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Preeclampsia, gestational hypertension and subsequent hypothyroidism

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Abstract

Objectives—To evaluate the effect of preeclampsia (PE) and gestational hypertension (GH) on subsequent hypothyroidism. Recent studies suggest that women with PE have increased risk for reduced thyroid function, but the association between PE and GH with overt hypothyroidism has not been examined.

Study design—Two prospective population-based cohort studies, the Northern Finland Birth Cohorts 1966 and 1986, followed women who had PE (N=955), GH (N=1449) or were normotensive (N=13531) during pregnancy. Finnish national registers were used to confirm subsequent hypothyroidism. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) estimated hypothyroidism risk when comparing women with PE or GH with normotensive women.

Main outcome measures—Primary hypothyroidism during follow-up of 20–40 years.

Results—The subsequent prevalence of hypothyroidism was higher among women with PE (4.0%) and GH (4.5%) compared with normotensive women (3.5%), but the risk increase was not significant (aHR for PE 1.13, 95%CI 0.80–1.59 and aHR for GH 1.11, 95%CI 0.85–1.45).

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Disclosure Summary: Dr. Karumanchi is a co-inventor of multiple patents related to angiogenic proteins for the diagnosis and therapy of preeclampsia. These patents have been licensed to multiple companies. Dr. Karumanchi reports having served as a consultant to Roche and Beckman Coulter and has financial interest in Aggamin LLC. The remaining authors report no conflicts.

Subgroup analysis among nulliparous women revealed a significant association between late PE and subsequent hypothyroidism (aHR 1.82, 95%CI 1.04–3.19).

Early or recurrent PE were not associated with hypothyroidism (aHR 0.93, 95%CI 0.46–1.81 and aHR 1.35, 95%CI 0.63–2.88, respectively).

Conclusions—Overall, PE or GH during pregnancy was not significantly associated with subsequent hypothyroidism in Finnish women after 20–40 years of follow-up. However, late PE in nulliparous women was associated with a 1.8-fold increased risk of subsequent hypothyroidism, a finding that merits further study in other populations.

Keywords

preeclampsia; gestational hypertension; thyroid; hypothyroidism

Introduction

Preeclampsia (PE) and gestational hypertension (GH) are new onset hypertensive disorders in pregnancy, occurring after mid-gestation with and without proteinuria, respectively [1]. They affect up to 5–10% of pregnancies and are important risk factors for maternal and fetal morbidity and mortality [1]. The pathophysiology of PE and GH is still largely unknown, but circulating antiangiogenic factors, like soluble fms-like tyrosine kinase 1 (sFlt1), are thought to play a role [2,3,4]. sFlt1 acts as an inhibitor of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) signaling and induces endothelial dysfunction and capillary regression in various organ systems [2,3,5]. sFlt1 is found in normal pregnancy but higher concentrations are measured in women with hypertensive disorders, even before their clinical onset [4,3].

Inhibition of VEGF to interfere with malignant cell growth during cancer treatment can produce a clinical condition resembling PE including hypertension and proteinuria [5,6,7,8], indicating a role for impaired VEGF signalling in PE. Hypothyroidism is also a well-known side-effect of anti-VEGF treatment due to capillary regression in the thyroid tissue [6].

Women with PE more often have elevated thyrotropin (TSH) levels at the end of pregnancy and women with history of one or more episodes of PE have been shown to have higher risk of developing subsequently reduced thyroid function [9]. Long-term thyroid dysfunction may result from the effects of exposure to antiangiogenic factors during pregnancy complicated by PE or GH [4,9]. Thyroid dysfunction in early pregnancy has also been associated with the development of PE and GH in some studies [10,11], but not in all [12].

The aim of this study was to investigate whether women with PE or GH during pregnancy are at increased risk of subsequent overt autoimmune hypothyroidism during a follow-up of 20–40 years. The association of thyroid dysfunction or thyroid antibodies during early pregnancy combined with these conditions on subsequent hypothyroidism was also evaluated.

Subjects and methods

Northern Finland Birth Cohort (NFBC) 1966

The prospective NFBC 1966 comprised all expected births between January 1st and December 31st 1966, drawn from the two northernmost provinces of Finland (N=12055 women, N=12068 deliveries). It included all live-born and stillborn infants of more than 28 weeks gestation or birth weight of at least 600 grams (coverage 96.3%). Information on the women was collected by local midwives during routine visits in the free-of-charge

communal maternity welfare clinics (MWCs) using a questionnaire. Women visited MWCs on average seven times during pregnancy, beginning between 10–16 weeks gestation. The final recruitment to the study was at 28 weeks gestation. Maternal questionnaire data was collected at 24 to 28 weeks with 10.1% completing it later during pregnancy or after delivery. Maternal health data was obtained from the antenatal cards filled during routine MWC visits or via questionnaire [13].

Northern Finland Birth Cohort 1986

The prospective NFBC 1986 comprised of 99% of all expected births between July 1, 1985 and June 30, 1986 (N=9362 women, N=9362 deliveries). Data was collected during routine visits in MWCs as well as via questionnaires beginning at 12 weeks gestation and all mothers were recruited by 24 weeks. Over 95 % of women attended MWCs with an average of nine visits per women. Questionnaire data included demographic, biologic and socioeconomic characteristics of the mothers/families, maternal health data during pregnancy and items about the pregnancy, and delivery. The MWC nurses helped the women fill in the questionnaire and ensured that all questions were answered [14,15].

Study population

The primary analyses are based on 15,796 women with singleton pregnancies and clinical blood pressure measures indicating they were normotensive or had PE or GH.

Women who had chronic hypertension without superimposed preeclampsia (N=1082), normotensive women with proteinuria (N=421), women with only elevated systolic or diastolic blood pressure (BP) (N=1748) and all multiple pregnancies (N=558) were excluded. In NFBC 1966, women, who delivered twice (N=13) were considered only once in the data.

Sensitivity analyses were performed among nulliparous women and among NFBC 1986 women with TSH, thyroid hormone and antibody levels analyzed during pregnancy. Additionally we analyzed the data after excluding women with the highest socioeconomic position, as these women were thought to be less likely to apply for reimbursement for inexpensive medication like levothyroxine and be more likely to be misclassified.

The subjects gave informed consent and this study has been accepted by the Ethical Committee of Northern Ostrobothnia Hospital District.

Definitions and incidence of hypertensive disorder in NFBC 1966 and 1986

BP measurements and urinary dip stick test were performed at every MWC visit and documented in cohort databases. This data was carefully evaluated by principal investigators (A-L H and AP) and supplemented with hospital discharge register data for NFBC 1986 (TM). In the 1960's, BP was recorded by rounding up or down to the nearest 5 mmHg, thus values ≥145/95 represent hypertension in NFBC 1966, while BP values ≥140/90 represent hypertension in NFBC 1986. The following categories were used:

Normotensive: BP <145/95 mmHg (NFBC 1966) or BP <140/90 mmHg (NFBC 1986) before and throughout pregnancy (N=6526 and N=6895, respectively), total N=13421.

PE: Normotensive before 20th gestational week. Hypertension after 20 weeks gestation and proteinuria in at least in one sample during pregnancy (NFBC 1966 N=240) or hypertension and proteinuria (≥0.3 g/L) after 20 weeks of pregnancy (NFBC 1986 N=387). Alternatively, PE superimposed on chronic hypertension (NFBC 1966 N=116 and NFBC 1986 N=199). Total N=942.

GH: Normotensive before 20th gestational week with hypertension after 20 weeks gestation, no proteinuria (NFBC 1966 N=987 and NFBC 1986 N=446), total N=1433.

Recurrent PE: PE during index pregnancy and in subsequent pregnancies as ascertained from registries (NFBC 1966 N=24) or PE in index pregnancy and history of PE in the questionnaire and/or PE in subsequent pregnancies as ascertained from the registries (NFBC 1986 N=143), total N=167.

Early PE: diagnosis of PE before 37 weeks gestation, NFBC 1966 N=71 and NFBC 1986 N=190, total N=261.

Late PE: diagnosis of PE ≥37 weeks gestation, NFBC 1966 N=275 and NFBC 1986 N=397, total N=672.

Follow-up

Only primary hypothyroidism not resulting from thyroid surgery or ablation was considered an end-point of this study. The hypothyroidism diagnosis was assessed using Finnish national registers, with a follow-up of 20–40 years. The first year of follow-up for each woman was not included in the analyses to reduce the immediate effect of pregnancy on the outcome.

In Finland, special reimbursement for hypothyroidism medication is tied to medical certification of a valid diagnosis for the National Social Security Insurance Institution, recorded in the Special Refund Entitlement Register (data available 1964–2007). All hypothyroidism discharge diagnoses from hospital wards or outpatient clinics were captured from the Finnish Hospital Discharge Register for years 1972–2008 (with general accuracy of 83–95%),[16,17] using International Classification of Diseases (ICD) codes. All deaths and causes of death were captured from Population Register and Register of Causes of Death (available 1966–2006). We considered receiving reimbursement for medication to treat hypothyroidism or having a diagnosis of hypothyroidism in any of the registers as verification of the disease. Hypothyroidism was defined as having codes ICD-8 code 244 or 245, ICD-9 codes 244.9, 245.2, or 245.9, ICD-10 codes E03.5, E03.80, E03.82, E03.89, E03.9 or E06. The register-based data were combined with the NFBC databases by using Finnish individual social security numbers by personnel uninvolved in this study. The researchers had no access to identifiable data.

Laboratory data

The women of NFBC 1986 had routine screening for infectious diseases in early pregnancy and the leftover serum samples (N=5805) were analyzed for TSH, thyroid hormones [free triiodothyronine (fT3), and free thyroxine (fT4)] and thyroid autoantibodies [thyroid-peroxidase antibody (TPO-Ab) and thyroglobulin antibody (TG-Ab)] using the Abbott Architect analyzer (Abbott Diagnostics, Abbott Park, IL). This data collection and associated definition of thyroid conditions based on the distribution of TSH and fT4 (i.e. hypothyroidism, hyperthyroidism or hypothyroxinemia) and thyroid autoantibody positivity have been previously described [12].

Statistical methods

Student's *t* test, Fisher's exact test and Mann-Whitney *U* test was used as appropriate to compare unadjusted differences between women with PE, GH and normotensive mothers. Laboratory data was skewed and logarithmically transformed to achieve normality. Some of the covariate and laboratory data was missing (4.7% on maternal weight, 4.9% on MWC visits, 0.2% on parity, 3.2% on smoking and 1.1% on both fT4 and fT3) and excluded pair-wise in the analyses. Cox's regression analysis was applied to assess the effects of

hypertensive disorders on subsequent hypothyroidism. Because the rates of hypothyroidism appeared to be different in the two cohorts, the models were run with cohort as a stratum to avoid the potential violation of the proportional hazards assumption. The model was adjusted for maternal age and pre-pregnancy weight. Both crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) are presented. All analyses were also performed stratified by fetal gender, as studies suggest that the proportion of male fetuses is higher among cases of PE [18]. All statistical analyses were performed with SPSS 18.0 and 19.0 programs (IBM Statistics).

Results

Demographic characteristics

Women with PE or GH were older, heavier and less often smokers than normotensive women. The infants of mothers with PE or GH were also generally of lower birth weight than the infants of normotensive mothers with the exception of late preeclampsia. Women with PE had higher socioeconomic position and women with GH had lower socioeconomic position than normotensive women. Women with PE also had more MWCs visits than normotensive women, with the exception of early PE where the opportunity for late pregnancy visits is curtailed (Table 1).

Subsequent hypothyroidism

Subsequent hypothyroidism was observed in 3.5% of the normotensive women. Slightly higher prevalence was observed among women with PE (4.0%) and GH (4.5%). The adjusted risks for hypothyroidism were aHR 1.13 (95% CI 0.80–1.59) for PE and aHR 1.11 (95% CI 0.85–1.45) for GH (Table 2).

The prevalence of hypothyroidism was similar among women with early (3.1%), late (4.5%) and recurrent PE (4.2%) and normotensive women (3.5%). The risks for hypothyroidism were aHR 0.93 (95% CI 0.46–1.87) for early PE, aHR 1.23 (95% CI 0.84–1.81) for late PE and aHR 1.35 (95% CI 0.63–2.88) for recurrent PE (Table 2).

Analyses stratified by fetal gender showed very similar results (data not shown).

Nulliparous women

To eliminate bias due to missing data on previous pregnancies, we did a subanalysis on only nulliparous women (N=5314). Of them, 4330 were normotensive with a 2.6% prevalence of hypothyroidism. Prevalence of 3.9% and 3.3% was observed among women with PE and GH, with respective adjusted risks of aHR 1.39 (95% CI 0.79–2.42) and aHR 1.05 (95% CI 0.63–1.73), (Table 2). Notably, we observed a significant increase in hypothyroidism risk among nulliparous women with late PE, aHR 1.82 (95% CI 1.04–3.19).

Subjects with PE both in their first and in a recurrent pregnancy did not have an increased risk for hypothyroidism, aHR 1.03 (95% CI 0.25–4.26), (Table 2).

Stratifying the analyses by fetal gender did not change the results. However, the risk for hypothyroidism among nulliparous women with late PE and male fetus was aHR 2.25 (95% CI 1.14–4.44), whereas that of nulliparous women with late PE and female fetus was aHR 1.23 (95% CI 0.44–3.44).

Thyroid dysfunction or antibodies during pregnancy

Women with PE had similar early pregnancy TSH and fT4 concentrations but significantly higher fT3 concentrations than normotensive women. Women with GH had higher TSH and

fT3 concentrations during early pregnancy, but similar fT4 concentrations compared with normotensive women (Table 3). Thyroid antibody status was similar in all study groups (data not shown).

As anticipated, normotensive, euthyroid and thyroid autoantibody negative women had smaller risk for hypothyroidism (1.1%) than euthyroid antibody negative women with PE (2.1%) or GH (1.4%), (Table 4). Women with PE and thyroid dysfunction or thyroid antibody positivity during pregnancy (N=62) had similar prevalence of future hypothyroidism (8.1%) as normotensive women with thyroid dysfunction or thyroid antibody positivity (N=731).

Excluding women with the highest socioeconomic position from the analyses resulted in poorer precision due to loss of statistical power, but the exclusion did not change the results (data not shown).

Discussion

In this first prospective, population-based study evaluating the association between PE, GH and subsequent hypothyroidism, no clear association was found, although the risk appeared to be somewhat increased for nulliparous women with late PE.

One previous study has found that women with PE have higher TSH concentrations in late pregnancy than normotensive mothers [9]. Some studies have found that thyroid dysfunction in early pregnancy might increase the risk of PE, especially late PE [10,11], but others have not [12]. Similarly, women with history of recurrent PE have been found to have elevated levels of TSH [9], a finding that has not been confirmed by others [19]. We observed an association between late PE and hypothyroidism, which is a novel finding.

The increased risk for thyroid dysfunction among women with PE is thought to be mediated through antiangiogenic proteins, secreted in high amounts in hypertensive pregnancies [2,3]. These proteins act as antagonists for VEGF and PlGF, causing endothelial dysfunction and capillary regression in several tissues, including the thyroid [2,3]. This is thought to play an important role in the subsequent morbidity observed in PE patients [20]. The effect of antiangiogenic proteins on thyroid function has been shown among cancer patients receiving tyrosine kinase inhibitors, which also act through VEGF antagonism and can produce a condition resembling PE [5,6]. In the thyroid tissue, up to 60% of capillaries may regress during treatment with anti-VEGF agents, but the phenomenon is reversible [21]. Still 30% patients receiving tyrosine kinase inhibitors have increased risk for temporary or persistent hypothyroidism [22,23], possibly due to destructive thyroiditis. The association is dose-effective with higher risk observed with prolonged treatment with the inhibitors [22,23].

Our observed association between late PE and subsequent hypothyroidism among nulliparous women was unexpected and needs to be validated in other studies. Women with early PE have generally higher levels of antiangiogenic proteins than those with late PE [4,24,25,26], but exposure time might be shorter than among those with late PE. The study by Ashoor et al. [11] suggested that women developing late PE have higher TSH and lower fT4 in early pregnancy. We did additional testing in NFBC 1986 to check if women with late PE had higher TSH levels or more thyroid autoantibodies than normotensive women, but we observed no differences (data not shown), suggesting that underlying thyroid dysfunction might not be the cause. Why the association with late PE and hypothyroidism was statistically significant only in nulliparous women is unknown. Interestingly, the association was stronger in pregnancies with male fetuses. One previous study has shown that fetal gender is important in the peripheral microvascular response of women with PE, with women with male fetuses and PE having a poor response [27]. This might suggest that

fetal gender might affect the antiangiogenic protein release and possibly even later disease risk [28]. Studies also suggest that microchimerism might be an important risk factor for Hashimotos thyroiditis [29], and women with PE might have higher feto-maternal trafficking than normotensive women [30].

In the current study we also found that women with PE and GH had higher fT3 concentrations in early pregnancy than normotensive women, and those with GH had higher TSH concentrations. No differences were seen in fT4 concentrations or rates of thyroid antibody positivity. Our findings could reflect increased release of fT3 from the thyroid or increased fT4 to fT3 turnover. The higher TSH concentration among women with GH was an interesting finding as women with GH usually have lower levels of sFLt1 than those with PE [4], suggesting that cases with PE should be more susceptible to hypothyroidism than cases with GH. Age and parity might contribute to these findings, as women with GH were somewhat older and less often nulliparous than those with PE. Age has been found to be a significant risk factor for autoimmune-based hypothyroidism [31].

Interestingly, our data suggest an increased risk of hypothyroidism among euthyroid, thyroid antibody negative women with PE who should have low risk for hypothyroidism. Although non-significant, the elevated risk estimate for this group suggests a potential independent role for PE. Similar association was not seen among those with GH. These findings may suggest an effect related to sFlt1 during pregnancy complicated by PE.

Based on the hypothesis that elevated levels of sFlt1 lead to destructive thyroiditis, cases of recurrent PE should have increased risk for subsequent hypothyroidism, as they are exposed recurrently to high levels of sFlt1 [4], but this was not evident in our study.

Our study has some advantages and limitations. The data is based on large, prospective population based cohorts with extensive data collection during the index pregnancy and follow-up using high-quality Finnish registries with complete population coverage. Our data on hypertensive complications during the NFBC index pregnancies is reliable, based on measurements and diagnoses made during routine visits to MWCs which all Finnish women attend and recurrence of complications could be defined using the registries. Data on recurrent PE was scarce, resulting in limited power in those analyses.

Data on hypothyroidism is based on three registers which allowed verification and accurate identification of cases with hypothyroidism over a long follow-up time (from 20 to 40 years). This setting has a limitation, however, since it only includes cases with verified thyroid disease. Therefore we may be lacking information on subclinical disease with no symptoms or treatment and this would underestimate the prevalence of hypothyroidism in the population. These limitations may explain why our results differ from those by Levine et al., who measured TSH concentrations in women with history of PE and found they had elevated TSH concentrations during follow-up [9]. In our study, it was not possible to obtain TSH or thyroid hormone concentrations at the end of the follow-up.

Based on our results, we conclude that PE or GH have no clear association with subsequent overt symptomatic hypothyroidism, but due to the limitations of the study, the association with subclinical hypothyroidism could not be resolved. Our finding of a 1.8-fold increased risk of long-term hypothyroidisms in nulliparous women with late PE needs to be confirmed in other populations.

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Abbreviations

PE	preeclampsia
GH	gestational hypertension
sFlt1	soluble fms-like tyrosine kinase 1
VEGF	vascular endothelial growth factor
PlGF	placental growth factor
TSH	thyrotropin
NFBC	Northern Finland Birth Cohort
MWC	maternity welfare clinic
BP	blood pressure
fT3	free triiodothyronine
fT4	free thyroxine
TPO-Ab	thyroid-peroxidase antibody
TG-Ab	thyroglobulin antibody
HR	hazard ratio
CI	confidence interval
SD	standard deviation
aHR	adjusted hazard ratio

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Table 1

The demographic data during index pregnancies of women of the Northern Finland Birth Cohorts 1966 and 1986.

Demographics	Normotensive (N=13421)	Gestational hypertension (N=1433)	Preeclampsia (N=942)	Non-recurrent preeclampsia (N=775)	Recurrent preeclampsia (N=167)	Early preeclampsia (N=261)[a]	Late preeclampsia (N=672)
Maternal age, y	27.0 (5.7)	28.0 (6.9)*	28.8 (6.7)*	28.9 (6.8)*	29.0 (6.0)*	30.0 (7.1)*	28.4 (6.4)*
Maternal pre-pregnancy weight, kg	58.9 (9.2)	60.6 (10.4)*	62.8 (11.7)*	61.7 (10.6)*	67.5 (14.8)*	62.2 (11.1)*	63.0 (11.9)*
Birth weight of the offspring, g	3516 (539)	3458 (594)*	3330 (777)*	3331 (763)*	3348 (813)*	2849 (906)*	3514 (620)
Mean parity (min-max)	1.6 (0–20)	1.7 (0–13)	1.6 (0–15)	1.5 (0–14)*	1.9 (0–15)	1.9 (0–15)	1.4 (0–13)*
Nulliparous at index pregnancy – no. (%)	4330 (32.3)	570 (39.8)*	414 (43.9)*	368 (47.7)*	45 (26.9)	104 (39.8)*	308 (45.8)*
Smoking before pregnancy – no. (%)	3497 (26.9)	287 (20.6)*	199 (21.9)*	175 (23.3)*	24 (15.3)*	65 (25.8)	133 (20.5)*
Mean visits to maternity welfare clinics	8.3	8.2*	9.4*	9.2*	10.1*	8.8	9.6*
Sosioeconomic position- no. (%)							
Manager/office worker	2652 (19.8)	222 (15.5)*	197 (20.9)*	157 (20.3)*	40 (24.0)*	57 (21.8)*	139 (20.7)*
Worker	6637 (49.5)	597 (41.7)	517 (54.9)	418 (53.9)	98 (58.7)	147 (56.3)	370 (55.1)
Farmer	1599 (11.9)	263 (18.4)	98 (10.4)	80 (10.3)	16 (9.6)	27 (10.3)	67 (10.0)
Housewife/unknown	2533 (18.9)	351 (24.5)	130 (13.8)	120 (15.5)	13 (7.8)	30 (11.5)	96 (14.3)

Figures are mean (SD) unless otherwise specified.

[a]Early preeclampsia is a diagnosis of preeclampsia before 37 weeks gestation

*P<0.05 with Student's *t* test, Mann Whitney U test or Fisher's exact test when comparing hypertensive subjects by group individually to normotensive subjects.

Table 2

Subsequent hypothyroidism morbidity of mothers of Northern Finland Birth Cohorts 1966 and 1986

Hypertensive disorder	Hypothyroidism observed/Total	% of total	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]
	All cohort women			
Normotensive	464/13421	3.5	1.00	1.00
Preeclampsia	38/942	4.0	1.29 (0.93–1.80)	1.13 (0.80–1.59)
Gestational hypertension	65/1433	4.5	1.18 (0.91–1.53)	1.11 (0.85–1.45)
Early preeclampsia[c]	8/261	3.1	1.06 (0.53–2.13)	0.93 (0.46–1.88)
Late preeclampsia	30/672	4.5	1.41 (0.97–2.03)	1.23 (0.84–1.81)
Recurrent preeclampsia	7/167	4.2	1.56 (0.74–3.31)	1.35 (0.63–2.88)
	Only nulliparous mothers			
Normotensive	112/4330	2.6	1.00	1.00
Preeclampsia	16/414	3.9	1.61 (0.95–2.72)	1.39 (0.79–2.42)
Gestational hypertension	19/570	3.3	1.13 (0.69–1.85)	1.05 (0.63–1.73)
Early preeclampsia	0/105	0	0.05 (0.00–17.43)	NA
Late preeclampsia	16/308	5.2	2.11 (1.25–3.56)	1.82 (1.04–3.19)
Recurrent preeclampsia	2/94	2.1	1.05 (0.26–4.28)	1.03 (0.25–4.26)

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable.

[a] The model is stratified by cohort.

[b] The model is stratified by cohort and adjusted for maternal age and pre-pregnancy weight (kg).

[c] Early preeclampsia is a diagnosis of preeclampsia before 37 weeks gestation

Table 3

Geometric means with 95% confidence intervals of TSH and thyroid hormones among women with or without hypertensive complications in NFBC 1986

	Normotensive	Preeclampsia	Gestational hypertension
N	4540	381	286
TSH (mU/L)	1.03 (1.00–1.06)	1.11 (1.00–1.22)	1.17 (1.04–1.31) *
fT4 (pmol/L)	15.33 (15.25–15.42)	15.39 (15.13–15.66)	15.14 (14.86–15.43)
fT3 (pmol/L)	5.10 (5.07–5.12)	5.35 (5.25–5.44) *	5.24 (5.15–5.35) *

All figures are geometric mean (95 % confidence interval). Numbers vary due to missing data.

* P<0.05 when comparing PE or GH group to the normotensive group.

Table 4

Association of PE and GH on subsequent hypothyroidism among euthyroid and thyroid antibody negative women in Northern Finland Birth cohort 1986

Hypertensive disorder	Hypothyroidism observed/Total	% of total	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Normotensive	37/3424	1.1	1.00	1.00
Preeclampsia	6/281	2.1	2.01 (0.85–4.76)	1.43 (0.58–3.51)
Gestational hypertension	3/215	1.4	1.30 (0.40–4.21)	1.11 (0.34–3.65)

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable.

[a]The model is adjusted for maternal age and prepregnancy weight (kg).