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

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KEYWORDS: Doppler; fetal development; fetal growth restriction; neonatal complications; placenta; ultrasonography

ABSTRACT

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

Methods *A cohort of 126 SGA singleton fetuses with normal UA Doppler indices that were delivered after 34 weeks' gestation was studied. For each case, the placenta was evaluated histologically for signs of PUP using a hierarchical and standardized classification system. Neonatal morbidity was assessed according to the score calculated from the morbidity assessment index for newborns (MAIN), a validated outcome scale. The independent association between PUP and neonatal morbidity was evaluated using multivariable median regression analysis.*

Results *In 84 (66.7%) placentae, 97 placental histological findings that qualified as signs of PUP were observed. These PUP cases had a significantly higher incidence of emergency Cesarean section for non-reassuring fetal status (44.1%* vs *21.4%, respectively;* $P = 0.013$*) and neonatal metabolic acidosis at birth (33.3%* vs *14.3%, respectively;* $P = 0.023$*), than did those without PUP. The median MAIN score differed significantly between those with PUP and those without (89* vs *0, respectively;* $P = 0.025$*). This difference remained significant after adjustment for potential confounders. The proportion of cases with scores indicative of mild to severe morbidity was also significantly higher in the PUP group (31%* vs *14.3%, respectively;* $P = 0.043$*).*

Conclusion *In late-onset SGA fetuses with normal UA Doppler indices, signs of PUP imply a higher neonatal morbidity. These findings allow the 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 their umbilical artery (UA) Doppler indices, are typically viewed as constitutionally small neonates displaying satisfactory perinatal outcomes[1,2]. However, recent studies have reported poor perinatal outcome, suboptimal neurodevelopment and higher postnatal cardiovascular risk in these newborns[3–5], supporting the hypothesis that a subset of SGA fetuses undergo late-onset fetal growth restriction (FGR), in which placental insufficiency is not detected by UA Doppler ultrasound. Thus, latent placental insufficiency is a key aspect in differentiating true FGR from constitutional smallness[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 known

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to occur in roughly two-thirds of placentae[11,12], and the presence of PUP has been correlated with abnormal uterine artery and umbilical vein Doppler indices before delivery[13].

This finding suggests that this pattern constitutes the pathological basis of placental insufficiency, developing late in pregnancy; however, the association between PUP and neonatal outcome in late-onset SGA has not yet been explored. This information is critical for the consideration of PUP as a criterion for defining 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[14–16]. The morbidity assessment index for newborns (MAIN) score overcomes such limitations by including a comprehensive inventory of standard assessment items that reflect pathophysiology in the early newborn period[17]. This inventory has been shown previously to be sensitive in a population of term SGA babies[18].

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

METHODS

Between January 2012 and January 2014, a cohort of consecutive pregnant women who were attending a single university hospital was created from those that fulfilled the following inclusion criteria: (1) singleton pregnancy; (2) estimated fetal weight (EFW) below the 10th centile at the routine third-trimester ultrasound examination (30–34 weeks' gestation); and (3) normal UA Doppler, defined as UA pulsatility index (PI) < 95th centile at the time of diagnosis of SGA[19]. The following exclusion criteria were applied: (1) congenital or chromosomal abnormalities; (2) GA at delivery less than 34 weeks; (3) development of abnormal UA Doppler indices during follow-up; and (4) a birth weight ≥10th centile[20]. Pregnancies were dated according to first-trimester crown–rump length measurement[21], and EFW was calculated using the Hadlock formula[22]. The hospital ethics committee approved the study protocol, and written consent was obtained from all patients recruited (IRB 2008/4422).

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 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 during voluntarily suspended maternal breathing. Spectral Doppler parameters were obtained automatically from three or more consecutive waveforms, with the angle of insonation as close to 0° as possible. The UA-PI was measured from a free-floating cord loop and the middle cerebral artery (MCA)-PI 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.

The need for induction of labor was indicated by the presence of a persistent (12 h apart) CPR < 5th centile beyond 37 weeks' gestation and at 40 weeks' gestation if the CPR remained within the normal range[23]. Induction of labor was initiated by cervical ripening with a slow-release prostaglandin E2 vaginal pessary (10 mg). If onset of labor did not occur within 12 h, oxytocin induction was started. Indication for delivery by Cesarean section for non-reassuring fetal status (NRFS) 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-tier system[24]: (1) normal, i.e. baseline 110–160 beats per minute (bpm), variability > 5 bpm and an absence of decelerations; (2) suspicious i.e. one non-reassuring criterion present out of: baseline 100–109 or 161–180 bpm, variability < 5 bpm for less than 90 min, recurrent (> 50% of contractions) typical variable decelerations for more than 90 min and a single prolonged deceleration for up to 3 min; or (3) pathological, i.e. 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 a pathological fetal heart rate or a suspicious pattern not presenting with a fetal heart rate acceleration after digital fetal scalp stimulation[25], fetal scalp blood sampling was performed. pH was considered abnormal if it was less than 7.15, or 7.20 on two occasions within 30 min. If cervical conditions did not allow fetal scalp sampling, Cesarean section was considered for NRFS based on the persistence of abnormal tracings after pessary withdrawal, oxytocin suspension and 10 min of intravenous infusion with 200 μg/min of ritodrine. All cases with adverse outcome were formally assessed to ensure that the management protocol had been followed correctly.

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 obstetric history were recorded in the hospital database at inclusion in the study. In addition, data regarding pregnancy follow-up, complications that developed during pregnancy, ultrasound evaluation and perinatal data were collected prospectively. Pre-eclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[26]. Neonatal metabolic acidosis at birth was defined as UA

pH < 10th centile (7.18) for term babies and a base excess > 90th centile (−12 mEq/L) at birth[27].

Placental examinations were performed according to a standard laboratory protocol. Weights of fresh placentae and trimmed placentae (after removal of the membranes, cord and any blood clots) were recorded. Trimmed-placenta weight centiles were assigned based on gestational age (GA)-specific placenta weight charts[28]. The fetoplacental weight ratio (birth weight:fresh-placenta weight) was also expressed as a centile, based on GA-specific ranges[29].

Placentae 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. In addition, all macroscopic lesions were sampled. 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 performed by pathologists blinded to the Doppler results and perinatal outcomes.

For the purposes of this study, PUP-related histological manifestations were further designated as maternal or fetal in origin[30,31]. Among disruptions of the maternal vascular supply, specific vascular alterations that qualified as maternal vascular maldevelopment included superficial implantation/decidual arteriopathy (acute atherosis and mural hypertrophy (a mean wall diameter > 30% of the overall vessel diameter of arterioles in the decidua parietalis)), undergrowth/distal villous hypoplasia (a 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 (a basal layer of fibrinoid material involving > 30% of the maternal surface of the placenta) and migration disorders (including accessory lobes, peripheral cord insertions and placenta previa). Specific vascular alterations that qualified as maternal vascular obstruction were syncytial knots (aggregates of syncytial nuclei at the surface of terminal villi) involving > 50% of terminal villi, > 50% villous agglutination, intervillous fibrin deposition (eccentric aggregates of intervillous fibrin affecting > 50% of the proximal and distal villi) and villous infarcts (> 30% of villus loss). Specific vascular alterations that qualified as maternal vascular loss of integrity were arterial rupture (placental abruption) and venous rupture (acute or chronic marginal abruption).

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

Morbidity was calculated using the MAIN score[17,32]. This score was designed to provide a numerical index of early neonatal outcome, reflecting prenatal care and adverse prenatal exposures, in babies delivered after 28 weeks' gestation. The 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, pCO_2, temperature, oxygen saturation, Apgar score and the presence of apnea. These data were obtained from the hospital discharge records by a single evaluator (S.S.), who was blinded to the histology findings of the placentae. According to normative ranges, the scores were divided into two morbidity categories: no/minimal morbidity (< 150) and mild to severe morbidity (≥ 150)[17].

Statistical analysis

Normal distributions were examined using the Shapiro–Wilk test. Student's *t*-test and Pearson's chi-square test were used to compare quantitative and categorical data, respectively. Non-normally distributed quantitative variable data were compared using Mood's median test[33].

The association between PUP-related histopathological 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, CPR and birth-weight centile. All statistical analyses were performed using SPSS Statistics v. 20 (SPSS Inc., Chicago, IL, USA) and R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria; quantreg package 5.05). $P \leq 0.05$ was considered to be statistically significant.

RESULTS

A total of 134 pregnancies fulfilled the inclusion criteria. Subsequently, three cases were excluded owing to preterm birth before 34 weeks' gestation (one case with clinical and histological evidence of chorioamnionitis), three additional cases were excluded because of the development of abnormal UA Doppler indices before delivery and two cases were excluded owing to birth weight ≥ 10th centile. The baseline characteristics of the remaining 126 included 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 (81.0%) women underwent induction of labor and the remaining 17 (13.5%) cases had spontaneous onset of delivery.

In 84 (66.7%) cases, 97 findings that qualified as PUP were identified. Table 2 details the histological

Table 1 Maternal and obstetric characteristics of the 126 small-for-gestational-age fetuses included in the study

Characteristic	*Value*
Maternal age (years)	32.6 ± 5.8
Non-Caucasian ethnicity	24 (19.0)
Low socioeconomic class*	44 (34.9)
Maternal body mass index (kg/m^2)	22.9 ± 4.1
Nulliparous	78 (61.9)
Smoking status	
Non-smoker	91 (72.2)
< 10 cigarettes/day	16 (12.7)
≥ 10 cigarettes/day	19 (15.1)
Chronic hypertension	7 (5.6)
Diabetes mellitus	2 (1.6)
Renal disease	—
Autoimmune disease	1 (0.8)
Gestational hypertension	2 (1.6)
Pre-eclampsia	18 (14.3)
Gestational age at delivery (weeks)	37.8 ± 3.8
Cesarean delivery	46 (36.5)
Operative vaginal delivery	7 (5.6)
Birth weight (g)	2239 ± 431
Birth-weight centile	1.9 ± 2.3
Admission to NICU	35 (27.8)
Duration of stay in NICU (days)†	4.7 ± 12.5

Data given as mean ± SD or *n* (%). *Routine occupations, long-term unemployment or never worked. †Refers only to neonates admitted to neonatal intensive care unit (NICU) ($n = 35$).

Table 2 Categories and subcategories of 97 histological findings consistent with placental underperfusion in 84 small-for-gestational-age pregnancies

Placental injury	n *(%)*
Maternal vascular supply	77 (79.4)
Maldevelopment	45/77 (58.4)
Obstruction	26/77 (33.8)
Loss of integrity	6/77 (7.8)
Fetal vascular supply	20 (20.6)
Maldevelopment	5/20 (25.0)
Obstruction	12/20 (60.0)
Loss of integrity	3/20 (15.0)

findings in the study population. Placentae showing signs of PUP were not statistically significantly different from those without signs of PUP with regard to weight (383.5 g *vs* 396.2 g; $P = 0.45$) or fetoplacental weight ratio (5.8 *vs* 6.2; $P = 0.053$). Similarly, when expressed as GA centiles, these parameters were not statistically significantly different between the two groups (weight, 3.20 *vs* 3.26; $P = 0.95$ and fetoplacental weight ratio, 34.3 *vs* 37.1; $P = 0.62$).

Table 3 presents the ultrasound findings before delivery and the perinatal outcomes, according to the presence or absence of PUP. Of note, the proportion of cases requiring emergency delivery for NRFS differed significantly 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 than in the group without signs of PUP (33.3% *vs* 14.3%; $P = 0.023$). The proportion of newborns with

Table 3 Ultrasound including Doppler findings before delivery and perinatal parameters of 126 small-for-gestational-age pregnancies, according to presence or absence of histological signs of placental underperfusion (PUP)

Parameter	*PUP* (n = *84*)	*No PUP* (n = *42*)	P†
EFW (g)	2074 ± 411	2277 ± 339	0.007
EFW centile	1.51 ± 2.2	2.32 ± 2.6	0.1
UA-PI	1.05 ± 0.24	0.97 ± 0.21	0.07
MCA-PI	1.54 ± 0.35	1.51 ± 0.47	0.69
CPR	1.57 ± 0.52	1.65 ± 0.51	0.453
Pre-eclampsia	17 (20.2)	1 (2.4)	0.007
Induction of labor	67 (79.8)	35 (83.3)	0.279
GA at delivery (weeks)	37.8 ± 1.9	37.7 ± 6.1	0.925
Birth weight (g)	2161 ± 448	2394 ± 353	0.04
Birth-weight centile	1.5 ± 1.9	2.8 ± 2.7	0.02
Emergency delivery for NRFS*	37 (46.3)	9 (23.1)	0.015
Neonatal metabolic acidosis	28 (33.3)	6 (14.3)	0.023
NICU admission	29 (34.5)	6 (14.3)	0.017
MAIN score ≥ 150	26 (31.0)	6 (14.3)	0.043

Data given as mean ± SD or *n* (%). *Cases with elective Cesarean section ($n = 7$) not included in the denominator. †Student's *t*-test or Pearson's chi-square test, as appropriate. CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; MAIN, morbidity assessment index for newborns; MCA, middle cerebral artery; NICU, neonatal intensive care unit; NRFS, non-reassuring fetal status; PI, pulsatility index; UA, umbilical artery.

a moderate to severe MAIN score (≥ 150) was also significantly higher in the PUP group than in the group without signs of PUP (31.0% *vs* 14.3%; $P = 0.043$). Figure 1 shows the distribution of MAIN scores according to the presence or absence of PUP. The median MAIN scores differed significantly between the 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, in which we have previously found that the degree of placental damage is not reflected in the UA Doppler indices[11], the presence of histological signs of PUP implies 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-onset SGA babies correspond with true late-onset FGR secondary to placental insufficiency.

Previous studies have shown that PUP and adverse perinatal outcome are linked to a variety of clinical conditions[30,31,34–38]. This study extends this association to late-onset FGR, even in the presence of normal UA Doppler ultrasound. 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[39]. Taken together, this evidence points to PUP as a surrogate of placental insufficiency and indicates that it is worthy of targeting in clinical practice. These findings are particularly

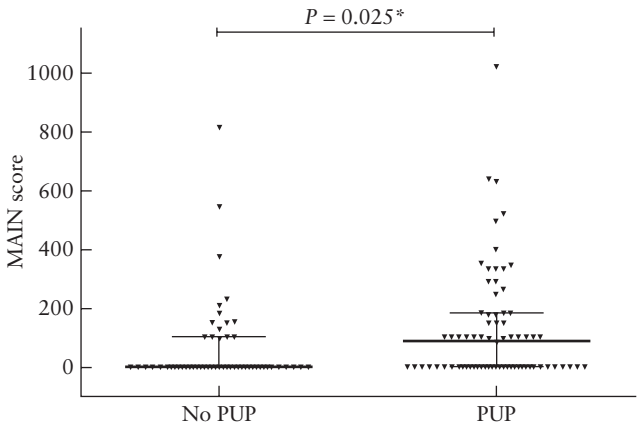

Figure 1 Morbidity assessment index for newborns (MAIN) score distribution according to presence of placental underperfusion (PUP). MAIN score < 150, no or normal morbidity; MAIN score ≥ 150, mild to severe morbidity. *Mood's median test. Median and interquartile range are shown.

Table 4 Multivariable median regression analysis of association between placental underperfusion (PUP) and morbidity assessment index for newborn log-transformed scores, adjusting for potential confounders

Potential confounder	*Estimate*	*Standard error*	P
PUP	1.2	0.53	0.026
Nulliparity	0.64	0.52	0.217
Smoker	−0.94	0.55	0.093
Cerebroplacental ratio	0.31	0.61	0.611
Birth-weight centile	−0.11	0.1	0.289

important because late-onset SGA occurs in 5–10% of all pregnancies, and this pattern has been documented in roughly two-thirds of placentae[12].

We found that UA pulsatility was higher in the PUP group, albeit not significantly. The precise reason why maternal underperfusion almost always corresponds with abnormal UA Doppler indices and results in early-onset FGR, although rarely in late-onset FGR, is open to debate, but because the nature of the pathology is similar, one might speculate that the extent of the pathology is key. Indeed, animal models and mathematical projections of placental vascular obliteration have suggested that UA Doppler abnormalities become evident only in advanced stages of placental dysfunction[40,41]. Nevertheless, term SGA babies suffering lesser degrees of placental underperfusion, and that escape detection on Doppler ultrasound, may be exposed to subtle, but chronic, hypoxia and undernutrition, with delayed neurological consequences[39].

SGA is a descriptive term that is applied to all infants with a birth weight below a given threshold (generally the 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 as 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 grouping together pregnancies with and without placental insufficiency, which, in essence, collapses several phenotypes into one single condition. As with other obstetric syndromes[42], we believe that the key to more effective clinical management of pregnancies with late-onset SGA lies in identifying biomarkers that reflect the placental-insufficiency phenotype, as supported by histological evidence of PUP.

In The Netherlands, a large trial that 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 the two strategies[18,43]. This evidence has been translated into guidelines that generally recommend induction of labor at 37–38 weeks[44–46], in order to avoid the rare but devastating outcome 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 fulfilment in the birth experience[47]. In a previous study, we found that in late-onset SGA pregnancies, abnormal uterine artery PI and abnormal umbilical vein flow are surrogates of PUP[13]. We speculate that prenatal selection 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 (uterine artery Doppler or umbilical vein) was not obtained for a substantial fraction of our cases. This information may have shed additional light on 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 perinatal study including late-onset SGA fetuses, we demonstrated that both abnormal MCA-PI and maternal levels of placental growth factor were associated with an adverse perinatal outcome, with respect to neonatal acidosis and NRFS requiring an emergency Cesarean section[48]. 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 UA Doppler indices, signs of PUP imply a higher neonatal morbidity. These findings should allow better phenotypic profiling of FGR cases among the general population of late-onset SGA fetuses.

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