestation (Männistö et al., 2011).

The ultrasound examination from 11 to 13 weeks gestation may reveal high uterine artery resistance and bilateral notches, and at weeks 16-18 umbilical artery Doppler waveform with absent diastolic flow, which in connection to maternal history, and maternal serum TSH measurement may predict the risk of pre-eclampsia like syndrome (Ashoor et al., 2010).

Treatment of Pre-Eclampsia like Syndrome

The pre-eclampsia like syndrome is more difficult to treat in comparison to gestational hypertension, the answer to hypotensive drugs is bad, being necessary more medication, and higher doses, and in the absence of pathophysiologic medication- levothyroxine, one record fetal death and maternal severe complications. It is important to achieve an euthyroid state (defined by normal TSH levels) (Milanesi and Brent, 2011) if necessary by employing larger than conventional doses of levothyroxine integrated with liothyronine sodium, especially when proteinuria is a complicating factor.

Pregnancy termination is sometimes necessary, if

treatment is not working, or if is registered fetal death, which is reported in all published cases (Table 1).

Prognosis

In the absence of an universal screening for thyroid dysfunction pre-pregnancy or in early pregnancy, and adequate correction of hypothyroidism from the beginning of the pregnancy, even with good iodine intake (a value of serum thyroglobulin < 20 µg/L may indicate iodine sufficiency in pregnant women- 47), the pre-eclampsia like syndrome has an adverse outcome for mother, and specially for fetus - who will die, even if hypothyroidism is treated with levothyroxine immediately after the onset of syndrome, because the control of homeostasis is difficult to be accomplished, the euthyroidism is apparently restored, being discussed that the treatment displays a compensatory adaptation, but does not completely re-enact normal euthyroid physiology (Hoermann et al., 2013). The reduction of proteinuria in association to the decrease of TSH to values of 2.5 mIU/L to 3.0 mIU/L, which defines euthyroidism (Abalovich et al., 2007; Alexander et al., 2007; Yassa et al., 2010) is considered a better sign than the response of blood pressure for short term maternal prognosis (40), and for long term it is discussed the high risk for morbidity in later life (Männistö et al., 2010), as future development of cardiovascular disease (Gencer et al., 2013).

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