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Neurodevelopmental outcomes of near-term small-for-gestational-age infants with and without signs of placental underperfusion

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ABSTRACT

Objective: To evaluate 2-year neurodevelopmental outcomes of near-term, small-for-gestational-age (SGA) newborns segregated by presence or absence of histopathology reflecting placental underperfusion (PUP).

Patients and methods: A cohort of consecutive near-term (≥34.0 weeks) SGA newborns with normal prenatal umbilical artery Doppler studies was selected. All placentas were inspected for evidence of underperfusion and classified in accordance with established histologic criteria. Neurodevelopmental outcomes at 24 months (age-corrected) were then evaluated, applying the Bayley Scale for Infant and Toddler Development, Third Edition (Bayley-III) to assess cognitive, language, and motor competencies. The impact of PUP on each domain was measured via analysis of covariance, logistic and ordinal regression, with adjustment for smoking, socioeconomic status, gestational age at birth, gender, and breastfeeding.

Results: A total of 83 near-term SGA deliveries were studied, 46 (55.4%) of which showed signs of PUP. At 2 years, adjusted neurodevelopmental outcomes were significantly poorer in births involving PUP (relative to SGA infants without PUP) for all three domains of the Bayley scale: cognitive (105.5 vs 96.3, adjusted-$p = 0.03$), language (98.6 vs 87.8, adjusted-$p<0.001$), and motor (102.7 vs 94.5, adjusted-$p = 0.007$). Similarly, the adjusted likelihood of abnormal cognitive, language, and motor competencies in instances of underperfusion was 9.3-, 17.5-, and 1.44-fold higher, respectively, differing significantly for the former two domains.

Conclusions: In a substantial fraction of near-term SGA babies without Doppler evidence of placental insufficiency, histologic changes compatible with PUP are still identifiable. These infants are at greater risk of abnormal neurodevelopmental outcomes at 2 years.

1. Introduction

Neurodevelopmental problems arising from intrauterine insults are a major socioeconomic burden [1]. Small-for-gestational-age (SGA) infants more often display lower intelligence levels, poor academic performance, low social competence, behavioral problems [2–4], and long-term cognitive impairments [5–10]. Such deficits are well documented in preterm SGA infants, who are more inclined (vs preterm, normal-sized infants) to show behavioral [11,12], sensory [13,14], and cognitive [5,7,8,15] dysfunctions later in life. However, emerging evidence suggests that near-term SGA babies are also at higher risk for adverse neurodevelopmental outcomes [10,16–18]. This prospect is of particular concern, given that, according the definition used, between 3 and 10% of newborns are small at birth. A recently published meta-analysis, pooling several studies varying in neurodevelopmental measures, showed that standardized scores in term SGA babies were distinctly below (0.35 standard deviation [SD]) those of normal-sized controls [19].

Abbreviations: AGA, appropriate for gestational age; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; GA, gestational age; IUGR, intrauterine growth restriction; OR, odds ratio; SD, standard deviation; SGA, small for gestational age; PUP, placental underperfusion; UA, umbilical artery.

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Near-term SGA babies overall are thought to include both constitutionally small newborns as well as infants with true intrauterine growth restriction (IUGR), whereby in most cases fetal genetic growth potential suffers due to placental insufficiency [20]. The clinical standard to assess placental function is umbilical artery (UA) Doppler study, which is used in preterm babies to reliably distinguish between SGA and IUGR [21–23]. However, UA Doppler results are less decisive in differentiating near-term SGA and IUGR [24]. Neurobehavioral competencies at birth [25] and neurodevelopment at 2 years of life [18] may subsequently be diminished, even if Doppler studies are normal. This underscores a need to focus on signs of placental dysfunction, which may serve as markers of neurodevelopmental risk in near-term SGA births.

In both preterm [26] and term [27,28] births, placental insufficiency is attributable to underperfusion. Related histologic manifestations in placentas of preterm babies correspond with observed deficits in mental development at 2 years and rightly should be factored into the neurodevelopmental status of markedly preterm infants [29]. However, there is a dearth of evidence linking histologic signs of PUP to neurodevelopmental outcomes in near-term births.

The objective of this study was to evaluate 2-year neurodevelopmental outcomes in near-term, small-for-gestational-age (SGA) newborns segregated by presence or absence of PUP-related histopathology.

2. Patients and methods

2.1. Participants

A cohort of consecutive SGA singleton deliveries (gestational age [GA] $\geq$ 34 weeks) was recruited between January, 2010 and November, 2012 at a single institution. In each instance, SGA birth was suspected prenatally and confirmed as birth weight <10th percentile by local standards [30]. Pregnancies were dated according to first-trimester crown–rump length [31], while estimated fetal weight (EFW) was calculated using the Hadlock formula [32]. Only those with normal UA pulsatility index at diagnosis were included (<95th percentile [33]). Parental drug consumption, congenital malformations (including chromosomopathies and infections), chorioamnionitis, and transition to abnormal UA Doppler study during prenatal follow-up were criteria for exclusion. The study protocol was approved by the hospital Ethics Committee, and written consent was obtained for the study from all recruited patients.

2.2. Placental function assessment

In all instances, prenatal Doppler ultrasound studies were performed by experienced operators (SS and FF), using a General Electric Voluson E8 (GE Medical Systems, Zipf, Austria) ultrasonograph equipped with 6-2 MHz linear curved-array transducer. UA pulsatility index was calculated from at least three consecutive waveforms obtained from a free-floating segment of umbilical cord, in the absence of fetal movements and at an insonation angle of <30°. Values considered normal were below 95th percentile [33] at the last examination within one week of delivery.

2.3. Data collection and definitions

Baseline maternal characteristics, including age, ethnicity, body mass index (BMI), parity, maternal and paternal smoking, known chronic disease (i.e., hypertension, diabetes mellitus, renal disease, and autoimmune disorders), and obstetric history were recorded in the hospital database upon study admittance. Data on postpartum follow-up or subsequent complications of pregnancy, ultrasound evaluations, and perinatal progress were also collected prospectively. Preeclampsia was defined in accordance with guidelines of the International Society for the Study of Hypertension in Pregnancy [34].

2.4. Management

All pregnancies were monitored monthly. Labor induction (recommended after 37 weeks) was achieved by cervical ripening with a slow-release prostaglandin E2 vaginal pessary (10 mg). Oxytocin induction was indicated thereafter, for failure of labor onset within 18 h. Cesarean or operative vaginal delivery for non-reassuring fetal status was indicated on abnormal fetal heart-rate tracing [35] and a pH of fetal scalp blood <7.20 during intrapartum monitoring.

2.5. Placental evaluation

Placental examinations adhered to standard laboratory protocol. Fresh and trimmed (after removal of the membranes, cord, and any blood clots, the placenta) placental weight were recorded. Trimmed placental weight centiles were assigned based on GA-specific placental weight charts [36]. The fetoplacental weight ratio (birth weight:fresh placental weight) was also expressed as a percentile, drawn from GA-specific ranges [37].

Placentas were fixed in 10% buffered formalin. After gross examination, routine samples of each specimen were taken for routine processing: one transverse section of cord, one rolled strip of membranes, and three blocks of villous parenchyma. All macroscopic lesions were sampled as well. Finished slides were hematoxylin and eosin-stained. A single senior pathologist (AN) supervised all examinations.

For purposes of this study PUP-related histologic manifestations were further designated as maternal or fetal in origin [38,39]:

Among maternal vascular supply disruptions, specific vascular alterations qualifying for maternal vascular maldevelopment were: 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. Specific vascular alterations qualifying for maternal vascular obstruction were: syncytial knots 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 qualifying for maternal vascular loss of integrity were: arterial rupture (abruption placenta), venous rupture (acute chronic marginal abruption).

Among fetal vascular supply disruptions, lesions qualifying for maldevelopment were: chorioangioma, chorioangiosis and distal villous immaturity. Lesions qualifying for obstruction were considered those secondary to vascular thrombo-occlusive disease (thrombosis of chorionic plate and stem villous channels and villous avascularity affecting large groups).

When any of these lesions above described were present, the placental was considered to qualify for PUP.

To address reproducibility, a sampling of 20 placentas was selected at random for blinded re-evaluation by the same pathologist. Overall agreement was 90% (18/20), with limited underdiagnosis (1/20, 5%) or overdiagnosis (1/20, 5%) relative to second attempts.

2.6. Neurobehavioral outcomes

Developmental function was evaluated at a corrected age (SD) of 24 [2] months, utilizing the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), a revision of the prior edition (Bayley, 1993) [40]. The Bayley-III is an individually administered test of infant competency across three domains: cognitive, language, and motor development. All evaluations were performed by one of three trained psychologists, each blinded to perinatal outcomes and pathologic findings. According to the test manual, abnormal neurodevelopment outcomes were defined as a Bayley score below 1 SD (<85).

2.7. Statistical analysis

Student's-*t* test for independent samples and Pearson-χ^2 or exact Fisher's tests were used to compare quantitative and qualitative data, respectively. Multivariate analysis was conducted with Multiple Analysis of Covariance (MANCOVA) and logistic regression; a model was run for each domain set (cognitive, language, and motor) with the study group as a factor (underperfusion vs no underperfusion) and the following variables as covariates: (i) parental smoking ($\geq$1 cigarettes/day); (ii) low socioeconomic class, defined as routine occupations, long-term unemployment, or never employed (UK National Statistics Socio-Economic Classification); (iii) gestational age at delivery; (iv) gender; and, (iv) breastfeeding ($\geq$3 months after delivery). For MANCOVA models, multivariate significance of the *F*-value was assessed with Wilk's lambda *p*-value. The odds ratio (OR) of having low scores (<1 SD below mean) was assessed by logistic regression, adjusting for the same set of covariates. The impact of placental underperfusion on neurodevelopment was also tested by ordinal regression, where the association between the presence of underperfusion and the number of abnormal domains was adjusted by the same set of covariates describe above. Standard software (SPSS 17.0, SPSS Inc., Chicago, IL, USA) was engaged for all statistical computations.

3. Results

A total of 104 potential SGA pregnancies were recruited (mean GA [SD], 33.4 [2.0] weeks; range 32–36.3 weeks). Of these, 11 were excluded for various reasons, including abnormal UA Doppler study during follow-up ($n = 2$), birth weight >10th percentile ($n = 6$), clinical chorioamnionitis ($n = 1$), and lack of parental consent for required placental exam ($n = 2$). Another 10 births were lost during follow-up, having no means of contact for neurocognitive