

Maternal thyroid function at 11 to 13 weeks of gestation and subsequent development of preeclampsia

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Objective To determine if maternal thyroid function in the first trimester is altered in pregnancies that subsequently develop preeclampsia (PE).

Methods Mean arterial pressure (MAP), uterine artery pulsatility index (PI) maternal serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) at 11 to 13 weeks of gestation were measured in 102 singleton pregnancies that subsequently developed PE, and the values were compared to the results of 4318 normal pregnancies.

Results In both the PE groups that required delivery before 34 weeks (early-PE) and the late-PE group, compared with the unaffected group, the median MAP multiple of the normal median (MoM) and uterine artery PI MoM were significantly increased. In late-PE but not in early-PE, compared with the unaffected group, the median TSH MoM was significantly increased and the median FT4 MoM was decreased. Logistic regression analysis demonstrated that TSH MoM provided a significant contribution in the prediction of late-PE.

Conclusion Impaired thyroid function may predispose to the development of late-PE, and measurement of maternal serum TSH can improve the prediction of late-PE provided by a combination of factors in the maternal history and the measurements of MAP and uterine artery PI. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: thyroid function; hypothyroidism; preeclampsia; uterine artery Doppler; mean arterial pressure

INTRODUCTION

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality Witlin *et al.*, 2000; Irgens *et al.*, 2001; World Health Organization (WHO), 2005; Lewis, 2007; Confidential Enquiry into Maternal and Child Health (CEMACH), 2008. Recent evidence suggests that PE can be divided into early-PE requiring delivery before 34 weeks, and late-PE with the former, being associated with a high incidence of fetal growth restriction, whereas in late-PE fetal growth is usually normal (Yu *et al.*, 2008). The underlying mechanism for the development of PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control (Brosens *et al.*, 1967; Khong *et al.*, 1986; Pijnenborg, 1996). Indirect evidence for impaired placental perfusion in pregnancies destined to develop PE has been provided by Doppler studies of the uterine arteries which showed increased pulsatility index (PI) which is evident from 11 to 13 weeks of gestation, and this increase is particularly marked for early-PE (Martin *et al.*, 2001; Plasencia *et al.*, 2007; Poon *et al.*, 2009). Effective first-trimester screening for both early-PE and late-PE is provided

by a combination of maternal demographic characteristics and medical history, uterine artery PI and maternal mean arterial pressure (MAP) (Poon *et al.*, 2008, 2009, 2010).

Several studies have reported that in patients presenting with the clinical features of PE, thyroid function is disturbed with increase in maternal serum thyroid stimulating hormone (TSH) and decrease in the levels of thyroid hormones (Lao *et al.*, 1988, 1990; Başbuğ *et al.*, 1999; Khaliq *et al.*, 1999; Larijani *et al.*, 2004; Kumar *et al.*, 2005). The results of a population-based study in which serum TSH was measured in women on average 20 years after their first pregnancy highlighted further the interrelation between hypothyroidism and PE (Levine *et al.*, 2009b). Women who had PE in their first pregnancy were 1.7 times as likely to have increased serum TSH than women who had not had PE and those who had PE in both their first and second pregnancies had a five- to sevenfold increased likelihood for having high TSH. It was postulated that the effect of PE on thyroid function during and after pregnancy is mediated by the antiangiogenic factor-soluble fms-like tyrosine kinase 1 (sFlt-1) which is elevated in patients with PE (Levine *et al.*, 2009b). Patients with cancer treated with vascular endothelial growth-factor inhibitors are at increased risk of developing hypothyroidism (Desai *et al.*, 2006; Wolter *et al.*, 2008; Feldman *et al.*, 2009). Studies in mice have shown that the administration of sFlt-1 causes a major reduction in thyroid tissue capillary density and increased concentrations of TSH (Kamba *et al.*, 2006; Kamba and McDonald,

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2007). However, the suggestion that PE causes hypothyroidism is at least in part contradicted by the finding that women with hypothyroidism have an increased risk of developing PE (Echt and Doss, 1963; Davis *et al.*, 1988; Leung *et al.*, 1993). Consequently, an alternative explanation for the findings of Levine *et al.*, 2009b is that subclinical hypothyroidism may predispose to the development of PE, rather than the other way round. However, a first-trimester screening study reported that thyroid hypofunction in early pregnancy was not associated with increased risk for subsequent development of PE (Cleary-Goldman *et al.*, 2008).

The aims of this study are to investigate further if the prevalence of maternal thyroid hypofunction at 11 to 13 weeks of gestation is higher in pregnancies that subsequently develop PE and whether the assessment of thyroid function can improve the prediction of PE provided by a combination of factors in the maternal history and the measurements of MAP and uterine artery PI.

METHODS

This was a prospective screening study for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11⁺⁰ to 13⁺⁶ weeks of gestation, the following steps are carried out. First, we record maternal characteristics, including age, racial origin (White, Black, South Asian, East Asian and mixed), weight, height and body mass index (BMI). Second, we measure the MAP by automated devices (3BTO-A2, Microlife, Taipei, Taiwan) (Poon *et al.*, 2008). The pressure was measured in both arms simultaneously and a series of recordings are made at 1-min intervals until variations between consecutive readings fall within 10 mmHg in systolic blood pressure and 6 mmHg in diastolic blood pressure in both arms. When this point of stability is reached we calculate the MAP of each arm as the average of the last two stable measurements and take the arm with the highest final MAP. Third, an ultrasound scan is carried out to confirm gestational age from the measurement of the fetal crown-rump length (CRL), to diagnose any major fetal abnormalities and to measure fetal nuchal translucency thickness (NT) (Snijders *et al.*, 1998). Fourth, the uterine artery PI is measured (Poon *et al.*, 2009). Essentially, transabdominal ultrasound and color flow mapping are used to identify each uterine artery, pulsed wave Doppler is performed to measure the PI in the left and right arteries and one with the lowest PI is recorded. Fifth, the maternal serum free β -hCG and PAPP-A (DELFI EXPRESS analyzer, PerkinElmer, Waltham, USA) are measured as part of screening for chromosomal abnormalities by a combination of fetal NT and serum biochemistry (Kagan *et al.*, 2008). Sixth, blood sample is collected for research, and the separated plasma and serum are stored at -80°C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

In this study, we measured the maternal serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), TSH, anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) at 11 to 13 weeks in 102 singleton pregnancies that subsequently developed PE. None of the PE patients had a history of thyroid disease. The values were compared to the results of our previous study in 4318 singleton pregnancies with no history of thyroid disease, which did not develop PE and resulted in live birth after 34 weeks of phenotypically normal neonates with birth weight above the 5th centile (Ashoor *et al.*, 2010). In that study there were 726 (16.8%) pregnancies in which the concentration of one or both antithyroid antibodies was 60 U/mL or more. Normal ranges for TSH, FT3 and FT4 were derived from the study of the 3592 pregnancies with no antithyroid antibodies (Ashoor *et al.*, 2010).

Outcome measures

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy (Davey and MacGillivray, 1988). The diastolic blood pressure should be 90 mmHg or more on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women. In addition there should be proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE, superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

Sample analysis

The maternal serum concentrations of FT3, FT4, TSH, anti-TPO and anti-Tg were measured by immunoassay using direct, chemiluminometric technology (Siemens Advia Centaur assays, Siemens Healthcare Diagnostics Ltd, Surrey, UK). The minimum detectable concentrations of FT3, FT4, TSH, anti-TPO and anti-Tg were 0.3, 1.3 pmol/L, 0.003 mIU/L, 15 and 30 U/mL, respectively. The intra-assay coefficients of variation were 3.08, 2.35 and 2.47% at FT3 concentrations of 2.9, 6.6 and 14.2 pmol/L, respectively; 4.69, 2.31 and 2.22% at FT4 concentrations of 6.1, 13.9 and 39.9 pmol/L, respectively; 2.48, 2.44 and 2.41% at TSH concentrations of 0.74, 5.65 and 18.98 mIU/L, respectively; 7.93, 4.54 and 6.26% at anti-TPO concentrations of 1.70, 10.01, 14.95 U/mL respectively; and 5.5 and 2.9% at anti-Tg concentrations of 62 and 333 U/mL respectively. If the serum concentration of anti-TPO and anti-Tg was less than 60 U/mL, which was the manufacturer's reference limit, the patients were considered to be antibody negative.

Table 1—Maternal demographic characteristics in the three outcome groups

Variables	Unaffected (<i>n</i> = 3592)	Early-PE (<i>n</i> = 25)	Late PE (<i>n</i> = 77)
Gestation at sampling in weeks (median, IQR)	12.4 (12.3–12.9)	12.7 (12.1–13.1)	12.4 (12.1–12.7)
Gestation at delivery in weeks (median, IQR)	40.0 (39.0–40.9)	32.4 (29.1–33.2)*	38.6 (37.3–39.9)*
Maternal age in years (median, IQR)	32.2 (28.0–36.0)	29.5 (23.7–34.9)	32.3 (27.4–37.2)
Body mass index in Kg/m ² , median (IQR)	24.7 (22.2–27.9)	25.1 (22.5–30.8)	27.8 (23.7–31.2)*
Racial origin			
White, <i>n</i> (%)	2,543 (70.8)	9 (36.0)	34 (44.2)
Black, <i>n</i> (%)	708 (19.7)	13 (52.0)*	34 (44.2)*
South Asian, <i>n</i> (%)	148 (4.1)	1 (4.0)	3 (3.9)
East Asian, <i>n</i> (%)	57 (1.6)	0	2 (2.6)
Mixed, <i>n</i> (%)	136 (3.8)	2 (8.0)	4 (5.2)
Parity			
Nulliparous, <i>n</i> (%)	1684 (46.9)	12 (48.0)	44 (57.1)
Parous—no previous preeclampsia, <i>n</i> (%)	1818 (50.6)	8 (32.0)	20 (26.0)*
Parous—previous preeclampsia, <i>n</i> (%)	90 (2.5)	5 (20.0)*	13 (16.9)*
Cigarette smoker, <i>n</i> (%)	322 (9.0)	1 (4.0)	5 (6.5)
Family history of preeclampsia, <i>n</i> (%)	128 (3.6)	5 (20.0)*	9 (11.7)*
Conception by ovulation drugs, <i>n</i> (%)	101 (2.8)	2 (8.0)	5 (6.5)
Chronic hypertension, <i>n</i> (%)	38 (1.1)	3 (12.0)*	5 (6.6%)*

Comparison between each hypertensive disorder group and unaffected was by Chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables, both with *post hoc* Bonferroni correction (critical statistical significance $p < 0.025$): * $p < 0.025$. IQR, interquartile range.

Statistical analysis

The characteristics of the early-PE, late-PE and the unaffected group used for the construction of normal ranges were compared by Mann Whitney test for continuous variables and Fisher's exact test or Chi-square test for categorical variables. The measured MAP and uterine artery lowest pulsatility index (L-PI) were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal age, BMI or weight, smoking, parity, racial origin and method of conception as previously described (Poon *et al.*, 2008, 2009). Similarly, the measured concentrations of FT3, FT4 and TSH were converted to MoMs corrected for gestational age, maternal age, racial origin and BMI (Ashoor *et al.*, 2010). Comparison of MAP MoM, uterine artery L-PI MoM, TSH MoM, FT3 MoM and FT4 MoM between early-PE, late-PE and the unaffected group was performed by Mann Whitney-U test, with *post hoc* Bonferroni correction (critical statistical significance $p < 0.025$). The risks for early-PE and late-PE based on combinations of maternal factors, MAP and uterine artery L-PI were determined as previously described and were then logarithmically transformed (Poon *et al.*, 2008, 2009, 2010). Logistic regression analysis was used to determine if the log-transformed risk based on maternal factors, MAP and uterine artery L-PI and TSH MoM had a significant contribution in predicting early-PE and late-PE. The performance of screening was determined by receiver operating characteristic (ROC) curves.

In the early-PE, late-PE and unaffected groups the Chi-square test was used to compare the proportion of cases with anti-TPO and anti-Tg antibodies and those with serum TSH above the 97.5th centile and serum FT3 and FT4 below the 2.5th centile.

The statistical software packages SPSS 16.0 (SPSS Inc., Chicago, IL) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

RESULTS

The patient characteristics of the early-PE, late-PE and unaffected groups are compared in Table 1. In both the early-PE and late-PE groups, compared to the unaffected group, there was a higher prevalence of Black women, chronic hypertensives and women with a personal or family history of PE. In women who developed late-PE the BMI was increased. None of the patients in all three groups had a previous history of PE.

In both the early-PE and late-PE groups, compared to the unaffected group, the median MAP MoM and uterine artery L-PI MoM were significantly increased (Table 2). In late-PE but not in early-PE, compared to the unaffected group, the median TSH MoM was significantly increased and the median FT4 MoM was decreased. In late-PE the proportion of cases with high TSH, low FT4 or low FT3 was higher than in the controls (Table 2, Figure 1).

Regression analysis demonstrated that in the PE group there were no significant associations between TSH MoM and uterine artery L-PI MoM ($p = 0.315$), or between TSH MoM and MAP MoM ($p = 0.533$).

Logistic regression analysis demonstrated that in the prediction of late-PE there were significant contributions from TSH MoM to the prediction from the combination of maternal factors, uterine artery L-PI and MAP (Table 3). The areas under the ROC curves and detection rates for fixed false positive rates of 5% and 10% are given in Table 3.

Table 2—Mean arterial pressure, uterine artery lowest pulsatility index L-PI and maternal serum thyroid stimulating hormone, free thyroxine and free triiodothyronine in the unaffected group and in those who subsequently developed early and late-preeclampsia

	Unaffected	Early preeclampsia	Late-preeclampsia
Mean arterial pressure			
MoM (median, IQR)	0.98 (0.93–1.04)	1.06 (1.01–1.15)**	1.07 (1.00–1.13)**
mmHg (median, IQR)	84.67 (79.83–89.5)	91.3 (88.0–101.9)	94.4 (87.0–99.5)
Uterine artery L-PI			
MoM (median, IQR)	1.01 (0.82–1.22)	1.54 (1.17–1.64)**	1.20 (0.87–1.50)*
units (median, IQR)	1.41 (1.14–1.71)	2.10 (1.67–2.34)	1.68 (1.21–2.13)
Thyroid stimulating hormone			
MoM (median, IQR)	1.007 (0.608–1.511)	1.08 (0.556–1.781)	1.390 (0.708–2.122)*
m IU/L (median, IQR)	1.096 (0.670–1.665)	1.094 (0.500–1.583)	1.357 (0.730–2.346)
>97.5 centile (%)	89 (2.5)	2 (8.0)	10 (13.0)*
Free thyroxine			
MoM (median, IQR)	0.992 (0.908–1.086)	0.966 (0.868–1.043)	0.951 (0.843–1.052)*
Pmol/L (median, IQR)	14.9 (13.6–16.3)	14.1 (13.1–15.5)	14.0 (12.4–15.6)
% < 2.5 centile (%)	89 (2.5)	1 (4.0)	6 (7.8)*
Free triiodothyronine			
MoM (median, IQR)	0.991 (0.935–1.059)	0.954 (0.881–1.054)	1.010 (0.934–1.064)
Pmol/L (median, IQR)	4.6 (4.4–5.0)	4.5 (4.1–5.0)	4.7 (4.4–5.0)
% < 2.5 centile (%)	89 (2.5)	2 (8.0)	6 (7.8)*

Comparison between each hypertensive disorder group and unaffected was by Chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables, both with *post hoc* Bonferroni correction (critical statistical significance $p < 0.025$): * $p < 0.025$, ** $p < 0.001$. IQR, interquartile range.

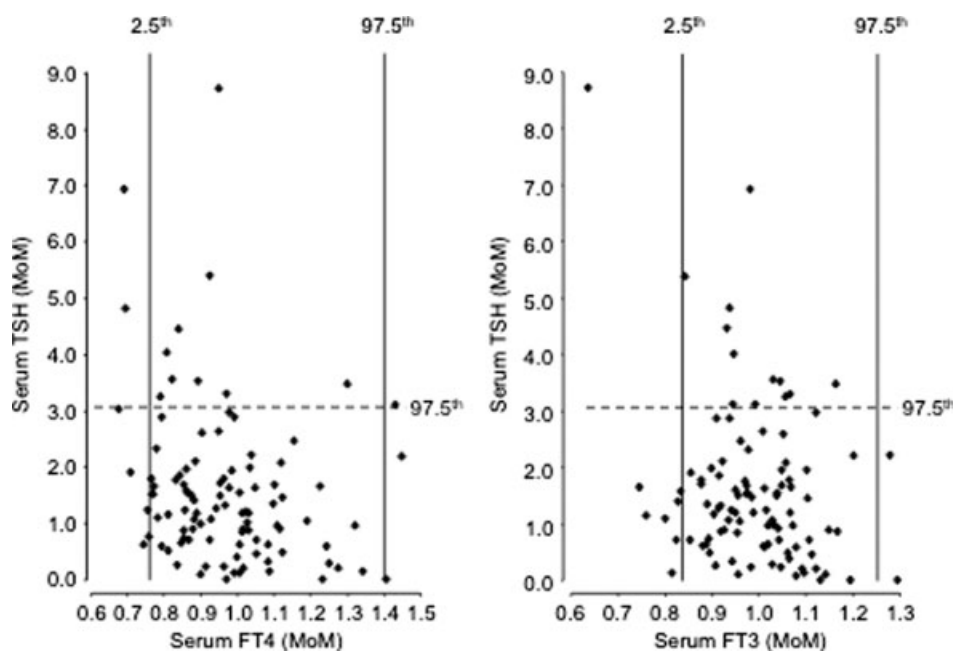


Figure 1—Relationship between maternal serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) in multiples of the expected normal median (MoM) at 11 to 13 weeks of gestation in pregnancies that subsequently developed preeclampsia. The vertical lines represent the 2.5th and 97.5th centiles of the normal ranges for FT4 and FT3, and the interrupted horizontal lines the 97.5th centile for TSH

Antithyroid antibodies

In our previous screening study 726 (16.8%) of the 4318 pregnancies were positive for one or both antithyroid antibodies, 308 (7.1%) were positive for both, 285 (6.6%) were positive for anti-Tg only and 133 (3.1%)

were positive for anti-TPO antibody. In this study of pregnancies complicated by PE the prevalence of antithyroid antibodies was not significantly increased; in late-PE 11 (14.3%) of the 77 pregnancies had positive antibodies, 6 (7.8%) were positive for both, 4 (5.2%) were positive for anti-Tg and 1 (1.3%) was positive for

Table 3—Performance of screening for late-preeclampsia by maternal factors only

Screening test	Area under receiver operating characteristic curve (95% CI)	
	Late-preeclampsia	
Maternal risk factor	0.785 (0.770–0.799)	
TSH MoM	0.603 (0.586–0.621)	
Maternal risk factor plus		
TSH	0.793 (0.778–0.807)	
MAP, uterine artery L-PI	0.856 (0.843–0.868)	
All markers	0.860 (0.848–0.872)	
	Detection rate (%) for fixed false positive rate (95% CI)	
	5%	10%
Maternal risk factor	27.5 (17.5–39.6)	37.7 (26.3–50.2)
TSH MoM	21.7 (12.7–33.3)	27.5 (17.5–39.6)
Maternal risk factor plus		
TSH	36.2 (25.0–48.7)	47.8 (35.6–60.2)
MAP, uterine artery L-PI	39.1 (27.6–51.6)	53.6 (41.2–65.7)
All markers	43.5 (31.6–56.0)	59.4 (46.9–71.1)

TSH MoM, a combination of maternal factors with TSH MoM, a combination of maternal factors, lowest uterine artery pulsatility index (L-PI) and mean arterial pressure (MAP) and a combination of maternal factors, uterine artery L-PI, MAP and TSH MoM.

anti-TPO; in early-PE 3 (12.0%) of the 25 pregnancies ($p = 0.687$) were positive for both antibodies, 2 (8%) were anti-Tg positive and 1 (4%) was anti-TPO positive.

DISCUSSION

The findings of this study demonstrate an association between impaired maternal thyroid function at 11 to 13 weeks and subsequent development of late-PE. High serum TSH was observed five times as many with late-PE compared with those who did not develop PE. This association of hypothyroidism and PE is independent of autoimmune mechanisms because the prevalence of antithyroid antibodies was not higher in the PE than in the non-PE group. A study of 5505 patients examining early pregnancy serum samples for thyroid function reported that in the group with subclinical hypothyroidism the incidence of subsequent development of PE was higher than in the euthyroid group (3.8 vs 1.9%) but this difference did not reach statistical significance (Mannisto *et al.*, 2010). Another first-trimester screening study involving 10 990 patients reported that the subclinical hypothyroidism group was not associated with the development of PE but the reported prevalence of PE in this study was only 1% (Cleary-Goldman *et al.*, 2008). These studies did not

report separately their findings of early and late-PE (Cleary-Goldman *et al.*, 2008; Mannisto *et al.*, 2010).

Our results raise the possibility that the findings of the population-based study, in which serum TSH was measured in women 20 years after their pregnancies and found to be higher in those who had developed PE (Levine *et al.*, 2009b), may merely reflect a preexisting thyroid dysfunction that preceded their pregnancies. Another population-based cohort with follow-up for 20 years reported that thyroid dysfunction in early pregnancy was not associated with the development of PE but those with subclinical hypothyroidism were at increased risk of developing overt hypothyroidism in the long term (Mannisto *et al.*, 2010).

The study has confirmed the association between the development of PE and factors in the maternal history and the measurements of MAP and uterine artery PI (Poon *et al.*, 2008, 2009, 2010). Increased risk for both early-PE and late-PE was observed in women of Black racial origin and those with a family or personal history of PE and chronic hypertension. Late-PE was also associated with increased BMI. In both early-PE and late-PE, MAP and uterine artery PI were increased but the increase in PI was more pronounced in those with early-PE. Impaired thyroid function was more pronounced in pregnancies that developed late-PE than early-PE.

The strengths of this study are: first, examination of a large number of appropriately documented cases of PE and normal controls; second, assessment of confounding factors in the prediction of PE, including maternal history, MAP and uterine artery PI; third, use of normal ranges of thyroid function corrected for maternal characteristics, including age, racial origin and BMI (Ashoor *et al.*, 2010); and fourth, assessment of thyroid function in the first trimester of pregnancy providing the option for therapeutic interventions in future studies to determine if the incidence of PE can be reduced. The weakness of the study was its cross-sectional nature, which did not allow longitudinal assessment of thyroid function from early pregnancy to the development of PE.

There is extensive evidence that the underlying mechanism for early-PE is impaired trophoblastic invasion of the maternal spiral arteries, reduced placental perfusion and fetal growth restriction (Plasencia *et al.*, 2007; Yu *et al.*, 2008; Poon *et al.*, 2009). In contrast, in late-PE, placental perfusion and fetal growth are often normal, and the main pathophysiological processes resemble those of the metabolic syndrome with an increase in adipose tissue and impaired glucose and lipid metabolism (Witlin *et al.*, 2000; Moldenhauer *et al.*, 2003; Vatten *et al.*, 2004; D'Anna *et al.*, 2006; Egbor *et al.*, 2006; Poon *et al.*, 2009). The association between hypothyroidism and late-PE may be mediated by the well-described role of thyroid hormones in glucose homeostasis and in the synthesis, metabolism and mobilization of lipids (Duntas, 2002; Pearce, 2004; Chidakel *et al.*, 2005). Hypothyroidism may also play a direct role in causing pregnancy hypertension because thyroid hormones act directly on peripheral arterioles to cause dilation (Dernellis and Panaretou, 2002). Studies in nonpregnant individuals reported that hypothyroidism

is associated with an increase in peripheral resistance due to increased arterial wall thickness (Giannattasio *et al.*, 1997) and endothelial dysfunction (Virdis *et al.*, 2009). This can be reversed by the treatment with thyroid hormones (Giannattasio *et al.*, 1997; Dernellis and Panaretou, 2002).

CONCLUSION

Measurement of maternal serum TSH can improve the prediction of late-PE provided by a combination of factors in the maternal history and the measurements of MAP and uterine artery PI. The ability to predict in very early pregnancy those women at high-risk for PE might decrease maternal and fetal morbidity through closer surveillance by physicians experienced or specialized in high-risk obstetrics, as well as delivery at tertiary care centers (Levine and Lindheimer, 2009a). Effective identification of the high-risk group can also be useful for future studies investigating the potential role of pharmacological interventions starting from the first trimester to reduce the prevalence of the disease.

ACKNOWLEDGEMENTS

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116). The assays were performed by Ms Tracy Dew at the Department of Clinical Biochemistry at King's College Hospital, London, UK. The assays were sponsored by PerkinElmer, Inc., Wallac Oy, Turku, Finland. The funders have not influenced any aspect of the study.

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