Running title: Lp(a) in obstetric and vascular disease

Title: Searching for a common mechanism for placenta mediated pregnancy complications and cardiovascular disease: role of Lipoprotein (a)

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**Capsule:** This study shows an association between Lp(a) concentrations and history of Stillbirth and Preeclampsia; this well-known atherothrombotic marker might represent one of the mechanisms shared by obstetric and cardiovascular disease.
Abstract

Objective: To investigate Lipoprotein (a) [Lp(a)], a well-know cardiovascular risk factor, in women with history of placenta mediated pregnancy complications (PMPC) compared with healthy uneventful pregnancy women (HW), and the role of LPA functional polymorphisms in modulating both Lp(a) levels and PMPC risk.

Design: Retrospective, observational study.

Setting: Gender Medicine Clinic, Centre for Atherothrombotic Disease, University Hospital.

Patients: 360 women with history of PMPC [154 preeclampsia (PE), 121 stillbirth (SB), 85 small for gestational age (SGA)] and in 270 HW.

Intervention(s): None

Main Outcome Measure(s): Lp(a) levels measurement and LPA +93C>T and +121G>A polymorphisms genotyping.

Results: In PMPCs we observed higher Lp(a) levels than those found in HW, and an association with PMPC risk [OR= 1.93 (1.20-3.09)], also after adjustment for age, familial history of cardiovascular disease, and traditional risk factors. By analyzing Lp(a) concentrations according to each pregnancy complication, we observed significantly higher Lp(a) levels in women with history of SB and PE, conferring a 2.5-fold and a 2-fold increased risk, respectively; no association with SGA was observed. Lp(a) concentrations progressively and significantly increased as LPA unfavorable allelic burden increased; unfavorable allelic burden influenced SB and PE risk.

Conclusions: We evidenced, for the first time, an association between high Lp(a) concentrations and history of SB, and we confirmed the role of Lp(a) in PE risk; this well-known atherothrombotic marker might represent one of the possible mechanisms shared by PMPC and cardiovascular disease.

Key-words: Lipoprotein(a), Stillbirth, Preeclampsia, LPA gene.
Introduction

Data from literature evidenced that a history of placenta mediated pregnancy complications (PMPC) such as preeclampsia, small for gestational age neonate, and stillbirth increased risk of cardiovascular disease (CVD) later in life (1,2), and entered as major risk factor for CVD in the AHA/ASA guidelines (3,4).

There is a common pathophysiologic pathway of endothelial dysfunction linking placental and vascular disorders. Beyond traditional cardiovascular risk factors, there is a wide variety of cardiovascular biomarkers endothelial dysfunction-related, which are still not widely explored in the clinical studies, such as lipoprotein (a) [Lp(a)]. Lipoprotein(a) is a plasma lipoprotein composed of a LDL particle and an additional lipoprotein, apolipoprotein(a), linked to apo B 100 of the LDL (5). Lp(a) plays a relevant role in the development of atherosclerosis, through multiple pathways, such as Lp(a)-derived cholesterol entrapment in the intima, inflammatory cell recruitment, and binding of pro-inflammatory-oxidized phospholipids to endothelial cells (6,7). Lp(a) also contributes to a prothrombotic phenotype through antifibrinolytic actions (8), due to its high homology to plasminogen, and to the inhibition of tissue factor pathway inhibitor.

Data from literature provided evidence that elevated Lp(a) concentrations represent an independent risk factor for premature cardiovascular disease (9-11).

Lp(a) concentrations are under genetic control at the concentration of biosynthesis of the apo(a) protein, which is encoded by the LPA locus; allelic differences at LPA locus may be responsible for the variations in Lp(a) phenotype (12). Variants at LPA locus have been associated with both an increased levels of Lp(a) and an increased risk of coronary disease (11).

The role of Lp(a) in pregnancy complications has been object of some clinical studies reporting not definite results (13). Few studies evaluate the relationship between Lp(a) and
preeclampsia (14, 15), only one study explored its role in affecting small for gestational age predisposition (15), but, at the best of our knowledge, no study is available concerning the influence of Lp(a) in modulating stillbirth risk.

In this scenario we investigated Lp(a) in women with history of stillbirth, preeclampsia or small for gestational age neonate in order to evaluate the role of this well-known atherothrombotic marker in obstetric negative outcome risk; we also investigated the role of LPA functional polymorphisms in modulating both Lp(a) levels and PMPC risk.

Methods

Study population

The entire study population comprised 870 consecutive women referred to Gender Medicine Clinic of the Center for Atherothrombotic Disease, Department of Experimental and Clinical Medicine, University Hospital, Florence, from 2010 to 2013, in order to be framed for vascular risk.

In Supplemental Figure 1 the study population is reported. Three hundred and sixty women with history of pregnancy complications related to uteroplacental vascular insufficiency (PMPC) [154 with history of preeclampsia (PE), 121 stillbirth (SB), 85 small for gestational age (SGA) neonates] were referred from gynecologists to Gender Medicine Clinic in order to be framed for their cardiovascular risk, as history of placenta mediated pregnancy complications represents a new cardiovascular risk factor; information concerning the adverse obstetrical outcomes derived from written gynecologists’ clinical report (PE defined as systolic blood pressure >140 mmHg or diastolic blood pressure ≥90 mmHg and 24-hour proteinuria ≥0.3 g; SB defined as late intrauterine fetal death after 24 completed weeks of pregnancy; SGA defined as infant born with a birth weight less than the 10th centile, according to RCOG guidelines).
Two hundred and seventy healthy women (HW) with no history of vascular disease, referred to Gender Medicine Clinic for evaluating thrombotic risk before taking estrogen-progesterone therapy or for family history of vascular disorders were considered as controls. These women delivered after uneventful pregnancy. In order to identify disease free controls, and to exclude women who were thought to have any form of vascular disease, a detailed interview addressing personal and familial history was performed. All women were investigated for Lp(a) after a minimum of 12 weeks postpartum. None were pregnant or had use oral contraceptive for at least 8 weeks before testing.

Exclusion criteria were the presence of diabetes mellitus, renal failure, pregnancy complications explained by anatomic, chromosomal, endocrine or immunological abnormalities, or intercurrent infectious events. Non-Caucasian origin (primarily because of the difference in the prevalence of the genetic polymorphisms) represented a further exclusion criterium. Finally, women who refused to assent with the genetic analysis were not included.

Informed written consent for anonymous data analysis was obtained from all women and the study was approved by the local Ethical Review Board. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes by using GeneCatcher™ gDNA Blood Kit (Invitrogen) with the aid of automated platform Freedom EVO 150 (Tecan). LPA +93C>T (rs1853021) and +121G>A (rs1800769) polymorphisms have been detected with PCR-RFLP analysis. The sequence surrounding the two SNPs has been amplified through PCR reaction with the following settings: one denaturation cycle at 95 °C for 5’, 35 cycles with denaturation at 94 °C for 1’, annealing at 54 °C for 50” and extension at 72 °C for 50”, followed by a final extension at 72 °C for 7’. The reaction has been performed in a final volume of 25 μl with 100 ng of genomic DNA, 0.2 mM of each dNTP, 1 μl of a 10 μM
forward primer (5′-TGACATTGCACTCTCAAATATTTT-3′), 1 µl of a 10 µM reverse primer (5′- AGAACCACCTCCTTATGTCCA-3′) and 0.5 U of Taq polymerase (GoTaq, Promega Italia, Milano, Italy) in 1× PCR Buffer.

In order to detect LPA +93C>T SNP, 10 µl of the PCR products (222 bp) are subjected to digestion with TaqI restriction enzyme (Fermentas International Inc., Burlington, Canada) while the evaluation of LPA+121G>A transition requires an enzymatic digestion with SduI (Fermentas International Inc., Burlington, Canada). Both the reactions are carried out at 37 °C for 16 h and the digestion fragments are separated on 3.5% agarose gel.

**Lipoprotein (a) measurements**

Blood samples were collected from the antecubital vein into evacuated plastic tubes (Vacutainer), after an overnight fast. Sera samples were obtained by centrifuging blood collected in evacuated tubes without anticoagulant at 2000×g for 10 min at 4 °C, subsequently stored at −20 °C. Lp(a) levels were detected by an immune-nephelometry method on serum samples through the use of the LPAX reagent in conjunction with IMMAGE800 Immunochemistry Systems and Lipoprotein(a) Calibrator (Beckman Coulter, Milan, Italy). The cut-off for this analyte is represented by values equal to 300 mg/l which represented an independent risk factor for vascular disease (16, 17). Intra-assay and inter-assay coefficients of variation were <5%.

**Statistical analysis**

Few data are available concerning Lp(a) levels in women with history of obstetric events (14); these studies documented a prevalence of high Lp(a) levels of about 30% and 10% in women with history of obstetric events and uneventful pregnancy, respectively. Based on this observation, a sample size of at least 100 women for each group was deemed sufficient to prove/exclude an association between high Lp(a) levels and placenta mediated pregnancy complications with a statistical power of 90% (β) and a significance value of 5% (α).
Statistical analyses were performed using the SPSS software (Chicago, IL, USA) for Windows (Version 11.5).

Age was expressed as median (range), and the categorical variables were expressed as frequencies and percentages. The only continuous variable which shows a normal distribution (age) was analyzed by using a parametric test (t-Student test); the nonparametric Mann–Whitney test for unpaired data was used for comparisons of the other continuous variables between single groups. Chi-square test was used to test for proportions and for deviation of genotype distribution of LPA polymorphisms from the Hardy-Weinberg equilibrium. Because Lp(a) distribution was right-skewed, values were log-transformed in regression analyses and back transformed for data presentation. A logistic regression analysis was used in order to evaluate the role of Lp(a) levels in modulating pregnancy complications risk. Variables which showed, at univariate analysis, a significant association with the disease were introduced into the multivariate model, as well as age and smoking habits. During multivariate analysis, a first model (Model 1) was created by adjusting for age and familial history of cardiovascular disease; subsequently, a second model (Model 2) was created by also adjusting for hypertension, dyslipidemia, smoking habit, and BMI>25 Kg/m². Odds ratios and 95% confidence intervals are presented. A $p$-value less than 0.05 was considered to indicate statistical significance.

In order to investigate the relationship between Lp(a) concentrations and LPA functional alleles, the study population was divided into five subgroups according to allelic burden: group 0 (women homozygous for LPA 120GG and 93TT), group 1 (women carrying one LPA functional variant related to increased gene expression), group 2 (women carrying two LPA functional variants related to increased gene expression), group 3 (women carrying three LPA functional variants related to increased gene expression), and group 4 (women
homozygous for LPA 120AA and 93CC). Kruskall–Wallis test was performed to compare
Lp(a) concentrations among different groups of allelic burden.

In order to evaluate the influence of allelic burden on pregnancy complications risk, a linear
regression analysis was performed and results were expressed as regression coefficient
(β)±SE.
Results

Lipoprotein(a) concentrations and placenta mediated pregnancy complications

Demographic, clinical and laboratory characteristics of the study population are reported in Table 1. A higher prevalence of hypertension, BMI>25 Kg/m², dyslipidemia, and familial history of cardiovascular disease was observed in women with history of PMPC in comparison to that found in controls. By analyzing traditional cardiovascular risk factors according to each pregnancy complication, we observed a significantly higher prevalence of hypertension and BMI>25 Kg/m² in women with history of SB and PE; with regard to lipid profile, higher percentage of dyslipidemic women in SB, PE and SGA group with respect to that observed in controls was found (Supplemental Table 1). Lp(a) concentrations have been assessed between 12 to 25 weeks after delivery; a significant higher percentage of women with history of PMPC (31.9%) exhibited Lp(a) concentrations above 300 mg/L cut-off respect to that found in healthy controls (17.1%) (p< 0.0001) (Table 1). Higher Lp(a) concentrations in both patients and controls with familial history of CVD [338.2 (237.2-440.1) and 205.9 (138.3-273.7), respectively] in comparison to those observed in patients and controls without familial history of CVD [253.4 (199.3-307.5) and 182.2 (154.2-210.2), respectively] were found.

Patients with pregnancy complications were more likely to have cardiovascular risk factors which may represent confounders, therefore, we performed an additional analysis by excluding potential confounders such as smoking, chronic hypertension, BMI>30 Kg/m² dyslipidemia and familial history of CVD; our results evidenced a significantly higher Lp(a) concentrations in women with history of placenta mediated pregnancy complications in comparison to that observed in controls (Supplemental Table 2).

When we analyzed Lp(a) concentrations according to each pregnancy complication (SGA, PE, SB), we observed a significantly higher Lp(a) levels in women with history of SB and
PE, whereas in women with history of SGA Lp(a) levels were higher, even if not significantly, in comparison to those found in controls (Figure 1).

In order to search a possible association between high Lp(a) levels and PMPC, we performed a logistic regression analysis, which showed a significant association between Lp(a) concentrations and obstetric negative outcomes [OR= 1.93 (1.20-3.09), p=0.006]; after adjustment for age and familial history of cardiovascular disease (Model 1), as well as for hypertension, smoking habit, BMI and dyslipidemia and timing from delivery (Model 2), high Lp(a) concentrations remained significantly associated with PMPC (Table 2); in particular, high Lp(a) levels conferred, a 2.5-fold increased risk of SB, and a 2-fold increased risk of PE, also after adjustment for Model 1 and Model 2. No association between high Lp(a) levels and SGA was observed (Table 2).

Because of its seems backwards to use Lp(a) measured after the obstetric complications to predict these negative outcomes, we performed a supplemental analysis in which Lp(a) concentrations are considered as the outcome. At linear regression analysis we observed a significant influence of a history of PMPC on Lp(a) concentrations (β =0.11±0.05; p = 0.04); in particular, both SB and PE significantly correlated with Lp(a) levels ((β =0.17±0.07; p = 0.02, β =0.14±0.06; p = 0.02, respectively).

LPA polymorphisms and Lp(a) concentrations

All subjects were genotyped for two LPA gene polymorphisms (LPA 93C>T and LPA 121G>A); genotype distribution and allele frequencies were in agreement with those predicted by Hardy-Weinberg equilibrium. As concerns the LPA 121G>A polymorphism, women with history of PMPC exhibited a higher, even if not significantly, 121A allele
frequency, in comparison to that observed in controls (0.12 vs 0.09, respectively); 93T allele frequency was comparable between patients and controls (0.13 vs 0.14, respectively). Due to the relatively small influence of each polymorphism on Lp(a) phenotype, we evaluated the weight of more than one unfavorable variant in influencing both Lp(a) concentrations and obstetric complications risk. Accordingly, we divided our study population in relation to allelic burden groups, and we observed that Lp(a) concentrations progressively and significantly increased as allelic burden increased (p=0.001) (Figure 2). As concerns the role of allelic burden in modulation obstetric complication risk, we performed a further analysis in order to investigate single allele or more than one unfavourable alleles role in influencing pregnancy negative events; at linear regression analysis a trend toward a significant influence of allelic burden on PE and stillbirth risk was observed (β =0.402±0.065; p = 0.06).
Discussion

Our findings provided evidence that women with history of pregnancy complicated by SB exhibited high Lp(a) concentrations, beyond a high prevalence of cardiovascular risk factors, such as unfavorable lipid profile, high blood pressure and BMI >25 Kg/m². These data could rekindle Lp(a) interest in relation to the history of obstetric complications, really the availability of new drugs which are showing novel therapeutic/safety profiles, could lead to introduce preventive strategies in clinical practice.

Data from literature evidenced that history of pregnancy complications determines an increased future cardiovascular risk (18, 19); because of its unique cardiovascular and metabolic stress, pregnancy permits to estimate a woman’s lifetime risk. Women who failed this stress test by experiencing placental disorders have an increased future cardiovascular risk, possibly unmasking early or pre-existing endothelial dysfunction and vascular disease (20); to date, a history of pregnancy complications entered as major risk factor for CVD in the AHA/ASA guidelines (3, 4).

Lp(a) represents a well known marker of cardiovascular disease (21-23), and it may also be used in risk assessment of subjects in the general population, particularly in intermediate-risk groups (24). During the last years advances have been achieved in understanding its pathophysiological role (9-11). Elevated Lp(a) concentrations can increase the risk of CVD mainly through a prothrombotic/anti-fibrinolytic effects, as apo(a) element possesses structural homology with plasminogen, and accelerated atherogenesis as a result of intimal deposition of Lp(a) cholesterol. Interestingly, plasma levels of Lp(a) are similar in both men and women, nevertheless at similarly high levels of plasma Lp(a), women are more likely to experience cardiovascular disease than men (25, 26).

Data concerning Lp(a) role in pregnancy complications are not clear-cut. To date, no previous study investigated Lp(a) levels in women with history of SB; in the present study we evidence
a role for Lp(a) in modulating SB risk, and this finding may be related to the prothrombotic
and anti-fibrinolytic Lp(a) effects which could lead to impaired placenta perfusion that can
alter oxygen and nutrient supply to the fetus.

We also observed that women with history of preeclampsia exhibited high Lp(a) levels, and
this finding is in keeping with data by Van Pampus MG et al (14), but are at variance with
those from Manten GTR et al. (15); the higher percentage of control women with high Lp(a)
levels (35%) in comparison to that observed in our control group (17%), and the different
assay used for Lp(a) determination, might explain this discrepancy; really, several different
assays are available to measure Lp(a) levels, and the standardization between Lp(a) assay is
still a critical point, which may contribute to affect the comparison among studies (25).

Lp(a) levels are under genetic control, and polymorphisms in LPA gene have been object of
interest, in particular in coronary artery disease (11) and in peripheral artery disease (27), as
well as in healthy subjects (28). In the present study we investigated the role of rs1853021
and rs1800769 LPA gene polymorphisms in modulating Lp(a) levels, and of novelty their role
in affecting placenta mediated pregnancy complications risk. Our data, showed for the first
time a progressive and significant increase of Lp(a) concentrations as LPA allelic burden
increased, and suggest a relationship between unfavorable allelic burden and negative
pregnancy events, in particular SB and PE. Therefore, present findings by evidencing a dose-
dependent relationship between LPA variants and both Lp(a) levels and risk of pregnancy
complications, might support the association between Lp(a) elevated plasma level and
negative pregnancy outcomes.

Patients are following up and these results will allow us to identify women who will early
experience atherothrombotic disease. Limitation of our study is the lack of information
concerning KIV repeat number, which better determines Lp(a) concentrations; really, we are
aware that the two polymorphisms investigated in the present study have a relatively small
influence on Lp(a) levels; nevertheless we selected these two functional polymorphisms based on others and our previous study (28, 29). Our is a follow-up referral Center, at which the most severely affected women as well as healthy women, who referred for other CVD risk factors, would attend, thus representing a further limitation.

Finally, the Lp(a) concentrations evaluated may be related to unresolved pregnancy effects as the measure were made in specimens collected between 12 to 25 weeks after delivery; pregnancy related changes may be not resolved until 6 months post-partum, nevertheless it is well know that Lp(a) increased until 35 weeks of gestation, subsequently decreased slightly until delivery, and fell to values below early pregnancy concentrations thereafter (30).

Our findings highlight the role of Lp(a) in modulating SB, and confirm the relationship between Lp(a) and PE risk; interestingly, by analyzing Lp(a) concentrations as the primary outcome, we provided evidence that a history of both SB and PE influenced Lp(a) concentrations, thus strengthening the relationship between this atherothrombotic marker and negative pregnancy outcomes.

Conflicts of interest

None of the authors have any conflict of interest.

Authorship:

I.R: conception and design of the study, writing the article, data collection, analysis and interpretation, final approval; E.S: statistical analysis, analysis and interpretation, final approval; M.A: analysis, final approval; E.G: data collection, final approval; G.C: data collection, final approval; A.R: analysis, interpretation of data; AP.C: analysis, interpretation of data; R.A: conception and design, critical revision of the article, final approval; C.F: conception and design of the study, writing the article, final approval.
Legends to figures:

Supplemental Figure 1. Flow chart

Figure 1. Lp(a) levels according to each placenta mediated pregnancy complications.
SGA=small for gestational age neonates, PE=preeclampsia, SB=stillbirth, CNTRL=Controls.

Figure 2. Lp(a) concentrations according to LPA gene unfavourable alleles burden.
<table>
<thead>
<tr>
<th></th>
<th>Patients (n=360)</th>
<th>Controls (n=270)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35 (19-49)</td>
<td>34 (22-40)</td>
<td>0.7</td>
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### Pregnancy Complications

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<table>
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<tbody>
<tr>
<td>Stillbirth</td>
<td>121 (33.6%)</td>
<td></td>
<td></td>
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<tr>
<td>Preeclampsia</td>
<td>154 (42.8%)</td>
<td></td>
<td></td>
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<tr>
<td>Small for gestational age neonate</td>
<td>85 (23.6%)</td>
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### CV Risk Factors

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<tbody>
<tr>
<td>Smoking habits, n(%)</td>
<td>59 (16.4%)</td>
<td>46 (17.0%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>36 (10.0%)</td>
<td>7 (2.6%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>BMI&gt;25 kg/m²</td>
<td>76 (21.0%)</td>
<td>38 (14.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia, n(%)</td>
<td>66 (18.3%)</td>
<td>15 (5.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total-C, mg/dL §</td>
<td>204.3 ± 51.0</td>
<td>187.4 ± 37.0</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL-C, mg/dL §</td>
<td>115.6 ± 33.9</td>
<td>102.4 ± 31.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C, mg/dL §</td>
<td>62.4 ± 18.0</td>
<td>67.4 ± 14.7</td>
<td>0.002</td>
</tr>
<tr>
<td>TG, mg/dL §</td>
<td>114.8 ± 53.2</td>
<td>88.9 ± 48.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Lp(a) mg/L ^</td>
<td>285.9 (236.5-335.4)</td>
<td>185.1 (159.4-210.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lp(a)&gt;300 mg/L</td>
<td>115 (31.9%)</td>
<td>46 (17.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of CVD, n (%)</td>
<td>96 (26.6%)</td>
<td>27 (10%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

§ media ± DS; ^ geometric mean (range); Total-C= total cholesterol; LDL-C= LDL cholesterol; HDL-C= HDL cholesterol; TG= Triglycerides; CVD= cardiovascular disease.
Table 2. Logistic regression analyses on the association between Lp(a) levels and placenta mediated pregnancy complications.

<table>
<thead>
<tr>
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<th>Univariate Analysis</th>
<th>Multivariate Analysis (Model 1)</th>
<th>Multivariate Analysis (Model 2)</th>
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<tbody>
<tr>
<td></td>
<td>OR (CI 95%)</td>
<td>p</td>
<td>OR (CI 95%)</td>
</tr>
<tr>
<td>PMPC (n=360)</td>
<td>1.93 (1.20-3.09)</td>
<td>0.006</td>
<td>1.75 (1.08-2.82)</td>
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<tr>
<td>Stillbirth (n=121)</td>
<td>2.55 (1.29-5.05)</td>
<td>0.007</td>
<td>2.36 (1.19-4.66)</td>
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<td>Preeclampsia (n=154)</td>
<td>2.43 (1.23-4.78)</td>
<td>0.01</td>
<td>2.19 (1.07-4.47)</td>
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<tr>
<td>Small for gestational age neonate (n=85)</td>
<td>0.98 (0.38-2.52)</td>
<td>0.9</td>
<td>-</td>
</tr>
</tbody>
</table>

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