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ORIGINAL ARTICLE

Fetal placental inflammation is associated with poor neonatal growth of preterm infants: a case-control study

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Abstract

Objective: To determine whether there is an association between histological chorioamnionitis (HCA) and postnatal growth of preterm infants in the neonatal period.
Method: This case–control study is part of a larger prospective histological study on placentas performed in all deliveries prior to 32 weeks of gestation. Eligible cases involved all placentas with a diagnosis of HCA. Control subjects were those without HCA, matched 1:1 with case subjects according to gestational age (±1 week). Placental inflammatory status and serial weight gain were analyzed for all infants during the first four postnatal weeks. Based on placental inflammation extension, HCA was defined as maternal HCA (MHCA) or fetal HCA (FHCA).
Results: Of the 320 mother–infant pairs, 71 (22.1%) presented with HCA (27 MHCA and 44 FHCA). Decreases in weight gain at 21 and 28 days were associated with the presence of FHCA (β coefficient $\pm$ SE $= -4.40 \pm 2.21$, $p = 0.05$ and -6.92 ± 2.96, $p = 0.02$, respectively), whereas no significant differences were found between MHCA and no-HCA groups. FHCA and MHCA were not identified as risk factors of weekly weight gain, after adjusting for possible confounders (maternal ethnicity, parity, smoking during pregnancy, infant gender, IUGR status, SGA status, antenatal steroids, total fluid intake, late-onset sepsis, BPD).
Conclusions: We found an association between fetal placental inflammation and poor neonatal growth but we were not able to identify a specific week wherein weight gain could be mostly affected. Placental findings may be used to identify preterm infants at risk of postnatal growth failure.

Keywords

Intrauterine inflammation, postnatal growth, preterm infant

History

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Introduction

Most very preterm infants remain in the neonatal intensive care unit (NICU) during the time that would be equivalent to their third trimester. In that period, one of the goals of the caregivers is to help the infant to achieve a growth velocity similar to intrauterine growth velocity. However, most infants gain less weight than third trimester fetuses in utero [1].

Postnatal growth failure (weight below the 10th centile for postmenstrual age) is extremely common in very preterm infants [2]. Data from the National Institute of Child and Human Development (NICHD) Neonatal Research Network indicate that 16% of extremely low birth weight infants (ELBWI) are small for gestational age at birth, but by 36 weeks corrected age, 89% have growth failure [3].

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Growth in the NICU influences neurodevelopmental and growth outcomes of ELBWI [4], and may have significant effects on health in childhood and adulthood [5–8].

Ehrenkranz et al. investigated the effect of growth rates during hospitalization on neurodevelopmental outcome in a large cohort of infants 500–1000 g at birth [9]. Logistic regression analyses, controlled for potential demographic and clinical co-founders, and adjusted for center, suggested that in-hospital growth velocity rates exerted a significant, and possibly independent, effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age.

Although beneficial in the short term, catch-up growth may be harmful in the long term. In fact, rapid rates of growth in childhood reportedly increase the risk for cardiovascular disease, hypertension, obesity, and type 2 diabetes later in life [1,7,10].

Intrauterine growth restriction (IUGR), postnatal reduced energy support, and presence of one or more major morbidities (i.e. bronchopulmonary dysplasia – BPD, severe intraventricular hemorrhage – IVH, necrotizing enterocolitis – NEC or late-onset infections, early and late-onset sepsis) are

associated with poor postnatal growth [11]. However, the mechanisms underlying the suboptimal postnatal growth in preterm infants are not completely understood [1,3,11].

Chorioamnionitis is the inflammatory response to an acute inflammation of the membranes and chorion of the placenta. It is involved in about 40–70% of preterm births and in about 1–13% of term births. Its incidence decreases with increasing gestational age, ranging from more than 50% at viability (23–24 weeks) to about 5% at term (>37 weeks) [12]. At our institution, histological studies on placentas are routinely performed in all deliveries prior to 32 weeks of gestation. This cut-off was chosen because eevidence of infection is higher in placentas obtained from women delivering at the lowest gestational age [12], and because this preterm population has the highest risk of adverse outcomes.

There is evidence that intrauterine inflammation plays a role in fetal growth restriction [8], and a recent cohort study including preterm infants with gestational age of <37 weeks showed that placental inflammation was associated with poor neonatal growth [8]. As intrauterine inflammation and postnatal growth failure are more frequently detected in very preterm infants [12], we hypothesized that this association could be more relevant in infants ≤32 weeks gestation. Furthermore, in agreement with previous work [13], we chose to focus on the weight gain during the first month of life because growth velocity is mostly impaired in this phase [14], and because the effect of antenatal exposure to inflammation is reasonably limited to the early postnatal period.

In this case–control study, we sought to determine whether histologic chorioamnionitis (HCA) is associated postnatal growth of preterm infants in the neonatal period. Furthermore, we assessed whether the magnitude of this association was different during the first 4 weeks of life.

Materials and method

Study population

This study is part of a larger prospective histological study on placentas performed in all deliveries prior to 32 weeks of gestation at the level III Maternity Hospital of the Institute of Gynecology and Reproductive Science of Padua University and consecutively admitted to the NICU at the Pediatric Department of Padua University from January 2004 to October 2008, and identified from a prospectively managed database [15].

For the present study, eligible cases involved all neonates born at <32 completed weeks of gestation with a placental diagnosis of HCA. Patients with major congenital defects were excluded from the study.

Control subjects were consecutive preterm infants <32 completed weeks of gestation without placental HCA, matched 1:1 with case subjects according to gestational age (±1 week).

The Institutional Review Board approval was obtained.

Demographic and clinical characteristics

After written informed consent was obtained, all maternal, obstetric and neonatal records were reviewed. Serial infant body weight measurements, and fluid intake were recorded from standardized flowsheets that contained daily data from birth to discharge.

The demographic and clinical variables examined included those suspected or known to affect growth, such as gestational age, birth weight, intrapartum management, pregnancy and neonatal complications. A positive exposure to prenatal steroid treatment was defined as ≥1 dose of betamethasone before delivery. Gestational age was calculated on the basis of a first trimester ultrasonographic examination and known dates of last menstrual period.

Clinical chorionamnionitis was defined as the presence of maternal fever (>38 °C) in addition to two other signs (uterine fundal tenderness, maternal heart rate >100 beats/min, fetal heart rate >160 beats/min and purulent/foul amniotic fluid) [16].

Subjects were classified as IUGR if the estimated fetal weight was <10th percentile and the umbilical artery pulsatility index (PI) >2 standard deviations above the mean [17,18].

Small for gestational age (SGA) was defined as birth weight of ≤10th percentile on the Italian Society of Neonatology neonatal growth chart [19].

BPD was defined as oxygen requirement at corrected age of 36 weeks. NEC was defined as stage II or above by using Bell's classification [20], and severe IVH was defined as grade 3 to 4 according to the cranial ultrasound classification described by Papile et al. [21].

Definitions of histological chorionamnionitis

The placentas were regularly submitted for histopathological diagnosis in all cases of preterm delivery. All neonates included in the analysis had placental histopatological analysis performed. An experienced pathologist in placental pathology examined and sampled the placentas, and issued the report according to the Guidelines of the College of American Pathologists [15,22].

Placental histological examination included a minimum of three cross-sections of the umbilical cord taken from fetal and placental side of the umbilical cord, three membrane rolls and a sample of the chorionic plate. The presence and location of inflammatory findings were accounted for the worst scored area and recorded by using well-established algorithms and a standardized abstraction form [15].

Placental inflammatory status was classified according to the following definitions: (1) no inflammatory response included births without any of the placental findings listed below for maternal histological chorionamnionitis (MHCA) and fetal histological chorionamnionitis (FHCA); (2) MHCA included births with subchorionitis, chorionamnionitis, deciduitis, or free membranitis (and the absence of funisitis or chorionic plate vasculitis); and (3) FHCA included births with placental evidence of inflammation extending to umbilical cord or chorionic plate [13,23].

Weight outcomes

According to Mestan et al.'s study [13], we calculated percentage weight gain at day 21 and 28 as follows: % weight gain = [(postnatal day – birth weight)/birth weight] × 100. % weekly weight gain was calculated as [(weight at day 7 of the

week – weight at day 1 of the week)/weight at day 1 of the week] × 100. Postnatal growth failure was defined as a weight below the 10th centile at 36 completed postmenstrual weeks. As the most part of our preterm patients are transferred to level II hospitals at different post-conceptional weeks for the last part of hospitalization, we chose the cut-offs of the first 4 postnatal weeks and the 36 postmenstrual weeks to make the growth's assessment among the groups more homogeneous.

Statistical methods

Continuous data were normally distributed and they were expressed as mean ± SD, whereas categorical data as number (%). Continuous data and categorical data were compared among the three groups (MHCA, FHCA, no HCA) using ANOVA test and Fisher's test; when appropriate, group-by-group comparisons were performed by using, respectively, Student's t test and Fisher test with Bonferroni's adjustment for multiple comparisons. In facts, Type I error increases when multiple comparisons are performed; Bonferroni's correction is a conservative method to adjust the p-values obtained in those multiple comparisons by multiplying them for the number of possible group-by-group comparisons (in the present study, the number was 3). A regression model was estimated to identify the independent effect of HCA on percentage weight gain, adjusting for the following possible confounders: maternal race/ethnicity, parity, smoking during pregnancy, infant gender, IUGR status, SGA status, antenatal steroids, total fluid intake, late-onset sepsis, BPD. The magnitude of difference in weight gain from the reference group (no-HCA) was expressed as β coefficient. A p value less than 0.05 was considered significant. Statistical analysis was performed by using R 2.12 software.

Results

Study group and clinical findings

Complete clinical and histological data were available for 320 mother–infant pairs. Of these, 71 (22.1%) presented with HCA and 249 (77.9%) without HCA (no-HCA). Of the 249 cases without HCA, 71 consecutive mother-infant pairs, matched with HCA cases for gestational age (±1 week), were considered as controls.

Of the 71 cases with HCA, 27 (38.0%) had MHCA and 44 (62.0%) FHCA. Maternal and neonatal characteristics are reported in Table 1.

Statistically significant differences were observed among groups about the rate of IUGR ($p = 0.006$), SGA ($p = 0.01$), preeclampsia or eclampsia or Hellp syndrome ($p < 0.001$) and antibiotic treatment ($p = 0.03$).

The comparison of birth weight, prolonged rupture of membranes and spontaneous preterm labour revealed small differences among the three groups that were very close to statistical significance ($p = 0.06$, $p = 0.06$, and 0.07, respectively).

Association between placenta histopathological features and postnatal weight

The association between placental inflammatory status and weight gain are reported in Table 2.

At both 21 days and 28 days, the weight gain from birth was significantly lower in FHCA than in the no-HCA group ($p = 0.04$ and $p = 0.05$ respectively, adjusted for multiple comparisons), whereas no significant differences were found between MHCA and no-HCA groups ($p = 0.99$ and $p = 0.99$ respectively, adjusted for multiple comparisons). At 1 postnatal week, a weight decrease was observed in the 3 groups and it was higher in FHCA group than in no-HCA group ($p = 0.04$, adjusted for multiple comparisons). No differences were found among the 3 groups during the 2nd ($p = 0.72$), the 3rd ($p = 0.76$), and the 4th ($p = 0.28$) postnatal week.

Multivariate analysis of the weight gain at 21 and 28 postnatal days is shown in Table 3.

FHCA was a risk factor for weight gain, both during the first 21 days (compared with no-HCA, $p = 0.05$) and the first 28 days (compared with no-HCA, $p = 0.02$), adjusting for possible confounders.

Multivariate analysis of the weekly weight gain is shown in Table 4. FHCA and MHCA were not identified as risk factors of weekly weight gain, after adjusting for possible confounders.

Discussion

In this study, we assessed whether the intrauterine inflammation may influence postnatal growth of preterm infants. Our results show that FHCA is an independent negative factor associated with postnatal growth at 21 and 28 postnatal days. During the first 28 postnatal days, we were not able to identify a postnatal week in which this effect was more relevant.

Extrauterine growth restriction is the most frequent morbidity among very preterm infant survivors at their time of discharge from the hospital [1,4]. Studies to elucidate the causes of poor postnatal growth have been inconclusive [1,11]. Recent research has found an association between extrauterine growth restriction, developmental outcomes, and long-term morbidity [4–6,24]. Low birth weight has also been associated with chronic diseases later in life [5,6,7]. These findings emphasize the critical nature of understanding the phenomenon of extrauterine growth restriction.

Previous works have shown that antenatal factors (i.e. maternal smoking during pregnancy, antenatal steroids exposure, IUGR condition) as well as poor caloric intake and/or a variety of postnatal illness episodes (i.e. severe IVH, NEC, late-onset sepsis, and BPD) are associated with suboptimal postnatal growth [1–4].

To our knowledge, there is only one previous study evaluating the association between placental inflammation and postnatal growth [13]. In their work, Mestan et al. found an independent association between intrauterine inflammation and postnatal growth at 21 and 28 days of life. This association was stronger for subjects born in condition of FHCA than those with MHCA. At 21and 28 days of life, they found a negative difference in percentage weight gain of 4.65% and 5.99%, respectively, between infants with FHCA and those without HCA [13].

In our study, we found a similar difference in percentage weight gain between infants with FHCA and those without HCA at 21 (−4.40%) and 28 (−6.92%) postnatal days.

Table 1. Maternal and infant characteristics according to placental inflammatory response status.

	Placental inflammatory response status			
	None ($n=71$)	MHCA ($n=27$)	FHCA ($n=44$)	p value*
Gestational age, mean ± SD (wks)	27.8 ± 3.5	27.7 ± 2.6	27.8 ± 2.8	0.99
Birth weight, mean ± SD (g)	989 ± 423	1225 ± 602	1121 ± 400	0.06
Male gender, *n* (%)	38 (53.5)	15 (55.5)	25 (56.8)	0.97
Maternal age, mean ± SD (years)	32.9 ± 6.2	32.6 ± 5,6	32.7 ± 6.4	0.81
Race/ethnicity, *n* (%)				
Black	9 (12.7)	5 (18.5)	8 (18.1)	0.61
Caucasian	62 (87.3)	22 (81.5)	36 (81.9)	
Parity, *n (%)*				
0	48 (67.6)	16 (59.2)	23 (52.2)	0.24
≥1	23 (32.4)	11 (40.8)	21 (47.8)	
Smoking during pregnancy, *n* (%)	13 (18.3)	3 (11.1)	6 (13.6)	0.71
Prenatal complications, *n* (%)				
IUGR	15 (21.1)	0 (0.0)	3 (6.8)	0.006
SGA	19 (26.7)	1 (3.7)	5 (11.3)	0.01
Preeclampsia, eclampsia or Hellp syndrome	22 (30.9)	0 (0.0)	1 (2.2)	<0.001
Chronic hypertension	8 (11.2)	1 (3.7)	2 (4.5)	0.40
Diabetes mellitus	5 (7.0)	1 (3.7)	3 (6.8)	0.99
Prolonged rupture of membranes (>24 h)	15 (21.1)	7 (25.9)	18 (40.9)	0.06
Spontaneous preterm labor	23 (32.3)	15 (55.5)	29 (65.9)	0.07
Clinical chorionamninitis, *n* (%)	1 (1.4)	2 (7.4)	11 (25.0)	0.0001
Intrapartum management, *n* (%)				
Antibiotic treatment	12 (16.9)	6 (22.2)	17 (38.6)	0.03
Antenatal steroids	63 (88.7)	24 (88.8)	39 (88.6)	0.99
Cesarean section	64 (90.1)	23 (85.1)	33 (75)	0.10
Tocolysis	10 (14.0)	5 (18.5)	13 (29.5)	0.13
Apgar score<7 at 5 min	11 (15.4)	5 (18.5)	6 (13.6)	0.87
Total fluid/caloric intake at: ml/kg/die				
1st week	135.7 ± 23.9	142.3 ± 19.5	138.9 ± 23.4	0.45
	78 ± 11	83 ± 19	81 ± 14	0.23
2nd week	139.8 ± 20.8	138.8 ± 17.9	141.2 ± 22.3	0.75
	113 ± 14	112 ± 17	117 ± 16	0.29
3rd week	135.1 ± 19.4	142.4 ± 18.7	139.3 ± 14.3	0.10
	117 ± 11	123 ± 15	119 ± 14	0.12
4th week	137.4 ± 15.4	142.0 ± 13.3	135.9 ± 17.2	0.41
	116 ± 18	121 ± 15	114 ± 11	0.18
Neonatal complications, *n* (%)				
Early-onset sepsis	16 (22.5)	5 (18.5)	14 (31.8)	0.39
Late-onset sepsis	8 (11.2)	2 (7.4)	5 (11.3)	0.88
Mortality	4 (5.6%)	3 (11.1)	1 (2.2)	0.27
CLD	22 (30.9)	8 (29.6)	15 (34.0)	0.66
NEC	1 (1.4)	2 (7.4)	3 (6.8)	0.17
Severe IVH	4 (5.6)	1 (3.7)	1 (2.2)	0.86
PVL	2 (2.8)	1 (3.7)	3 (6.8)	0.65
Weight at 36 weeks, mean ± SD (g)	1969 ± 361	2172 ± 451	2022 ± 346	0.13
Postnatal growth failure, *n* (%)	54 (76.0)	14 (51.8)	28 (63.6)	0.07
Maternal milk at discharge, *n* (%)	32 (45.0)	14 (51.8)	23(52.2)	0.72
Length of stay in the NICU, mean ± SD (days)	32 ± 13	29 ± 14	29 ± 11	0.37

*ANOVA.

Table 2. Percentage weight gain (univariate analysis).

	No-HCA ($n=71$)	MHCA ($n=27$)	FHCA ($n=44$)	p value*
Day 0–21	9.5 ± 12.9	7.5 ± 8.8	4.1 ± 8.9	0.03
Day 0–28	23.6 ± 17.1	19.8 ± 9.2	16.7 ± 11.8	0.05
1st week	−7.6 ± 9.4	−11.6 ± 6.5	−11.8 ± 5.7	0.04
2nd week	7.5 ± 7.4	9.8 ± 9.3	8.0 ± 7.8	0.72
3rd week	10.8 ± 7.7	9.7 ± 6.9	10.6 ± 5.3	0.76
4th week	12.8 ± 5.9	10.8 ± 5.5	12.4 ± 4.4	0.28

Data expressed as mean ± SD.
*ANOVA

Table 3. Percentage weight gain at 21and 28 days (multivariable analysis).

	n	β coefficient ± SE*	p value
Day 0–21			
No-HCA	71	Reference	–
MHCA	27	0.18 ± 2.72	0.95
FHCA	44	−4.40 ± 2.21	0.05
Day 0–28			
No-HCA	71	Reference	–
MHCA	27	−2.81 ± 3.65	0.44
FHCA	44	−6.92 ± 2.96	0.02

*Adjusted for maternal race/ethnicity, parity, smoking during pregnancy, infant gender, IUGR status, SGA status, antenatal steroids, total fluid intake, late-onset sepsis, BPD.
no-HCA, no-histological chorioamnionitis

Table 4. Weekly percentage weight gain (multivariable analysis).

	n	β coefficient ± SE*	*p* value
1st week			
No-HCA	71	Reference	–
MHCA	27	−1.22 ± 1.71	0.48
FHCA	44	−2.30 ± 1.38	0.10
2nd week			
No-HCA	71	Reference	–
MHCA	27	2.31 ± 1.88	0.22
FHCA	44	0.53 ± 1.55	0.73
3rd week			
No-HCA	71	Reference	–
MHCA	27	−0.70 ± 1.59	0.66
FHCA	44	−0.12 ± 1.28	0.93
4th week			
No-HCA	71	Reference	–
MHCA	27	2.22 ± 1.90	0.25
FHCA	44	0.61 ± 1.56	0.70

*Adjusted for maternal race/ethnicity, parity, smoking during pregnancy, infant gender, IUGR status, SGA status, antenatal steroids, total fluid intake, late-onset sepsis, BPD.

Comparing this study to Mestan et al. [13], the most important point is the difference in the study design. By using a matched case–control design, our study minimizes the confounding effect of the most important confounder of neonatal growth-gestational age.

Our findings are consistent with Mestan et al.'s work [13], and collectively these studies support further investigation of the pathway between intrauterine inflammation and postnatal growth.

Previous work showed increased concentrations of amniotic inflammatory substances in presence of intra-amniotic infection/inflammation [25–27]. Unlikely in our study, we did not get nor inflammatory markers nor cultures of amniotic fluid. The evaluation of the relationship between postnatal growth and biomarkers of placental inflammation could be a promising next step [25–28].

Differently from Mestan et al.'s study [13], we did not find a statistically significant difference in weight gain between no-HCA and MHCA groups, but this discrepancy can be due to the different gestational ages of the enrolled patients.

The underlying pathogenetic mechanisms of this association, however, remain to be elucidated.

Williams et al. showed that HCA was associated with multiple markers of fetal growth restriction, with stronger associations noted in prematurity [29].

Potential explanations for the increased frequency of fetal growth restriction in infants affected by HCA were previously given [29]. Subclinical infections that may develop during pregnancy may not immediately cause either fetal death or labor. With time, these infections may potentiate the release of cytokines and other vasoactive substances that cause vasospasm and alter blood flow to the fetus. Also during the postnatal period, cytokines could continue to play a negative effect on growth [30,31]. In a large cohort of infants born before the 28th post-menstrual week, a recent study showed that infectious organisms recovered from the placenta predict reduced head circumference at age of 2 [32]. Since recovery of these organisms from the placenta was associated with increased risk of sonographic expressions of white matter damage [33], but not with an increased risk of congenital microcephaly [34], the authors speculated that their findings were compatible with the view that some antenatal characteristics, such as the presence of low virulence organisms in the uterus/placenta, exert most of their effect on the brain shortly after delivery. It would not be surprising if the inflammatory stimuli associated with reduced head circumference at 2 years were similar to those associated with poor somatic postnatal growth found in our study. Further studies are needed to unveil in depth the extent of this association and its pathogenetic mechanisms.

The American Academy of Pediatrics and the Canadian Pediatric Society presently recommend that preterm infant growth should approximate intrauterine growth after allowing for a brief cessation in growth in the early neonatal period [35,36]. However, the intrauterine environment differs markedly from the extrauterine environment limiting postnatal growth [1,9,11,34]. In addition, due to several intrinsic and methodological factors, the best measure growth of preterm infants remains to be established [37].

It could be wondered whether a difference in the weight of −4.4% and −6.9% between FHCA and no-HCA infants is clinically relevant. Nevertheless, it is not possible to shown if the difference in the weight found in our study could be associated with neurodevelopmental outcomes in the future. In this regards, it is noteworthy that the majority of very preterm infants develop a significant growth deficit during hospitalization [1–4]. Considering the magnitude of the problem, the increasing number of very preterm infants who are surviving, and the effect of poor postnatal growth on long term outcomes, promoting growth in the NICU should always be deemed as a priority.

The most important question to ask is whether this growth deficit can be prevented or at least minimized [9,11]. In order to detect the most vulnerable postnatal period on neonatal growth, we performed a multivariate analysis of the weekly weight gain, but both FHCA and MHCA were not identified as risk factors of weekly weight gain, after adjusting for possible confounders. However, it is possible that we failed to detect this association because of the relatively small number of enrolled patients.

As we failed to identify the specific week wherein weight gain could be affected the most by placental inflammatory response, it is not easy to suggest specific corrective interventions in preterm infants with FHCA. Nevertheless, the consideration of placental histopathological features at birth may provide an important complement to our goal management to optimize neonatal growth [14].

There are some limitations to our study that must be considered in the interpretation of these results. As we did not serially monitored head circumference and length of our patients, we could not evaluate the impact of antenatal inflammatory status on postnatal whole body growth. However, body weight is the most commonly used measure for nutritional growth in neonatal period [11,35]. In our studied population, serial growth evaluation was limited to the first 4 weeks of life. Although neonatal period remains the most vulnerable moment for the growth of very preterm

infants, it would be of interest to know if the association found in this study may have an impact on long-term outcomes.

The cause of growth restriction in preterm infants is multifactorial and it seems that other factors influence postnatal growth besides placental inflammation [1,37]. In our control population, there was a high percentage of postnatal growth failure (76%). This percentage could be influenced by the high presence of IUGR/SGA subjects in this group [1,37]. However, multivariate analysis took into account these two variables.

In agreement with a previous study [14], we did not exclude the IUGR/SGA subjects from our study because they represent a large proportion of the preterm population. We recognize that the ''appropriate growth velocity'' can be different for IUGR/SGA and AGA infants. In fact, preterm infants who were born IUGR/SGA seem to have the highest risk to become growth restricted [1,37]. Possibly, the IUGR preterm infant is metabolically different from its appropriately grown counterpart and therefore has different nutritional needs. Although having favorable effects on neurodevelopmental outcome, rapid postnatal weight gain after a period of nutritional restriction is associated with the development of insulin resistance and metabolic syndrome in later life [1,7,38]. It seems likely that minimization of postnatal growth failure will decrease the need for catch-up growth and thereby decrease the risk of developing cardiovascular risk factors [14,38]. All these aspects need to be evaluated in depth and were beyond the scope of the present study.

In conclusion, we found a negative association between fetal placental inflammation and poor growth of very preterm infants during the first month of life, but we failed to identify a specific week wherein weight gain could be mostly affected.

Placental markers may be used to identify preterm infants at risk of postnatal growth failure and may provide an important complement to our goal management to optimize neonatal growth.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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