Correlation between placental underperfusion, histologic signs and perinatal morbidity in late-onset small for gestational age fetuses

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ABSTRACT

Objective: To investigate whether signs of placental underperfusion (PUP), defined as any maternal and/or fetal vascular pathology, confer a higher risk of neonatal morbidity in late-onset small for gestational age (SGA) fetuses with normal umbilical artery Doppler.

Methods: A cohort of 126 SGA singleton fetuses with normal umbilical artery Doppler delivered after 34 weeks was created. For each case, the placenta was histologically evaluated for signs of PUP using a hierarchical and standardized classification system. Neonatal morbidity was assessed by calculation of the morbidity assessment index for newborns (MAIN) score, a validated outcome scale. The independent association between PUP and neonatal morbidity was evaluated using multivariable median regression.

Results: In a total of 84 placentas (66.7%), there were 97 placental histological findings that qualified as signs of PUP. These cases had a significantly higher incidence of emergent delivery for non-reassuring fetal status (44.1% vs. 21.4%; \( p=0.013 \)) and neonatal metabolic acidosis at birth (33.3% vs. 14.3%; \( p=0.023 \)). The median MAIN score significantly differed between groups (89 vs. 0; \( p=0.025 \)). This difference remained significant after adjustment for potential confounders. The proportion of cases with mild to severe morbidity scores was also significantly higher in the PUP group (31% vs. 14.3%; \( p=0.043 \)).

Conclusion: In late-onset SGA with normal umbilical artery Doppler, signs of PUP confer higher neonatal morbidity. These findings allow phenotypic profiling of fetal growth restriction among the general population of late-onset SGA.

INTRODUCTION

Near-term babies born small for gestational age (SGA) with no signs of placental disease, as reflected in the umbilical artery (UA) Doppler, are typically viewed as constitutionally small
neonates displaying satisfactory perinatal outcomes\textsuperscript{1, 2}; however, recent studies have reported poor perinatal outcomes, suboptimal neurodevelopment, and higher postnatal cardiovascular risk in these newborns \textsuperscript{3, 4, 5}, supporting the hypothesis that a subset of SGA fetuses undergoes late-onset fetal growth restriction (FGR), in which placental insufficiency is not detected by UA Doppler. Thus, latent placental insufficiency is a key aspect in differentiating true FGR from constitutional smallness \textsuperscript{6-10}.

In pregnancies with late-onset SGA, hypoxic/ischemic injury due to placental underperfusion (PUP) defined as any maternal and/or fetal vascular pathology is documented in roughly two-thirds of placentas \textsuperscript{11, 12}, and the presence of PUP has been correlated with abnormal uterine and umbilical vein Doppler before delivery phenotype.\textsuperscript{13}

This finding suggests that this pattern constitutes the pathological basis of placental insufficiency late in pregnancy; however, the association between PUP and neonatal outcomes in late-onset SGA has not yet been explored. This information is critical for consideration of PUP as a criterion to define the late-onset FGR clinical phenotype.

Most tools used to assess neonatal morbidity are not sufficiently sensitive or precise to provide valid measurements in near-term babies \textsuperscript{14, 15, 16}. The morbidity assessment index for newborns \textsuperscript{17} (MAIN) score overcomes such limitations by including a comprehensive inventory of standard assessment items that reflect pathophysiology in the early newborn period. This inventory has previously been demonstrated to be sensitive in the population of term SGA babies \textsuperscript{18}. 

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The main purpose of this study was to determine whether signs of PUP confer a higher risk of neonatal morbidity in late-onset-SGA fetuses that exhibit normal umbilical artery Doppler.

**METHODS**

**Study population**

Between January 2012 and January 2014, a cohort of consecutive pregnancies that were attended at a single university hospital was created from those that fulfilled the following inclusion criteria: i) singleton pregnancy; ii) estimated fetal weight (EFW) below the 10th centile at the routine third trimester ultrasound (30-34 weeks’ gestation), after adjustment for gestational age (GA) at delivery and gender according to local standards	extsuperscript{19} and iii) normal UA Doppler [defined as UA pulsatility index (PI) <95th centile	extsuperscript{20}] at the time of diagnosis of SGA. The following exclusion criteria were considered: i) congenital or chromosomal abnormalities, ii) GA at delivery less than 34 weeks, and iii) development of abnormal UA Doppler during follow-up, and iv) a birth weight > the 10th centile	extsuperscript{19}.

Pregnancies were dated by first-trimester crown-rump length measurement	extsuperscript{21}. The EFW was calculated using the Hadlock formula	extsuperscript{22}. The hospital ethics committee approved the study protocol, and written consent was obtained from all recruited patients (IRB 2008/4422).

**Doppler measurements**

Prenatal Doppler ultrasound examinations were performed by one of three experienced operators (M.P., F.C., or S.S.) using either a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or a General Electric Voluson E8 (GE Medical Systems, Zipf, Austria) ultrasound machine equipped with a 6-2-MHz linear curved-array transducer. Doppler recordings were performed in the absence of fetal movements and voluntarily
suspended maternal breathing. Spectral Doppler parameters were performed automatically from three or more consecutive waveforms with the angle of insonation as close to 0° as possible. The UA pulsatility index (PI) was calculated from a free-floating cord loop. The middle cerebral artery (MCA) PI was measured in a transverse view of the fetal head at the level of its origin from the circle of Willis. The cerebroplacental ratio (CPR) was calculated as the ratio of the MCA PI to the UA PI. All cases had a Doppler examination within 7 days of delivery, and only the last Doppler examination was considered for this study.

**Clinical protocol**

Labor induction was indicated in the presence of a persistent (12-h apart) CPR <5th centile beyond 37 weeks’ gestation and at 40 weeks’ gestation if CPR remained within normal ranges. Labor induction was performed by cervical ripening with a slow-release prostaglandin E2 vaginal pessary (10 mg). If the onset of labor did not occur within 12 hours, oxytocin induction was initiated. Indication for cesarean delivery for non-reassuring fetal status was based on abnormal fetal heart rate monitoring and abnormal fetal scalp blood pH during intrapartum monitoring. Continuous fetal heart monitoring was carried out, and tracings were classified according to the following three-tiered system: (i) normal, baseline 110–160 beats per minute (bpm), variability >5 bpm and absence of decelerations; (ii) suspicious (one non-reassuring criterion present), baseline 100–109 or 161–180 bpm, variability <5 bpm for less than 90 min, recurrent (>50% contractions) typical variable decelerations for more than 90 min, and a single prolonged deceleration for up to 3 min; or (iii) pathological, more than one non-reassuring criterion or the presence of any abnormal feature, including baseline <100 or >180 bpm or sinusoidal patterns for more than 10 min, variability <5 bpm for more than 90 min, recurrent atypical variable decelerations for more
than 30 min, late decelerations for more than 30 min, and a single prolonged deceleration for more than 3 min.

In cases with pathological fetal heart rate or a suspicious pattern not presenting with a fetal heart rate acceleration after digital fetal scalp stimulation, fetal scalp blood sampling was performed. Levels were considered abnormal with values less than 7.15 or 7.20 on two occasions within 30 min. If cervical conditions did not allow fetal scalp sampling, cesarean delivery was considered for non-reassuring fetal status based on the persistence of abnormal tracings after pessary withdrawal, oxytocin suspension, and 10 min of intravenous infusion of 200 µg/min ritrodine. All cases with adverse outcome were formally assessed to ensure that the management protocol had been followed correctly.

Data collection and outcome measures

Data on maternal characteristics, including age, ethnicity, body mass index, parity, smoking status, known chronic disease (hypertension, diabetes mellitus, renal disease, and autoimmune disease), and previous obstetrical history, were recorded in the hospital database at inclusion. In addition, data regarding pregnancy follow-up, complications developed during pregnancy, ultrasound evaluation, and perinatal data were prospectively collected. Preeclampsia (PE) was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. Neonatal metabolic acidosis at birth was defined as the presence of a UA pH less than the 10th centile (7.18) for term babies and base excess greater than the 90th centile (-12 mEq/L) at birth.

Placental evaluation

Placental examinations were performed according to standard laboratory protocol. Fresh and trimmed (after removal of the membranes, cord, and any blood clots) placental weights were recorded. Trimmed placental weight centiles were assigned based on GA-specific
placental weight charts. The fetoplacental weight ratio (birth weight:fresh placental weight) was also expressed as a centile, based on GA-specific ranges.

Placentas were fixed in 10% buffered formalin. After gross examination, samples of each specimen were taken for routine processing: one transverse section of cord, one rolled strip of membranes, and three blocks spanning the entire thickness of the villous parenchyma. All macroscopic lesions were sampled as well. Slides were stained with hematoxylin and eosin.

A single senior pathologist (A.N.) blinded to the neonatal outcome supervised all examinations. All pathological examinations were made by pathologists blinded to the Doppler result and the perinatal outcome.

For purposes of this study PUP-related histologic manifestations were further designated as maternal or fetal in origin. Among maternal vascular supply disruptions, specific vascular alterations that qualified as maternal vascular maldevelopment included superficial implantation/decidual arteriopathy (acute atherosis and mural hypertrophy [mean wall diameter >30% of overall vessel diameter of arterioles in the decidua parietalis]), undergrowth/distal villous hypoplasia (decrease in the number and modal diameter of distal villi at the center of the lobule after adjustment for plane of section and gestational age in the lower 75% of a full-thickness section), excessive intervillous fibrin (basal layer of fibrinoid material involving >30% of the placental maternal surface), and migration disorders (including accessory lobes, peripheral cord insertions, and placenta previa). Specific vascular alterations that qualified for maternal vascular obstruction were syncytial knots (aggregates of syncytial nuclei at the surface of terminal villi) involving terminal villi (affecting >50% of the terminal villi), villous agglutination (>50%), intervillous fibrin deposition (eccentric aggregates on intervillous fibrin on proximal and distal villi affecting >50% of the villi), and villous infarcts (>30% of villous loss). Specific
vascular alterations that qualified for maternal vascular loss of integrity were arterial rupture (abruption placenta) and venous rupture (acute or chronic marginal abruption).

Among fetal vascular supply disruptions, lesions that qualified for maldevelopment were chorioangioma (in the form of proliferative nodules), chorioangiosis (more pervasive with a patchy or generalized increase in capillaries), and distal villous immaturity. Lesions that qualified for obstruction were those that were considered secondary to vascular thrombo-occlusive disease (thrombosis of chorionic plate and stem villous channels and villous avascularity [avascular villi are defined as more than 15 villi in a section showing a total lack of villous vessels and a hyalinised fibrotic stroma] affecting large groups). PUP was indicated for placentas with the presence of any of the above mentioned lesions.

**Neonatal morbidity assessment**

Morbidity was calculated using the MAIN score\(^1\). This score was designed to provide a numeric index of early neonatal outcomes reflecting prenatal care and adverse prenatal exposures in babies delivered after 28 weeks. This score is a sensitive and discriminative outcome measure for studies with outcomes other than preterm delivery. The MAIN score consists of 47 binary items that describe 24 attributes of early neonatal morbidity (including physiological variables, such as blood pressure, pCO2, temperature, oxygen saturation, Apgar score, and the presence of apnea). These data items were obtained from the hospital discharge records by a single evaluator (S.S.), who was blinded to the placental histology findings. According to normative ranges, the scores were divided into two morbidity categories: <150 (no/minimal) and \(\geq 150\) (mild to severe morbidity)\(^1\).

**Statistical analysis**

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Normal distributions were examined using the Shapiro-Wilk test. The Student’s t-test and Pearson’s Chi-squared test were used to compare quantitative and categorical data, respectively. Non-normally distributed quantitative variable data were compared using Mood’s median test. The association between PUP-related histopathologic lesions and the MAIN score (log-transformed) was analyzed using non-parametric quantile regression with a tau of 0.5 (median regression), where adjustment was performed for parity, smoking, cerebroplacental ratio, and birth weight centile. All statistical analyses were performed using SPSS Statistics 20 (SPSS Inc., Chicago IL) and R version 2.15.1 (The R Foundation for Statistical Computing; quantreg package 5.05). A p-value ≤ 0.05 was considered statistically significant.

RESULTS
A total of 134 pregnancies fulfilled the inclusion criteria. Subsequently, three cases were excluded due to preterm birth before 34 weeks (one case with clinical and histological evidence of choriomanionitis), and three additional cases were excluded because of the development of abnormal UA Doppler before delivery, and additionally two cases were excluded for a birth weight > the 10th centile. The baseline characteristics of the remaining 126 cases are displayed in Table 1.

Elective cesarean section was performed in seven cases (three breech presentations, three cases with more than one previous cesarean section, and one case with a previous vaginal delivery with an anal sphincter lesion). One hundred and two women (81%) underwent induction of labor; the remaining cases (n=17, 13.5%) had spontaneous onset of delivery.
In a total of 84 cases (66.7%), 97 findings that qualified for PUP were found. Table 2 details the histological findings in the study population. Placentas with signs of PUP were not statistically different from those without signs of PUP with regard to weight (383.5 vs. 396.2; \( p=0.45 \)) or feto-placental weight ratio (5.8 vs. 6.2; \( p=0.053 \)). Similarly, when expressed as GA centiles, these parameters were not statistically different between the two groups (weight, 3.20 vs. 3.26, \( p=0.95 \) and feto-placental weight ratio, 34.3 vs. 37.1, \( p=0.62 \)).

Table 3 presents the ultrasound and Doppler findings before delivery and the perinatal outcomes according to the presence of PUP. Of note, the proportion of cases requiring emergent delivery for non-reassuring fetal status significantly differed between cases with and without PUP (44.1% vs. 21.4%; \( p=0.013 \)). Similarly, the occurrence of neonatal metabolic acidosis was more frequent in the PUP group compared to the group without signs of PUP (33.3 vs. 14.3%; \( p=0.023 \)). The proportion of newborns with moderate to severe neonatal morbidity scores (\( \geq 150 \)) was also significantly higher in the PUP group compared to the group without signs of PUP (31% vs. 14.3%; \( p=0.043 \)). Finally, Figure 1 shows the distribution of MAIN scores by the presence of PUP. Median MAIN scores significantly differed between groups (89 vs. 0; \( p=0.025 \)). This difference remained significant after adjustment for potential confounders (Table 4).

**DISCUSSION**

In this study, we report that in late-onset SGA, where we have previously found that the degree of placental damage is not reflected in the UA Doppler \(^1\), the presence of histological signs of PUP confers a poorer neonatal outcome. This finding supports the notion that PUP is a key feature for phenotypic discernment of which cases among the
overall population of late SGA babies correspond with true late-onset FGR secondary to placental insufficiency.

Previous studies have shown that PUP and adverse perinatal outcomes are linked in a variety of clinical conditions. This study extends this association to late-onset FGR even in the presence of normal UA Doppler. One might speculate that PUP confers diminished placental reserve, which, in turn, lowers tolerance to labor and heightens the likelihood of neonatal morbidity. Moreover, we have also previously reported that in near-term SGA babies, PUP undermines the neurodevelopment of early infancy. Taken together, this evidence points to PUP as a surrogate of placental insufficiency and indicates that PUP is worthy of targeting in clinical practice. These findings are particularly important because late-onset SGA occurs in 5-10% of all pregnancies, and this pattern has been documented in roughly two-thirds of placentas.

We found that, albeit not significantly, UA pulsatility was higher in the PUP group. The precise reason why maternal underperfusion almost uniformly corresponds with abnormal UA Doppler results in early-onset IUGR, although rarely in late-onset IUGR, is open to debate; but because the nature of pathology is similar, one might speculate that the extent of pathology is key. Indeed, animal models and mathematical projections of placental vascular obliteration have suggested that abnormalities of UA Doppler studies surface only in advanced stages of placental dysfunction. Nevertheless, term SGA babies suffering lesser degrees of underperfusion that escape Doppler detection may be exposed to subtle but chronic hypoxia and undernutrition with delayed neurologic consequences.

SGA is a descriptive term that is applied to all infants with birth weights below a given threshold (generally 10th centile). Consequently, these infants comprise a heterogeneous
group containing infants with true FGR and newborns who are constitutionally small but otherwise healthy. Thus, SGA should not be considered an outcome in and of itself. In fact, ongoing research with respect to screening and monitoring of late-onset SGA fetuses has been hampered by consolidation of pregnancies with and without placental insufficiency, which in essence, collapses several phenotypes into one single condition. Similar to other obstetrical syndromes syndromes\textsuperscript{42}, we believe that the key to more effective clinical management of these pregnancies with late-onset SGA is identifying biomarkers that reflect the placental insufficiency phenotype as supported by histologic evidence of PUP.

In the Netherlands, a large trial compared systematic induction at term with expectant management for late-onset SGA showed no differences in the perinatal and neonatal outcomes (also measured by the MAIN score) between both strategies.\textsuperscript{18, 43} This evidence has been translated into some guidelines that generally recommend labor induction at 37-38 weeks\textsuperscript{44-46} in order to avoid the rare but devastating instances of stillbirth; however, with such a strategy, the births of a large fraction of constitutionally small yet healthy SGA babies are unnecessarily induced, which has the potential to result in lower satisfaction and poorer fulfillment in the birth experience.\textsuperscript{47} In a previous study, we found that in late-onset SGA pregnancies, uterine Doppler and umbilical vein flow are surrogates of PUP\textsuperscript{13}. We speculate that prenatal selecting for labor induction on the basis of these Doppler parameters may result in improved neonatal outcomes.

We concede that our study has limitations. First, complete Doppler information (i.e., uterine Doppler or umbilical vein) was not obtained for a substantial fraction of our cases. This information may have shed additional light on to the complex relationship between fetal-maternal hemodynamic parameters, placental insufficiency, and neonatal morbidity.
Additionally, examination of maternal levels of angiogenic factors may also have provided relevant information. In a previous study perinatal on late-onset SGA, we demonstrated that both cerebral Doppler and maternal levels of placental growth factor were associated with adverse perinatal outcome with respect to neonatal acidosis and non-reassuring fetal status requiring emergent cesarean delivery. Finally, our sample size may have rendered our study underpowered to evaluate specific histological findings and their clinical correlations.

In summary, in late-onset SGA pregnancies with normal umbilical artery Doppler, signs of PUP confer higher neonatal morbidity. These findings will allow better phenotypic profiling of FGR cases among the general population of late-onset SGA fetuses.

References


Table 1 Baseline characteristics of the study population (n=126)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>32.6 (5.8)</td>
</tr>
<tr>
<td>Non-Caucasian ethnicity</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Low socioeconomic class*</td>
<td>44 (34.9)</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>22.9 (4.1)</td>
</tr>
<tr>
<td>Nullipary</td>
<td>78 (61.9)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>91 (72)</td>
</tr>
<tr>
<td>&lt;10 cigarettes/day</td>
<td>16 (12.7)</td>
</tr>
<tr>
<td>≥10 cigarettes/day</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>18 (14.3)</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>37.8 (3.8)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>46 (36.5)</td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2239 (431)</td>
</tr>
<tr>
<td>Birth weight centile</td>
<td>1.9 (2.3)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>37 (29.4)</td>
</tr>
<tr>
<td>NICU (days)†</td>
<td>4.7 (12.5)</td>
</tr>
</tbody>
</table>

BMI, body mass index; GA, gestational age; NICU, neonatal intensive care unit.
*Routine occupations, long-term unemployment, or never worked.
†Refers only to neonates admitted to NICU (n=37)
Table 2 Categories and subcategories of placental findings (n=97) consistent with placental underperfusion in 84 SGA pregnancies

<table>
<thead>
<tr>
<th>Categories of placental injury</th>
<th>n (%)</th>
<th>Subcategories of placental injury</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal vascular supply</td>
<td>77 (79.4)</td>
<td>Maldevelopment</td>
<td>45 (58.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstruction</td>
<td>26 (33.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of integrity</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Fetal vascular supply</td>
<td>20 (20.6)</td>
<td>Maldevelopment</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstruction</td>
<td>12 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of integrity</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>
Table 3 Ultrasound, Doppler, and perinatal parameters of the study group according to placental findings

<table>
<thead>
<tr>
<th>Placental underperfusion</th>
<th>No placental underperfusion</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=84) mean (SD) or n (%)</td>
<td>(n=42) mean (SD) or n (%)</td>
<td></td>
</tr>
<tr>
<td>EFW (g)</td>
<td>2074 (411)</td>
<td>2277 (339)</td>
</tr>
<tr>
<td>EFW centile</td>
<td>1.51 (2.2)</td>
<td>2.32 (2.6)</td>
</tr>
<tr>
<td>UA PI</td>
<td>1.05 (0.24)</td>
<td>0.97 (0.21)</td>
</tr>
<tr>
<td>MCA PI</td>
<td>1.54 (0.35)</td>
<td>1.51 (0.47)</td>
</tr>
<tr>
<td>CPR</td>
<td>1.57 (0.52)</td>
<td>1.65 (0.51)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>17 (20.2)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>67 (79.8)</td>
<td>35 (83.1)</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>37.8 (1.9)</td>
<td>37.7 (6.1)</td>
</tr>
<tr>
<td>BW (g)</td>
<td>2161 (448)</td>
<td>2394 (353)</td>
</tr>
<tr>
<td>BW centile</td>
<td>1.5 (1.9)</td>
<td>2.8 (2.7)</td>
</tr>
<tr>
<td>Emergent delivery for NRFS*</td>
<td>37 (44.1)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Neonatal metabolic acidosis</td>
<td>28 (33.3)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>29 (34.5)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>MAIN score &gt;150</td>
<td>26 (31)</td>
<td>6 (14.3)</td>
</tr>
</tbody>
</table>

EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; MCA, middle cerebral artery; CPR, cerebroplacental ratio; GA, gestational age; BW, birth weight; NRFS, non-reassuring fetal status; NICU, neonatal intensive care unit.

*Cases with elective cesarean section (n=7) not included in the denominator.
†Student’s t-test or Pearson’s Chi-squared test, as appropriate
Table 4 Multivariable analyses (median regression) of the association between PUP and MAIN scores (log-transformed)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>PUP</td>
<td>1.2</td>
<td>0.53</td>
<td>0.026</td>
</tr>
<tr>
<td>Nullipary</td>
<td>0.64</td>
<td>0.52</td>
<td>0.217</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.94</td>
<td>0.55</td>
<td>0.093</td>
</tr>
<tr>
<td>CPR</td>
<td>0.31</td>
<td>0.61</td>
<td>0.611</td>
</tr>
<tr>
<td>BW centile</td>
<td>-0.11</td>
<td>0.1</td>
<td>0.289</td>
</tr>
</tbody>
</table>

SE, standard error; PUP, placental underperfusion; CPR, cerebroplacental ratio; BW, birth weight
**Figure 1** Morbidity Assessment Index for Newborns (MAIN) score distribution by the presence of placental underperfusion (PUP)

^Mood’s median test

\[ p=0.025^* \]