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Placental findings in late-onset SGA births without Doppler signs of placental insufficiency

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ABSTRACT

Objectives: To describe placental pathological findings in late-onset small-for-gestational age (SGA) births for which Doppler signs of placental insufficiency are lacking.
Methods: A series of placentas were evaluated from singleton pregnancies of SGA births (birth weight below the 10th percentile) delivered after 34 weeks with normal umbilical artery Doppler (pulsatility index below the 95th percentile), that were matched by gestational age with adequate-for-gestational age (AGA) controls. Using a hierarchical and standardized system, placental lesions were classified histologically as consequence of maternal underperfusion, fetal underperfusion or inflammation.
Results: A total of 284 placentas were evaluated (142 SGA and 142 AGA). In the SGA group, 54.2% (77/142) of the placentas had weights below the 3rd percentile for GA while it was a 9.9% (14/142) in the AGA group ($p < 0.001$). Only 21.8% (31/142) of SGA placentas were free of histological abnormalities, while it was 74.6% (106/142) in the AGA group ($p < 0.001$). In the abnormal SGA placentas (111/142) there were a total of 161 lesions, attributable to MUP in 64% (103/161), FUP in 15.5% (25/161), and inflammation in 20.5% (33/161).
Discussion: In most placentas of term SGA neonates with normal UA Doppler histological abnormalities secondary to maternal underperfusion prevail, reflecting latent insufficiency in uteroplacental blood supply. This is consistent with the higher risk of adverse perinatal outcome reported in this population and underscores a need for new markers of placental disease.
Conclusions: A significant proportion of late-onset SGA births with normal umbilical artery Doppler may still be explained by placental insufficiency.

1. Introduction

The placenta has been described as a "diary of intrauterine life", with the potential to reflect many aspects of fetal development [1]. Proper development of the placenta encourages normal intrauterine growth, whereas aberrant stimuli or insults may produce varied outcomes through adaptive responses. Intrauterine growth restriction (IUGR), the failure to achieve the biologically endorsed potential growth, exemplifies this tenet and is the most studied scenario. In the vast majority of cases, IUGR is due to placental insufficiency [2]. Accordingly, placental weight, in absolute terms and relative to birth weight, has long been recognized as influential in perinatal outcome [3,4].

To clarify the extent of this relationship, studies have recently begun to differentiate early from late IUGR [5,6]. Early-onset IUGR, presenting prior to 34 weeks' gestation, is marked by escalating blood flow resistance in the umbilical artery (UA)—an important determinant of adverse perinatal outcome [7–10]. In contrast, placental insufficiency in late-onset IUGR often goes undetected by UA Doppler scan [6], posing a problem in assessing those fetuses

Abbreviations: SGA, small for gestational age; GA, gestational age; IUGR, intrauterine growth restriction; EFW, estimated fetal weight; BW, birth weight; FUP, fetal underperfusion; MUP, maternal underperfusion; UA, umbilical artery.

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with an estimated fetal weight below a given threshold, that is, the small-for-gestational-age (SGA) infants. This group comprises both cases with true growth restriction cases and constitutional small babies. Formerly considered a benign condition [11], it is now widely acknowledged that significant numbers of near-term SGA infants with normal UA Doppler studies qualify as late-onset IUGR and thus are at risk of adverse perinatal outcomes [7,12,13].

In past years, many efforts have been made to classify histological abnormalities of the feto-maternal vasculature, correlating such findings with placental effects [1,14–17]. The Redline classification (adopted by the International Federation of Placenta Associations and the Perinatal Section of Society for Pediatric Pathology) is one of the most accepted systems [1,18]. It provides a hierarchical and standardized classification with acceptable reproducibility [19,20] and good clinical correlation [1].

Despite a broad general body of literature referencing placentas of IUGR pregnancies [17,21–30], there is a surprising void in late-onset SGA with normal UA Doppler. This subset is far more prevalent than early-onset forms and it accounts for most instances of perinatal morbidity attributable to placental insufficiency [31], being a major source of perinatal mortality [32]. An investigation is therefore warranted, given the clinical relevance and the as yet uncertain pathogenesis of this particular state.

The objective of this study was to describe gross and histologic placental findings in late-onset SGA births for which no signs of placental insufficiency were evident by UA Doppler studies.

2. Methods

2.1. Study population

Between January, 2011 and January, 2012, consecutive singleton pregnancies were selected, based on low (<10th percentile) values for estimated fetal weight (EFW) at routine third trimester ultrasound (30–34 weeks' gestation) and birth weight (BW), adjusting for gestational age (GA) and gender according to local standards [33]. Qualifying infants were those delivered after 34 weeks of gestation, with normal UA Doppler (defined as UA pulsatility index [PI] below the 95th percentile) [34] in the week prior to delivery. Pregnancies complicated by neonatal chromosomal or structural abnormalities, premature rupture of membranes, and suspected intrauterine infection was excluded. As controls, singleton pregnancies with a birth weight above the 10th percentile were included during the same study period, matched with cases by GA at delivery (±1 week). The hospital ethics committee approved the study protocol, and written consent was obtained for the study from all recruited patients (IRB 2011/4422).

2.2. Ultrasound evaluation

Pregnancies were dated by fetal crown-rump lengths measured at first trimester [35], and EFW was calculated using the Hadlock formula [36]. All pregnancies were monitored by serial prenatal ultrasound exams, performed by one of three experienced operators (M.P., S.S., or F.F.) and utilizing either a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or a General Electric Voluson E8 (GE Medical Systems, Zipf, Austria) unit equipped with a 6-2 MHz linear curved-array transducer. UA Doppler recordings were done in the plane of a free-floating cord loop, in absence of fetal movements and with voluntary suspension of maternal breathing. The PI was automatically calculated from three or more consecutive waveforms, aiming as closely as feasible for zero-degree insonation. A Doppler examination was performed within 7 days of each delivery.

2.3. Data collection and definitions

Baseline maternal characteristics, including age, ethnicity, body mass index (BMI), parity, smoking status, 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. In addition, data on follow-up or subsequent complications of pregnancy, ultrasound evaluations, and perinatal progress were collected prospectively. Preeclampsia was defined in accordance with guidelines of the International Society for the Study of Hypertension in Pregnancy [37].

2.4. Management

All pregnancies were monitored fortnightly with fetal growth evaluation, amniotic fluid assessment and umbilical artery Doppler. 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 was performed for non-reassuring fetal status, based on abnormal fetal heart rate tracing [38] and adverse fetal scalp blood pH during intrapartum monitoring.

2.5. Placental evaluation

Placental examinations were performed according to a standard laboratory protocol. Fresh weights were recorded, and percentiles were determined by GA-specific placental weight charts [39]. Weights below the 3rd percentile for GA at delivery were considered qualifying for severe placental smallness. The calculated ratio of placental weight to fetal birth weight was also expressed as a percentile derived from GA-specific ranges [39] and was considered abnormal if below the 3rd percentile for GA.

Placentas were fixed in buffered formalin. After gross examination, routinely samples were obtained from each specimen: one transverse section of cord, one rolled strip of membranes and three blocks from the placental parenchyma. Additional blocks were taken from all macroscopic lesions. Samples were routinely processed for histology and slides were stained using hematoxylin and eosin. A single senior pathologist (A.N.) supervised all examinations. For purposes of this study, placental lesions were histologically designated as maternal, fetal, or inflammatory in origin [1,18]. Placental findings signaling maternal underperfusion (MUP) consisted of specific vascular-related alterations (acute atherosis and mural hypertrophy), massive perivillous fibrinoid deposition (or maternal floor infarction) [basal layer of fibrinoid material involving >50% of the placental maternal surface] or villous changes (numerous syncytial knots [affecting >50% of the terminal villi], villous agglutination, 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]). Other vascular pathology (thrombosis of chorionic plate and stem villous channels) and villous changes (avascularity) were characteristic of fetal underperfusion (FUP). Inflammatory lesions principally entailed acute chorioamnionitis, corresponding with early inflammation of decidua capsularis as a maternal response that later spreads to contiguous membranes. The latter is usually clinically inapparent, but when umbilical and chorionic vessels are involved, a fetal inflammatory response syndrome is triggered. In addition, villitis of unknown cause or chronic villitis were identified by virtue of inflammatory changes in placental vessels of fetal derivation. If more than one category was applicable, the placenta was allocated by a panel of experts to a single overriding category (AN, EG and FF). To address reliability, a sample of 20 placentas were randomly selected and blindly rereviewed by the same pathologist: overall agreement was 85% (17/20), underdiagnosis occurred in the first relative to the second review occurred in 2 cases (10%) and overdiagnosis in one case (5%).

2.6. Statistical analysis

All statistical analyses were conducted using IBM SPSS 20.0 (New York, USA) software, and graphs were generated with GraphPad Prism 5 (California, USA). Data were expressed as numeric (%) or mean (standard deviation [SD]) values, as appropriate. Differences in continuous and categorical variables were evaluated by Students-t, Pearson-χ^2 and Mann–Whitney U tests, as appropriate. Statistical significance was set at $p \leq 0.05$.

3. Results

A total of 156 late-onset SGA pregnancies were recruited for study. Of these, 14 were excluded because of normal birth weight ($n = 6$), premature rupture of membranes ($n = 2$), spontaneous preterm delivery ($n = 2$), abnormal UA Doppler scan ($n = 3$), or suspected chorioamnionitis ($n = 1$), leaving 142 cases for analysis that were matched by gestational age with 142 controls.

Baseline and perinatal characteristics of the study and control groups are shown in Table 1. Of note, the last ultrasound before delivery was performed at a mean GA of 38.2 (SD 1.2) weeks, with a mean EFW at 2.2 (SD 2.4) percentile. In the study group, labor was induced in 118 (83.1%) births, for a mean GA at delivery of 38.6 (±1.2) weeks. During labor, 52 of the 131 (38.8%) births in which a vaginal delivery was attempted required emergency cesarean section for non-reassuring fetal status.

Mean values of placental weight (356 [SD 93] vs. 539 [SD 121]; $p < 0.001$) and placental weight-birth ratio (6.2 [SD 3.4] vs. 17 [SD 3]; $p < 0.001$) significant differed between cases and controls. These parameters expressed as percentiles were 7.7 [SD 12.9] vs. 49 [SD 12.9] ($p < 0.001$) and 42.3 [SD 33.6] vs. 52 [SD 18] ($p = 0.002$), respectively. In 77 (54.2%) cases and 14 (9.9%) controls ($p < 0.001$) placental weights were below the 3rd percentile for GA. Similarly, 14 (9.9%) cases and 7 (4.9%) controls ($p = 0.11$) displayed placental weight-birth ratios below the 3rd percentile.