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Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes

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Abstract

Context: High serum levels of thyroid stimulating hormone (TSH) have been associated with adverse pregnancy outcomes by some studies; and not by others.

Objective: To assess the association between high levels of TSH in first trimester of pregnancy and adverse pregnancy outcomes; and examine the predictive accuracy as a screening test.

Setting and Participants: Serum levels of TSH were measured in a cohort of 2,801 women with a singleton pregnancy attending first trimester Down syndrome screening. Information on maternal and infant outcomes was obtained through record linkage to population-based birth and hospital data. Association between high TSH (>95th and >97.5th centile) multiple of the median (MoM) levels and risk of adverse pregnancy outcomes was evaluated using multivariable logistic regression and the predictive accuracy of models was assessed.

Main Outcomes: Small for gestational age (SGA), preterm birth, preeclampsia, miscarriage and stillbirth.

Results: High TSH MoM levels were associated with SGA (<10th centile) (adjusted odds ratio (aOR) 1.71; 95%CI 0.99-2.94), preterm birth <37 weeks gestation (aOR 2.59; 95%CI 1.21-5.53), miscarriage (aOR 3.66; 95%CI 1.59-8.44) and a composite measure of any study outcome (aOR 2.10; 95%CI 1.23–3.59). The area under the receiver operator characteristic curves were 0.69 (95% CI 0.65-0.73) for SGA; 0.56 (95%CI 0.51-0.61) for preterm birth, 0.70 (95% CI 0.61-0.79) for miscarriage and 0.63 (95%CI 0.60–0.65) for any adverse pregnancy outcome.

Conclusions: High TSH serum levels during first trimester of pregnancy were associated with adverse pregnancy outcomes; however the predictive accuracy was poor. Screening for high TSH levels in first trimester would be of no benefit to identify women at-risk.

Introduction

The effect of thyroid malfunction in pregnancy and on subsequent pregnancies and infant outcomes is a subject of interest and controversy (1). *In vitro* studies suggest that thyroid hormones contribute directly to early placental development stimulating angiogenesis, and promoting invasion and differentiation of embryonic cells (2, 3). Thyroid hormone (T3) receptors are present in the trophoblast and thyroid hormone transporters are significantly reduced in pregnancies with intrauterine growth restriction (4). These findings attest to a possible effect of abnormal levels of thyroid hormones on the pathological pathways to adverse pregnancy outcomes.

Fetal thyroxine production does not occur until 8-10 weeks, therefore, the fetus depends upon maternal thyroid hormone transfer in early pregnancy for normal brain development (5, 6). Neurological impairment in children has been associated with maternal overt hypothyroidism (7) and hypothyroxinemia (8). Subclinical hypothyroidism is diagnosed in women with thyroid stimulating hormone (TSH) above a statistically defined upper limit of a reference range but normal levels of free thyroxine (fT_4) (9). Although, some studies have reported increased rates of pregnancy loss (10, 11), placental abruption (12), preterm delivery (12) and preeclampsia (13) in woman with elevated TSH level, other studies have not identified a significant association with any adverse pregnancy outcome (14, 15).

These inconsistent findings have led to conflicting support for screening asymptomatic women for high TSH levels in early pregnancy. Furthermore, studies suggests screening and treating women with subclinical hypothyroidism would be cost-effective if this resulted in improved child neurodevelopment (16, 17). First trimester screening would also provide an ideal opportunity to identify pregnancies at-risk and may be incorporated into existing routine antenatal testing when preventive interventions may be a realistic option. Despite these potential benefits and that a recent study found that screening and treating pregnant women with subclinical hypothyroidism was beneficial (18), current clinical guidelines by the American Thyroid Association highlight that there is

insufficient evidence to recommend it (19). There is also little information on the predictive accuracy of screening for TSH to identify pregnancies at risk.

The aim of this study was to evaluate the association between high maternal TSH levels measured at 10 to 14 weeks of pregnancy and the risk of adverse pregnancy outcomes; and to assess the predictive accuracy of TSH in predicting adverse outcomes in an unselected pregnant population.

Methods

Study Population and data sources

The study population included pregnant women who had first trimester Down syndrome screening between July & October 2006 by The Pacific Laboratory Medicine Services (PaLMs), a pathology screening service in New South Wales (NSW), Australia. This was the state's only public screening service and received samples from throughout NSW. A total of 3,103 serum samples were collected for women undergoing screening at 10-14 weeks gestation in pregnancy and all samples were archived at -80°C.

Serum TSH levels were measured by automated immunoassay system (Siemens IMMULITE® 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA). The inter and intra assay coefficient of variation was <8% and the reported analytic sensitivity of the immunoassay was 0.004 IU/L. The samples were analysed blind to the clinical outcomes.

Pregnancy and birth information for mothers and babies was ascertained from birth and hospital data and individual data were record-linked to each woman's corresponding laboratory (Down syndrome and TSH) results. Birth information was obtained from the NSW Perinatal Data Collection (PDC), a statuary collection of all livebirths and stillbirths in NSW of at least 400 grams birth weight, or at least 20 weeks gestation. It contains demographic, medical and obstetric information on the mother and information on the labor, delivery and condition of the infant. Hospital data were obtained from the

NSW Admitted Patient Data Collection (APDC), a census of hospital discharges from all NSW public and private hospitals and day procedure centres. It includes demographic, administrative and clinical information for each hospital admission. Information includes reason for admission, significant co-morbidities and complications, and procedures performed during the admission. Up to 20 diagnosis and procedure fields were available for each admission and coded according to the 10th revision of the International Classification of Diseases – Australian Modification (ICD10-AM) and the 5th edition of the Australian Classification of Health Interventions (AHCI) respectively.

In Australia unique identifiers are not available for record linkage of unit record data from multiple datasets (20). Consequently probabilistic linkage methods were utilised. This involves a complex process of blocking and matching combinations of selected variables (such as name, date of birth, address and hospital) using record-linkage software (21). Probability weights are calculated, adjusted for incomplete and missing data, and used to determine correct matches. The validity of the probabilistic record linkage is extremely high with less than 1% of records having an incorrect match (20-23). The NSW Centre for Health Record Linkage conducted the record linkage and identifying information was removed prior to the release of data for analysis. The study was approved by the NSW Population and Health Services Research Ethics Committee.

Linked health information relevant to the pregnancy was available for 2,907 (93.7%) samples. Importantly, there was no significant difference in TSH levels, maternal age and weight for women whose health information was not available compared to those included in the study. We then excluded 106 women whose blood sample was taken before 10 or after 14 weeks gestation, had a medical abortion, had a twin pregnancy or had an infant with major congenital anomalies. The study outcomes assessed included: small for gestational age (SGA), preterm birth, preeclampsia, miscarriage, stillbirth and a composite outcome of any adverse pregnancy outcome. SGA was defined as birthweight less than the 10th centile and less than the 3rd centile (severe SGA) of the distribution for gestational age and infant sex (24). Gestational age is reported in the birth data in completed weeks of gestation and determined by the best clinical estimate including early ultrasound (>97%) and

last menstrual period. Preterm birth was defined as delivery at less than 37 weeks and very preterm birth less than 34 weeks gestation. Information on preeclampsia was obtained from the hospital data, based on a diagnosis by the attending clinician that was coded according to ICD10-AM. During the study period, preeclampsia was defined as the onset of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) from 20 weeks' gestation onwards accompanied by proteinuria (25). Miscarriage was defined as a spontaneous pregnancy loss between 10-20 weeks gestation and were identified from hospital data. Stillbirth was defined as a pregnancy loss after 20 weeks gestation and were identified from birth data. A composite 'any adverse pregnancy outcome' variable was also developed comprising the occurrence of any of the pregnancy outcomes from above.

Explanatory variables applied in this study included; maternal age, parity (nulliparous/multiparous), smoking during pregnancy (yes/no), maternal weight (kilograms) and free β-hCG (corrected for gestational age at testing and maternal weight) collected at Down syndrome screening. Only factors that are well and accurately reported were included in the analyses (20, 26, 27). Maternal weight was missing in 550 (20%) of the records. We conducted a sensitivity analysis comparing model results when we included women with records missing weight assigning them with the mean weight of the total population, against excluding them from the analysis. As no significant difference was found, mean weight was applied to those missing values and included in the analyses. Other missing data were infrequent: there were no records with missing maternal age or parity. Smoking was missing in 58 records (2.1%) and there were 4 missing records for free β-hCG (0.1%) which were excluded from the analysis. Only SGA analyses were affected by the missing data exclusions and importantly, there were no SGA cases with missing data.

Statistical analysis

We compared women with each study outcome to those without the adverse outcome. Descriptive statistics were calculated and differences between groups were tested using Chi-squared and Fisher's exact test for categorical variables and student's t-test for continuous variables. Given a non linear distribution of the serum levels of TSH, a non-parametric Kruskal-Wallis test was used to determine

differences among medians of gestational age at testing grouped in weeks, and the Wilcoxon rank-sum test to determine differences in median TSH serum levels between mothers with and without each outcome of interest.

As TSH differed by gestational week at testing, we standardized TSH levels using Multiple of the Medians (MoM) as described by Cuckle and Wald(28). A regression model was fitted to the medians for each week of gestation at testing for the unaffected group and each individual value was divided by its regressed value to calculate each MoM. Logistic regression was used to determine the association between maternal TSH (MoM) and adverse pregnancy outcomes. TSH (MoM) levels were dichotomized to identify mothers with high values of TSH using percentile cut-offs above the 95th (2.92, n=140) and 97.5th (3.74, n=70) percentiles. Backward elimination method was then used to fit models with only significant explanatory variables retained. Results are reported as adjusted odds ratios (aOR) with 95 percent confidence intervals (95% CI).

The diagnostic performance of significant outcomes was assessed by examining the area under the Receiver Operating Characteristics (ROC) curves (AUC), derived from logistic regression analysis and using the TSH (MoM) 97.5th centile cut-off, as this was considered to be more clinically meaningful. AUC was calculated for both univariate and multivariable models and results examined whether the test performed better than chance (0.5). A standardized scale was used to assess the AUC result (29) where an AUC of 1 represents a perfect test, 0.9 – <1 an excellent test, 0.8 – <0.9 a good test, 0.7 – <0.8 a fair test, 0.6 – <0.7 a poor test and 0.5 – <0.6 a worthless test. Finally, estimates of predictive accuracy were calculated including sensitivity, specificity, positive (PPV) and negative predictive values (NPV) with exact binominal confidence intervals (30), based on the population prevalence of each outcome. Statistical analysis was performed using SAS software 9.2 (SAS Institute Inc., Cary, NC, USA) and a p-value of <0.05 was considered statistically significant.

Results

In total 2,801 women were included in the analysis. Table 1 presents the maternal characteristics by pregnancy outcome. The mean maternal age was 32.8 (SD 4.7) years, 1266 (45.2%) women were nulliparous and 168 (6.1%) smoked during pregnancy. There were 218 (7.8%) SGA infants, 142 (5.1%) preterm births, 73 (2.6%) women diagnosed with preeclampsia, 42 (1.5%) women had a miscarriage and 12 (0.4%) stillbirths. The median TSH levels for the total population was 0.84 UI/L (5–95th centile range: 0.08 – 2.37 UI/L) and for TSH (MoM) was 1.02 (5–95th centile range: 0.11 – 2.92). Compared with unaffected pregnancies, median TSH levels were significantly higher in women with SGA <10th centile infants (P<0.01) and in women who had a preterm birth (<37 weeks) (P<0.05).

The results of logistic regression analysis of TSH MoM for all pregnancy outcomes are shown in Table 2. High TSH MoM levels (>95th centile) were associated with increased risk of SGA (aOR 1.71; 95% CI 0.99 – 2.94), preterm birth <37 weeks (aOR 1.86; 95% CI 1.00 – 3.45) and miscarriage (aOR 3.66; 95% CI 1.59 – 8.44); and there was a significant increased risk of preterm birth <37 weeks for women with levels above the 97.5th percentile (aOR 2.59; 95% CI 1.21 – 5.53). Overall high TSH MoM levels >95th and >97.5th centile were associated with a 1.6 and 2.1 fold risk of any adverse pregnancy outcome, respectively (Table 2). There was no significant association between high TSH levels and SGA <3rd centile, very preterm birth (<34 weeks), preeclampsia and stillbirth.

Figure 1 presents the ROC curves for the adjusted models based on TSH MoM levels >97.5th centile and Table 3 presents the predictive accuracy results for SGA <10th centile, preterm birth (<37 weeks), miscarriage and any adverse pregnancy outcome. Assessment of the accuracy of high TSH levels (>97.5th centile) revealed it performed poorly in predicting adverse pregnancy outcomes. The area under the curve (AUC) of most univariate models were not different from chance; and after adjusting for risk factors, the predictive accuracy remained inadequate in identifying subsequent pregnancy complications.

Discussion

Our study highlights that women with high TSH levels at 10 to 14 weeks of pregnancy are at increased risk of experiencing an adverse pregnancy outcome, specially, having a small for gestational age infant (SGA <10th centile), preterm birth (<37 weeks) or miscarriage. Although we found no significant association for more severe outcomes of SGA <3rd centile, very preterm birth (<34 weeks), preeclampsia or stillbirth. Moreover, our results indicate that the predictive accuracy of high TSH levels was poor. Inclusion of additional maternal information and serum biomarker, β-hCG, did not improve results.

Overall, our findings do not support routine screening for high TSH levels to identify adverse pregnancy outcomes. Application of our results to a general maternity population of 10,000 women with an estimated 10% prevalence of SGA reveal that screening for high levels of TSH in first trimester would identify 2,130 women at risk but only 420 would truly have a SGA infant. 1,710 would be falsely labelled and a further 580 would be missed altogether. This is supported by a recent trial comparing universal screening for TSH with a high risk case-finding approach for the detection and treatment of thyroid hormone dysfunction in pregnancy. The trial found no significant difference in adverse pregnancy outcomes between groups, although women from the universal screening group that were low-risk, hypothyroid and treated had less adverse pregnancy outcomes compared with women from the case-finding group that were low-risk, hypothyroid (non-identified) and non-treated (18). These findings, as well as our own results, suggest that the majority of women having adverse pregnancy outcomes do not have elevated TSH and are euthyroid. Thus, TSH screening is likely to fail to identify the majority of women at risk because high TSH levels may represent only one specific pathological pathway, and the causes of adverse pregnancy outcomes are heterogeneous and multifactorial (31).

To date, there have been a number of studies investigating the association between high TSH levels and adverse pregnancy outcomes and findings have been inconsistent. Although, our results suggest some evidence of an increased risk of SGA <10th centile and preterm birth (<37 weeks), these may have been chance findings as we did not find any relationship for more severe cases, SGA <3rd centile

and very preterm birth <34 weeks; however these numbers were small. The strong association between high TSH levels and miscarriage has not been reported by previous studies, but should be replicated in future studies. Although, a study of euthyroid pregnant women with autoimmune thyroid disease found a reduction in miscarriage rates in a group of women treated with Levothyroxine compared with a non-treated group that had higher TSH levels, suggesting that high TSH levels may be a determinant risk factor (32). Also, two studies have found increased risk of fetal loss, which included miscarriages and/or stillbirths (10, 11). Overall, our findings suggest there is significant association between high TSH levels and some adverse pregnancy outcomes examined. Variation in study findings may be explained by differences in study design, population sample size or representativeness of the clinical population, ranging from case-control studies of 167 women to large cohort studies testing over 17,000 women; and differences in demographic characteristics such as maternal age, racial origin or parity.

Serum TSH was also variable across studies. We identified a 95th percentile cut point of 2.37 IU/L, although there is a degree of mild iodine deficiency in NSW (33) results are consistent with an iodine-replete population and reference intervals reported for first trimester of pregnancy in Western Australia (34). However, other studies have used various (95th and 97.5th centile) cut points to define high TSH levels, ranging from 2.78 to 4.8 IU/L (12, 14, 34-36). These differences suggest significant variability in distribution of TSH serum levels that may be explained by different levels of iodine status in populations, different immunoassay used in the analysis and underlying ethnic differences (37).

Strengths of this study were the assessment of a large sample and unselected consecutive cohort of women attending first trimester screening. Record linkage of laboratory to birth and hospital data ensured follow up and ascertainment of pregnancy outcomes with only minimal missing information. Missing health and pregnancy information was mostly attributable to women residing in bordering towns and giving birth in hospitals out of state. Nevertheless, women with missing health information had similar characteristics compared to those included in the study. Another strength was that the

exposure was measured independently of the outcome and were adjusted for β-hCG, with testing performed blinded to outcome. Low β-hCG has been identified as a risk factor or marker for miscarriage, preterm delivery and fetal growth restriction (26, 38); and maternal TSH function in pregnancy can be influenced by the thyrotrophic activity of β-hCG. Both hormones have similar structure, sharing a common α-subunit, and a reduction in TSH secretion in response to rising β-hCG levels in the first trimester of pregnancy has been previously reported (1, 39). However, one of the limitations of our study was the lack of clinical information such as supplementation use in pregnancy. Nevertheless, women in our study appeared to be healthier, reflected by the lower prevalence of adverse pregnancy outcomes compared with the maternity population in NSW (5.1% vs. 5.9% preterm birth, 7.8% versus 10% SGA infants, 2.6% versus 3.1% preeclampsia) (40). Finally, miscarriages were underrepresented because these were limited to only those occurring post-10 weeks gestation and not all those women are admitted to hospital for such an event.

In our study women were not tested for free thyroxine (fT_4), therefore, it was only possible to categorize woman as having high TSH levels but not to separate women with subclinical (high TSH and fT_4 within normal range) and clinical hypothyroidism (high TSH with fT_4 <5^{th} centile). Women with TSH levels of >10 mlIU/L, irrespective of their fT4 levels, are considered to have clinical hypothyroidism (19) In our population only four woman had TSH levels of >10 mlIU/L, consequently, the group was considered not significant to conduct a sub analysis. Thyroid antibody presence (TPO-Ab or TG-Ab) was also not tested in our study. A recent meta-analysis of studies (41), found that miscarriage and preterm birth was associated with the presence of thyroid antibodies and that antibody positive women have, on average, higher TSH levels compared to antibody negative women. However, the predictive usefulness of high TSH levels for miscarriage is questionable due to the very limited time to intervention.

Overall, our findings suggest that elevated TSH levels are associated with an increased risk of adverse pregnancy outcomes. Despite the positive associations, the poor predictive accuracy of our models

suggests that wide-spread screening for high levels of TSH in first trimester of pregnancy would not efficiently identify women at-risk of adverse pregnancy outcomes.

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Table 1: Maternal characteristics by pregnancy outcome

Maternal Characteristics (N=2801)	**Unaffected pregnancies N=2357 n (%)**	**SGA <10th N=218 n (%)**	**SGA <3rd N=57 n (%)**	**Preterm birth <37 weeks N= 142 n (%)**	**Preterm birth <34 weeks N= 36 n (%)**	**Preeclampsia N= 73 n (%)**	**Miscarriage N= 42 n (%)**	**Stillbirth N= 12 n (%)**
Age <35 years	1577 (66.9)	139 (63.8)	33 (57.9)	92 (64.8)	25 (69.4)	55 (75.3)	24 (57.1)	8 (66.7)
Age ≥35 years	780 (33.1)	79 (36.2)	24 (42.1)	50 (35.2)	11 (30.56)	18 (24.7)	18 (42.9)	4 (33.3)
Mean weight (SD)	67.4 (14.4)	61.0 (11.8)**	59.4 (11.2)**	67.1 (14.6)	66.4 (11.7)	72.9 (16.7)	67.5 (16.5)	65.4 (4.5)
Nulliparous	1018 (43.2)	129 (59.2)	34 (59.7)	66 (46.5)	13 (36.1)	48 (65.8)	23 (54.8)	6 (50.0)
Smoking	133 (5.7)	25 (11.5)	9 (15.8)	11 (7.9)	2 (5.6)	1 (1.4)	-	1 (11.1)
TSH (UI/L) Median (5th - 95th)	0.82 (0.08 - 2.22)	0.96 (0.09 - 2.83)**	0.84 (0.10 - 2.78)	0.92 (0.14 - 3.22)*	0.87 (0.14 - 2.96)	0.90 (0.21 - 2.24)	0.95 (0.05 - 3.33)	0.93 (0.23 - 2.01)
TSH MoM Median (5th - 95th)	1.00 (0.09 - 2.78)	1.15 (0.11 - 3.61)**	1.02 (0.12 - 3.36)	1.11 (0.16 - 4.00)*	1.05 (0.16 - 3.66)	1.15 (0.30 - 2.89)	1.13 (0.06 - 4.12)	1.12 (0.28 - 2.35)
TSH MoM >95th centile	106 (4.8)	17 (8.1)	4 (7.1)	12 (8.8)	3 (8.3)	3 (4.2)	7 (18)	0
TSH MoM 5th - 95th centile	2127 (95.3)	192 (91.9)	52 (92.9)	125 (91.2)	33 (91.7)	68 (95.8)	32 (82.1)	12 (100)

P<0.05, **P<0.01, compared with unaffected women; MoM: Multiple of the median; SGA: Small for gestational age

Table 2: Logistic Regression results of TSH MoM on adverse pregnancy outcomes

Birth Outcome	High TSH cases	Adj OR (95% CI)*	P value
SGA <10th centile			
>95th (MoM=2.92)	17	1.71 (0.99 - 2.94)	0.05
>97.5th (MoM=3.74)	9	1.76 (0.84 - 3.67)	0.13
SGA <3rd centile			
>95th (MoM=2.92)	4	1.46 (0.51 - 4.14)	0.48
>97.5th (MoM=3.74)	2	1.33 (0.31 - 5.70)	0.70
Preterm Birth (<37 weeks)			
>95th (MoM=2.92)	12	1.86 (1.00 - 3.45)	0.05
>97.5th (MoM=3.74)	8	2.59 (1.21 - 5.53)	0.01
Preterm Birth (<34 weeks)			
>95th (MoM=2.92)	3	1.77 (0.54 - 5.85)	0.35
>97.5th(MoM=3.74)	1	NA	NA
Preeclampsia			
>95th (MoM=2.92)	3	0.84 (0.26 - 2.72)	0.77
>97.5th (MoM=3.74)	1	NA	NA
Miscarriage			
>95th (MoM=2.92)	7	3.66 (1.59 - 8.44)	0.002
>97.5th (MoM=3.74)	3	3.06 (0.92 - 10.22)	0.07
Stillbirth			
>95th (MoM=2.92)	0	NA	NA
>97.5th (MoM=3.74)	0	NA	NA
Any adverse outcome			
>95th (MoM=2.92)	34	1.64 (1.10 - 2.47)	0.02
>97.5th (MoM=3.74)	20	2.10 (1.23 - 3.59)	0.01

* Adjusted for maternal age, maternal weight, smoking, parity or free β-hCG

SGA: Small for gestational age

Table 3: Screening results of TSH (MoM) >97.5th centile predicting adverse pregnancy outcomes

Birth outcome	AUC (95% CI)	P-value	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	LR (+)
SGA <10th centile							
Univariate	0.51 (0.50 - 0.52)	0.2	4.1 (1.9 - 7.7)	97.7 (97.0 - 98.2)	13.4 (6.3 - 24.0)	92.2 (91.1 - 93.2)	1.79
Adjusted	0.69 (0.65 - 0.73)	<0.001	71.1 (64.9 - 77.3)	55.7 (53.8 -57.7)	12.2 (10.5 - 14.2)	95.7 (94.6 - 96.7)	1.61
Preterm Birth (<37 weeks)							
Univariate	0.52 (0.50 - 0.54)	0.08	5.6 (2.5 - 10.8)	97.7 (97.1 - 98.3)	11.9 (5.3 - 22.2)	95.0 (94.1 - 95.8)	2.49
Adjusted	0.56 (0.51 - 0.61)	0.02	69.7 (61.5 - 77.1)	34.4 (32.6 - 36.3)	5.5 (4.5 - 6.6)	95.4 (93.9 - 96.7)	1.06
Miscarriage							
Univariate	0.52 (0.48 - 0.56)	0.24	7.1 (1.5 - 19.5)	97.6 (96.9 - 98.1)	4.3 (0.9 - 12.0)	98.6 (98.1 - 99.0)	2.94
Adjusted	0.70 (0.61 - 0.79)	<0.001	69.0 (52.9 - 82.4)	54.8 (52.9 - 56.7)	2.3 (1.5 - 3.3)	99.1 (98.5 - 99.5)	1.53
Any adverse outcome							
Univariate	0.51 (0.50 - 0.52)	0.02	4.5 (2.8 - 6.9)	97.9 (97.2 - 98.4)	28.6 (18.4 - 40.6)	84.5 (83.1 - 85.8)	2.14
Adjusted	0.63 (0.60 - 0.65)	<0.001	75.8 (71.6 - 79.8)	41.4 (39.4 - 43.4)	19.6 (17.7 - 21.5)	90.1 (88.2 - 91.8)	1.29

AUC: area under the Receiver Operating Characteristics (ROC) curves

AUC are test for significance against chance (0.5)

Models were adjusted for maternal age, weight, smoking, parity or free β-hCG

SGA: Small for gestational age; PPV: Positive predictive value; NPV: Negative predictive value;

LR (+): Positive likelihood ratio.