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Accessibility
Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study

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ABSTRACT
Objective To determine if pre-eclampsia is associated with reduced thyroid function during and after pregnancy.
Design Nested case-control study during pregnancy and population based follow-up study after pregnancy.
Setting Calcium for Pre-eclampsia Prevention trial of healthy pregnant nulliparous women in the United States during 1992-5, and a Norwegian population based study (Nord-Trondelag Health Study or HUNT-2) during 1995-7 with linkage to the medical birth registry of Norway.
Participants All 141 women (cases) in the Calcium for Pre-eclampsia Prevention trial with serum measurements before 21 weeks’ gestation (baseline) and after onset of pre-eclampsia (before delivery), and 141 normotensive controls with serum measurements at similar gestational ages, and 7121 women in the Nord-Trondelag Health Study whose first birth had occurred in 1967 or later and in whom serum levels of thyroid stimulating hormone had been subsequently measured.
Main outcome measures Thyroid function tests and human chorionic gonadotrophin and soluble fms-like tyrosine kinase 1 concentrations in the Calcium for Pre-eclampsia Prevention cohort and odds ratios for levels of thyroid stimulating hormone above the reference range, according to pre-eclampsia status in singleton pregnancies before the Nord-Trondelag Health Study.

Results In predelivery specimens of the Calcium for Pre-eclampsia Prevention cohort after the onset of pre-eclampsia, thyroid stimulating hormone levels increased 2.42 times above baseline compared with a 1.48 times increase in controls. The ratio of the predelivery to baseline ratio of cases to that of the controls was 1.64 (95% confidence interval 1.29 to 2.08). Free triiodothyronine decreased more in the women with pre-eclampsia than in the controls (case ratio to control ratio 0.96, 95% confidence interval 0.92 to 0.99). The predelivery specimens but not baseline samples from women with pre-eclampsia were significantly more likely than those from controls to have concentrations of thyroid stimulating hormone above the reference range (adjusted odds ratio 2.2, 95% confidence interval 1.1 to 4.4). Both in women who developed pre-eclampsia and in normotensive controls the increase in thyroid stimulating hormone concentration between baseline and predelivery specimens was strongly associated with increasing quarters of predelivery soluble fms-like tyrosine kinase 1 (P for trend 0.002 and 0.001, respectively). In the Nord-Trondelag Health Study, women with a history of pre-eclampsia in their first pregnancy were more likely than other women (adjusted odds ratio 1.7, 95% confidence interval 1.1 to 2.5) to have concentrations of thyroid stimulating hormone above the reference range (>3.5 mIU/l). In particular, they were more likely to have high concentrations of thyroid stimulating hormone without thyroid peroxidase antibodies (adjusted odds ratio 2.6, 95% confidence interval 1.3 to 5.0), suggesting hypothyroid function in the absence of an autoimmune process. This association was especially strong (5.8, 1.3 to 25.5) if pre-eclampsia had occurred in both the first and the second pregnancies.

Conclusion Increased serum concentration of soluble fms-like tyrosine kinase 1 during pre-eclampsia is associated with subclinical hypothyroidism during pregnancy. Pre-eclampsia may also predispose to reduced thyroid function in later years.

INTRODUCTION
Pre-eclampsia, a pregnancy specific syndrome characterised by new onset hypertension and proteinuria, causes substantial morbidity and mortality in mothers and infants.1,2 Women with a history of pre-eclampsia have an increased risk of dyslipidaemia, hypertension, and cardiovascular and renal disease.3-6

Although the cause of pre-eclampsia is still unclear, studies in both humans and animals suggest that excess circulating antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1 or sVEGFR1) may be responsible for the clinical phenotype of pre-eclampsia.7,9 Blood concentrations of soluble fms-like tyrosine kinase 1 increase during the last two months of normal pregnancy and increase to much greater levels in women with pre-eclampsia. Soluble fms-like
tyrosine kinase 1 acts by inhibiting vascular endothelial growth factor and placental growth factor signalling. Indeed, the use of vascular endothelial growth factor inhibitors for the treatment of cancer related angiogenesis has been associated with hypertension, proteinuria, glomerular endothelial damage, increased concentrations of circulating liver enzymes, cerebral oedema, and reversible posterior leucoencephalopathy—a constellation of conditions resembling those found in women with pre-eclampsia or eclampsia.10 11

More recently, patients with cancer who had received prolonged therapy with vascular endothelial growth factor inhibitors were found to be at greater risk of hypothyroidism.12 14 Furthermore, studies in mice using vascular endothelial growth factor inhibitors such as soluble fms-like tyrosine kinase 1 have shown substantial thyroid capillary regression and increased concentrations of thyroid stimulating hormone.11 15 We therefore hypothesised that the excess soluble fms-like tyrosine kinase 1 accompanying pre-eclampsia might be associated with reduced thyroid function during pregnancy and that women who have experienced pre-eclampsia would have an increased risk of hypothyroid function later in life.

To compare thyroid function in women who developed pre-eclampsia with those who remained normotensive during pregnancy, we carried out a nested case-control study within the Calcium for Pre-eclampsia Prevention trial (CPEP) trial cohort. We hypothesised that women with pre-eclampsia would experience a greater increase in thyroid stimulating hormone concentration during pregnancy than normotensive controls and that the extent of the increase would correlate with the magnitude of the soluble fms-like tyrosine kinase 1 concentration during pre-eclampsia. In addition, we used a Norwegian population based cohort study (the Nord-Trondelag Health Study or HUNT-2) to test whether pre-eclampsia in a previous pregnancy is associated with risk of reduced thyroid function in later life.

Calcium for Pre-eclampsia Prevention trial

Participants and specimens

The Calcium for Pre-eclampsia Prevention trial was a randomised, double blind clinical trial carried out during 1992-5 in healthy nulliparous women with singleton pregnancies to evaluate the effects of daily supplementation with calcium or placebo on the incidence and severity of pre-eclampsia.16 17 Calcium supplementation did not reduce the incidence or severity of pre-eclampsia or delay its onset.

Of the 4589 women enrolled in the trial we excluded 300 with incomplete information on outcomes or whose pregnancy ended before 21 weeks. Of 326 women who developed pre-eclampsia, 141 had at least one serum specimen collected before 21 weeks’ gestation (baseline specimen) and one collected after the onset of pre-eclampsia (predelivery specimen). If a woman had more than one specimen collected within each of these intervals, we selected the earliest before 21 weeks and the latest after the onset of pre-eclampsia.

Soluble fms-like tyrosine kinase 1 had previously been analysed in all serum specimens of a random sample of 2200 women in and all women with pre-eclampsia.18 After excluding women with pre-eclampsia, gestational hypertension, or gestational proteinuria, 1649 women remained who had been normotensive and without proteinuria during their pregnancies (controls). Each case of pre-eclampsia was matched to the control with two serum specimens that were closest in gestation to the two case specimens. Two case specimens—one baseline, one predelivery—were not located in the specimen repository.

Women with active dysfunction of the thyroid that required drugs were excluded from the Calcium for Pre-eclampsia Prevention trial except those with hypothyroidism who were stable while receiving thyroid replacement therapy. A check of drugs reported by the participants of this study showed that only one woman (who later developed pre-eclampsia) had received thyroxine. This woman had subclinical hypothyroidism at baseline, but concentrations of thyroid stimulating hormone and free thyroxine in her predelivery specimen were within clinical reference ranges.

Pre-eclampsia was defined as hypertension—that is, a diastolic blood pressure of at least 90 mm Hg on two occasions four to 168 hours apart—and proteinuria, characterised as one of the following: urine dipstick results of at least + (30 mg/dl) on two occasions four to 168 hours apart; a protein to creatinine ratio of at least 0.35; urine dipstick results of at least ++ (100 mg/dl), or a 24 hour urine specimen containing at least 300 mg of protein. Detailed definitions have been published previously.16 17

Procedures

We randomly ordered archived serum specimens, which had been stored at −70°C, for analysis. Assays were carried out by staff who were unaware of the outcome of the pregnancy. Enzyme linked immunosorbent assays for human soluble fms-like tyrosine kinase 1 had previously been done in duplicate by R&D Systems Analytical Testing Services (Minneapolis, MN, USA).18 Thyroid function tests (thyroid stimulating hormone, free thyroxine, free triiodothyronine, thyroid peroxidase antibodies) were carried out and human chorionic gonadotrophin measured using a Roche Diagnostics Modular Analytics E170 analyzer (Roche Diagnostics, Indianapolis, IN, USA). Human chorionic gonadotrophin was measured because it is known to stimulate the thyroid gland and to decrease concentrations of thyroid stimulating hormone.19 The Roche human chorionic gonadotrophin assay shows no cross reactivity with thyroid stimulating hormone. Coefficients of variation in normal serum in mid-pregnancy were less than 5%. Reference ranges for thyroid stimulating hormone (mIU/l) provided by the manufacturer were 0.33-4.60, 0.35-4.10, and 0.21-3.15 in sera from the first, second, and third trimester, respectively. The upper limits of the reference ranges for thyroid peroxidase antibodies (IU/ml) provided by the
Table 1 | Characteristics of women with pre-eclampsia and controls at enrolment in Calcium for Pre-eclampsia Prevention trial and characteristics of their infants and specimens*. Values are numbers (percentages) unless stated otherwise

| Characteristics                                      | Cases (n=141) | Controls (n=141) | P value |
|------------------------------------------------------|---------------|-----------------|---------|
| **Women**                                            |               |                 |         |
| Mean (SD) age (years)                                | 20.9 (4.0)    | 20.1 (3.8)      | 0.09    |
| Mean (SD) height (cm)                                | 161 (7)       | 162 (8)         | 0.08    |
| Mean (SD) weight (kg)                                | 71.9 (19.0)   | 65.3 (15.4)     | 0.002   |
| Mean (SD) body mass index†                           | 27.7 (6.9)    | 24.7 (5.2)      | <0.001  |
| Mean (SD) systolic blood pressure (mm Hg)            | 111 (8)       | 107 (9)         | <0.001  |
| Mean (SD) diastolic blood pressure (mm Hg)           | 63 (8)        | 60 (8)          | 0.003   |
| Mean (SD) gestational age at enrolment (weeks)       | 17.4 (2.6)    | 17.5 (2.5)      | 0.94    |
| Current smoker                                       | 11 (8)        | 23 (16)         | 0.03    |
| Calcium treatment                                    | 62 (44)       | 64 (45)         | 0.81    |
| Private health insurance                             | 8 (6)         | 12 (9)          | 0.35    |
| Ever married                                         | 33 (23)       | 27 (19)         | 0.38    |
| **Race or ethnic group‡**                            |               |                 |         |
| White, non-Hispanic                                  | 35 (24.8)     | 56 (39.7)       | <0.02   |
| White, Hispanic                                      | 19 (13.5)     | 24 (17.0)       |         |
| Black                                                | 81 (57.5)     | 58 (41.1)       |         |
| Other or unknown                                     | 6 (4.3)       | 3 (2.1)         |         |
| **Infants**                                          |               |                 |         |
| Mean (SD) birth weight (g)                           | 2964 (816)    | 3290 (410)      | <0.001  |
| Delivery at <37 weeks                                | 40 (28.4)     | 3 (2.1)         | <0.001  |
| Small for gestational age (<10th centile)§           | 25 (17.7)     | 8 (5.7)         | 0.002   |
| **Specimens**                                        |               |                 |         |
| Mean (range) gestational age of baseline specimen (days) | 111 (42-146) | 112 (49-147)   | 0.45    |
| Mean (range) gestational age of predelivery specimen (days) | 265 (156-296) | 260 (166-292) | 0.04    |

*P values are given only for significant differences.
†Weight (kg)/(height (m)²).
‡Self reported.
§According to US tables that account for race, parity, and sex of infants.21

Table 1: Characteristics of women with pre-eclampsia and controls at enrolment in Calcium for Pre-eclampsia Prevention trial and characteristics of their infants and specimens*. Values are numbers (percentages) unless stated otherwise.

Women

- Mean (SD) age (years): 20.9 (4.0) vs 20.1 (3.8), P = 0.09
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- Mean (SD) diastolic blood pressure (mm Hg): 63 (8) vs 60 (8), 0.003
- Mean (SD) gestational age at enrolment (weeks): 17.4 (2.6) vs 17.5 (2.5), 0.94
- Current smoker: 11 (8) vs 23 (16), 0.03
- Calcium treatment: 62 (44) vs 64 (45), 0.81
- Private health insurance: 8 (6) vs 12 (9), 0.35
- Ever married: 33 (23) vs 27 (19), 0.38

Race or ethnic group:

- White, non-Hispanic: 35 (24.8) vs 56 (39.7), <0.02
- White, Hispanic: 19 (13.5) vs 24 (17.0)
- Black: 81 (57.5) vs 58 (41.1)
- Other or unknown: 6 (4.3) vs 3 (2.1)

Infants

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For Pre-eclampsia Prevention trial and characteristics of their infants and specimens*. Values are numbers (percentages) unless stated otherwise.

Women

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- *P values are given only for significant differences.
- †Weight (kg)/(height (m)²).
- ‡Self reported.
- §According to US tables that account for race, parity, and sex of infants.21

With one exception the characteristics of the 141 women with pre-eclampsia and their infants from the Calcium for Pre-eclampsia Prevention trial included in this study (table 1) did not differ significantly from those of the 185 women with pre-eclampsia and their infants who had not been included owing to lack of specimens: infants of the women who had been included were more often delivered preterm (28% vs 16%, P=0.006).
Table 2 | Results of thyroid function test in baseline and predelivery specimens and predelivery to baseline ratio in cases and controls. Values are geometric means (standard deviations) unless stated otherwise

| Variables                  | Baseline          | Predelivery        | Predelivery to baseline ratio* |
|---------------------------|-------------------|--------------------|-------------------------------|
|                           | Controls          | Cases              | Controls                      | Cases              | P value†       | Controls       | Cases              | P value†       | Case ratio to control ratio (95% CI) |
| No of women               | 140               | —                  | 140                           | —                  | —              | 141            | 139               | —              |                                     |
| Gestational age (days)‡   | 120 (20)          | 111 (20)           | 0.92                          | 260 (18)           | 265 (22)       | 0.04           | —                | —              | —                                    |
| TSH (mIU/l)               | 1.22 (0.27)       | 0.99 (0.22)        | 0.14                          | 2.44 (0.67)        | 3.15 (0.83)    | 0.007          | 1.48 (0.11)      | 2.42 (0.24)    | 1.64 (1.29 to 2.08)                   |
| Free T4 (pmol/l)          | 13.87 (0.41)      | 13.81 (0.41)       | 0.81                          | 12.30 (0.82)       | 12.10 (0.77)   | 0.45           | 0.86 (0.01)      | 0.85 (0.01)    | 0.99 (0.95 to 1.03)                   |
| Free T3 (pmol/l)          | 4.94 (0.14)       | 5.09 (0.15)        | 0.11                          | 3.98 (0.23)        | 3.95 (0.22)    | 0.70           | 0.89 (0.01)      | 0.85 (0.01)    | 0.96 (0.92 to 0.99)                   |
| hCG (IU/l)                | 39051 (2539)      | 43637 (2837)       | 0.23                          | 16132 (1290)       | 21116 (1668)   | 0.02           | 0.42 (0.04)      | 0.48 (0.04)    | 1.15 (0.91 to 1.46)                   |

TSH=thyroid stimulating hormone; T4=thyroxine; T3=triiodothyronine; hCG=human choric gonadotrophin.

*Concentration units do not apply to ratios.
†Log transformed values were used for statistical testing of thyroid function tests and hCG concentration. Except for gestational age and hCG, statistical testing was done after adjustment for age, body mass index, race, smoking, log transformed human chorionic gonadotrophin concentrations, and presence or absence of thyroid peroxidase antibodies above reference range.
‡Presented as arithmetic mean (standard deviation). Difference in gestational age between predelivery and baseline specimens was 148 (SD 25) days and 154 (30) days for cases and controls, respectively (P=0.08). Two missing case specimens (one baseline, one predelivery) and their matched controls were excluded.

To investigate mechanisms by which pre-eclampsia may be associated with the development of hypothyroidism, the differences between predelivery and baseline values of thyroid function tests were examined according to quarters of soluble fms-like tyrosine kinase 1 concentrations in the predelivery specimens. Cases and controls were analysed separately. Among controls the increase in thyroid stimulating hormone concentration between baseline and predelivery specimens was strongly associated (P for trend <0.001) with increasing quarters of predelivery soluble fms-like tyrosine kinase 1 concentration: arithmetic means 0.01 (SD 1.14) mIU/l, 0.66 (1.04), 0.52 (0.75), and 0.92 (0.91), respectively (figure). The arithmetic mean of the difference in free thyroxine concentration between predelivery and baseline specimens was greater in the fourth quarter than in the first quarter (−2.70 v −1.67 pmol/l, P=0.03); but the test for trend was not significant. None of the other differences in thyroid function test results or the differences in human choric gonadotrophin concentration were associated with quarters of soluble fms-like tyrosine kinase 1 in predelivery specimens.

Among the cases with pre-eclampsia, the increase in thyroid stimulating hormone concentration between baseline and predelivery specimens was also strongly associated (P for trend 0.002) with increasing quarters of predelivery soluble fms-like tyrosine kinase 1 concentration: arithmetic means, respectively, 0.51 (SD 1.12) mIU/l, 0.94 (1.13) mIU/l, 1.41 (1.32) mIU/l, and 1.33 (1.29) mIU/l. Compared with controls, the increase in the pre-eclampsia group was consistently greater in each corresponding quarter. Differences between predelivery and baseline specimens for the other thyroid function tests and for human choric gonadotrophin were not associated with quarters of soluble fms-like tyrosine kinase 1 concentration in predelivery specimens.

Nord-Trondelag Health Study
Participants and specimens
Between 1995 and 1997 all inhabitants 20 years and older in Nord-Trondelag county in Norway were invited to participate in the Nord-Trondelag Health Study (HUNT-2).22 Nord-Trondelag county is characterised by a stable and ethnically homogeneous
Linkage to medical birth registry of Norway

The unique 11 digit identification number of every Norwegian citizen enabled linkage of parous women to information in the medical birth registry of Norway. This nationwide registry has recorded data on all births in Norway since 1967. We therefore restricted the analysis to women who had had their first birth registered during the period from 1967 until participation in the Nord-Trondelag Health Study. Among women with a measurement for thyroid stimulating hormone concentration, 7933 had had their first birth in 1967 or later. We excluded women with known thyroid disease (n=695), twin or triplet first pregnancies (n=74), pregnancy at the time thyroid stimulating hormone concentration was determined (n=33), and women without information on smoking habits (n=10), leaving 7121 women for analysis. Thyroid peroxidase antibodies were also measured in women with a thyroid stimulating hormone concentration greater than 4 mIU/l.

Criteria for pre-eclampsia used by the reporting midwives and obstetricians have been in accordance with the 1972 recommendations of the American College of Obstetrics and Gynecologists.24 These criteria include increased blood pressure after 20 weeks’ gestation (≥140/90 mm Hg), or an increase in systolic blood pressure of ≥30 mm Hg or in diastolic blood pressure of ≥15 mm Hg, from measurements made before 20 weeks’ gestation, and proteinuria (≥0.3 g in a 24 hour urine specimen or a urine dipstick result of ≥+).

Procedures

Serum concentrations of thyroid stimulating hormone were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (Wallac Oy, Turku, Finland). The coefficient of variation was less than 5%. The clinical reference range for thyroid stimulating hormone in this population was defined as 0.50-3.50 mIU/l.25 Thyroid peroxidase antibodies were also measured in people with concentrations of thyroid stimulating hormone greater than 4 mIU/l (BRAHMS Diagnostica, Berlin, Germany). Those with levels greater than 200 IU/ml were considered to have tested positive for thyroid peroxidase antibodies.

Statistical analysis

We used multiple logistic regression analysis to determine odds ratios and 95% confidence intervals. All analyses were adjusted for age and smoking status (current, former, or never).

Results

Analyses were carried out among 7121 women with thyroid stimulating hormone measurements who had delivered their first child during or after 1967, when the medical birth registry of Norway was established (table 3). Among women who had experienced pre-eclampsia in their first pregnancy the probability of having serum thyroid stimulating hormone concentrations greater than the clinical reference range (>3.5 mIU/l) was higher than for women who did not
Table 3 | Odds ratios for thyroid stimulating hormone (TSH) concentrations above the reference range (>3.5 mIU/l), and for high TSH concentrations (>4.0 mIU/l) with positive (>200 IU/ml) or negative (≤200 IU/ml) results for thyroid peroxidase (TPO) antibody status, according to pre-eclampsia status in previous singleton pregnancies

| Variables | TSH concentration >3.5 mIU/l | TSH concentration >4.0 mIU/l | TSH concentration >4.0 mIU/l |
|-----------|-------------------------------|-----------------------------|-------------------------------|
|           | Yes/No | Odds ratio (95% CI) | Yes/No | Odds ratio (95% CI) | Yes/No | Odds ratio (95% CI) |
| No pre-eclampsia in first pregnancy | 407/6444 | 1.0 (Reference) | 188/6651 | 1.0 (Reference) | 89/6750 | 1.0 (Reference) |
| Pre-eclampsia in first pregnancy | 29/241 | 1.7 (1.1 to 2.5) | 14/255 | 1.8 (1.0 to 3.1) | 10/259 | 2.6 (1.3 to 5.0) |
| No pre-eclampsia in first or second pregnancy | 350/5532 | 1.0 (Reference) | 167/5704 | 1.0 (Reference) | 72/5799 | 1.0 (Reference) |
| Pre-eclampsia in first or second pregnancy | 24/270 | 1.3 (0.9 to 2.1) | 12/281 | 1.4 (0.8 to 2.5) | 8/285 | 2.2 (1.0 to 4.6) |
| Pre-eclampsia in first and second pregnancy | 4/21 | 2.5 (0.9 to 7.5) | 2/23 | 2.6 (0.6 to 11.3) | 2/23 | 5.8 (1.3 to 25.5) |

Odds ratios are adjusted for age and smoking status at Nord-Trondelag Health Study examination.

Norwegian women who had experienced pre-eclampsia in their first pregnancy were more likely than other women to have concentrations of thyroid stimulating hormone above the clinical reference range many years after the pregnancy. The association was stronger if the high concentration of thyroid stimulating hormone was combined with absence of thyroid peroxidase antibodies, and particularly strong if pre-eclampsia had occurred in two pregnancies. This suggests that the hypothyroid function associated with increased circulating concentrations of thyroid stimulating hormone in pre-eclampsia may occur independent of the autoimmune mechanisms that are generally accepted as the most likely cause of subclinical and overt hypothyroidism in iodine replete women. 29, 30

The clinical syndrome of pre-eclampsia has been hypothesised to result from excessive release of antiangiogenic proteins—most notably soluble fms-like tyrosine kinase 1—from the placenta into maternal blood, resulting in an antiangiogenic state with low levels of free placental growth factor and free vascular endothelial growth factor. 8, 31 Administration of vascular endothelial growth factor inhibitors such as soluble fms-like tyrosine kinase 1 to rodents induces hypertension, proteinuria, and glomerular endotheliosis, the hallmarks of pre-eclampsia. The particular sensitivity of glomerular capillaries to reduced levels of vascular endothelial growth factor may be attributed to their fenestrated endothelium, which requires the constitutive expression of vascular endothelial growth factor by renal podocytes for health and function. 32 Thyroid capillaries also have a fenestrated endothelium. 15 In mice, two weeks’ exposure to exogenous soluble fms-like tyrosine kinase 1 or to other vascular endothelial growth factor inhibitors resulted in a reduction of thyroid tissue capillary density by two thirds and increased thyroid stimulating hormone concentration. Stopping soluble fms-like tyrosine kinase 1 from being administered led to a nearly complete recovery after three weeks. 15 This seems to be analogous to the recovery from hypertension and proteinuria in experimental animals after stopping inhibition of vascular endothelial growth factor and in women with pre-eclampsia after delivery of the placenta. 7, 10 Together with reports of hypothyroidism in patients with cancer treated with...
WHAT IS ALREADY KNOWN ON THIS TOPIC

Limited data suggest that pre-eclampsia may be associated with hypothyroid function during pregnancy.

Women with a history of pre-eclampsia are at increased risk of future cardiovascular and renal disease.

WHAT THIS STUDY ADDS

Hypothyroid function during pre-eclampsia may result from the antiangiogenic state.

Women with a history of pre-eclampsia may be at increased risk of future hypothyroid function.

onset of pre-eclampsia, were associated with subtle abnormalities of the thyroid during pregnancy. These in turn may predispose to the development of reduced thyroid function and possibly overt hypothyroidism in later life.

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Contributors: SAK and RJL had the original idea for the study. GLH carried out the thyroid function tests and measured the human chorionic gonadotrophin in the specimens from the Calcium for Pre-eclampsia Prevention trial. RJL, CQ, KFY, and SAK analysed data from the Calcium for Pre-eclampsia Prevention trial, and LJV, PRR, AH, and BOA analysed the data from the Nord-Trøndelag Health Study. RJL, SAK, and LJW wrote the paper assisted by GLH, CQ, PRR, KFY, ANH, BOA, and AH, who also helped interpret the results. RJL has access to the original data from the Calcium for Pre-eclampsia Prevention trial and is guarantor of the Calcium for Pre-eclampsia Prevention trial results. LJV has access to the original data from the Nord-Trøndelag Health Study and is guarantor of the Nord-Trøndelag Health Study results.

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