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Placental plasticity in monochorionic twins: Impact on birth weight and placental weight

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ABSTRACT

Introduction: The knowledge about adaptive mechanisms of monochorionic placentas to fulfill the demands of two instead of one fetus is largely speculative. The aim of our study was to investigate the impact of chorionicity on birth weight and placental weight in twin pregnancies.

Methods: Forty Monochorionic (MC) and 43 dichorionic (DC) twin pregnancies were included in this retrospective study. Individual and total (sum of both twins) birth weights, placental weights ratios between placental and birth weights and observed-to-expected (O/E)-ratios were calculated and analyzed. Additionally, we investigated whether in twin pregnancies placental and birth weights follow the law of allometric metabolic scaling.

Results: MC pregnancies showed higher placental O/E-ratios than DC ones (2.25 ± 0.85 versus 1.66 ± 0.61 ; $p < 0.05$), whereas the total neonatal birth weight O/E-ratios were not different. In DC twins total placental weights correlated significantly with gestational age ($r = 0.74$, $p < 0.001$), but not in MC twins. Analysis of deliveries ≤ 32 weeks revealed that the placenta to birth weight ratio in MC twins was higher than in matched DC twins (0.49 ± 0.3 versus 0.24 ± 0.03 ; $p = 0.03$). Allometric metabolic scaling revealed that dichorionic twin placentas scale with birth weight, while the monochorionic ones do not. **Discussion:** The weight of MC placentas compared to that of DC is not gestational age dependent in the third trimester. Therefore an early accelerated placental growth pattern has to be postulated which leads to an excess placental mass particularly below 32 weeks of gestation. The monochorionic twins do not follow allometric metabolic scaling principle making them more vulnerable to placental compromise.

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1. Introduction

The most important factors determining fetal growth and wellbeing are placental size and function. Placental weight has been shown to be closely associated with fetal size [1]. In multiple pregnancies, a reciprocal behavior of the mean birth weights with

increasing number of fetuses has been reported [2,3]. Mean birth weight of each neonate from multiple pregnancies was shown to be significantly lower than the expected mean of singletons. Papa-georghiou et al. showed by multiple regression analyses that the most important factors influencing birth weight of multiple pregnancies are the number of fetuses followed by the presence of a monochorionic placenta and gestational age [3]. It seems plausible that the individual birth weight of monochorionic twins is lower compared to dichorionic dizygotic or even dichorionic monozygotic twins [3–5]. However, the total twin birth weight (sum of birth weights of both twins) usually exceeds the 90th birth weight percentile for singletons; a phenomenon, which becomes apparent as early as 25 weeks of gestation [3–5]. Only few investigators have presented their data stratified by chorionicity [3,5]. Furthermore,

Abbreviations: MC, monochorionic placenta; DC, dichorionic; O/E, observed-to-expected; O, observed; E, expected; y, mean placental weight; x, given gestational age; x', mean birth weight; y', gestational age; NICU, neonatal intensive care unit; β -hCG, free β -hCG; PAPP-A, pregnancy-associated plasma protein-A.

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placental growth and its weight in relation to chorionicity and individual as well as total birth weights has rarely been analyzed. This subject needs further attention since monochorionic placentas, intrinsically programmed to supply the demands of only one fetus, are confronted with the need to support two fetuses. Chorionicity is established at or around the time of implantation and placental division is unlikely to occur after this period. In twin pregnancies, early and complex placental adaptation seems to be crucial for optimal fetal growth and wellbeing. However, it remains largely speculative how these adaptive processes are regulated.

In 1932, Kleiber, a Swiss agricultural chemist, demonstrated that the body weight raised to the power of $\frac{3}{4}$ is the most reliable way of predicting basal metabolic rate in mammals and birds [6]. Inspired by this allometric metabolic scaling model Aherne formulated a pregnancy-equivalent: total placental weight = $\alpha(\text{total birth weight})^\beta$, where α is a normalization constant [7]. Slafia et al. have shown that in singleton pregnancies the behavior of placental and birth weights is congruent with the Aherne's law and determined the exponent β to be 0.78, which is close to the value of $\frac{3}{4}$ in Kleiber's law [8]. Whether twin pregnancies follow this general law of metabolic scaling has not been elucidated yet.

The objectives of our study were to investigate the impact of chorionicity on birth weight and placental weight, and to determine whether the principle of allometric metabolic scaling applies to twin pregnancies.

2. Methods

Consecutive twin pregnancies delivered at our tertiary referral institution between 2003 and 2006 were analyzed in this retrospective study. Inclusion criteria were known gestational age (determined by a reliable recollection of the last menstrual period and confirmed by an ultrasonographic examination between 11 and 14 weeks of gestation) and availability of follow-up data and pregnancy outcomes. Exclusion criteria were twin-to-twin transfusion syndrome, monoamniotic twins, intrauterine demise of one or both twins and fetal structural or chromosomal abnormalities. All other cases, such as selective intrauterine growth restriction (IUGR) were not excluded since the focus of the study was not on the birth weight of the single fetus, but on the combined weights of the twins. The fetuses with estimated fetal weight below the 10th percentile and abnormal umbilical artery Doppler were diagnosed as being IUGR and all neonates with a birth weight below the 10th centile were considered to be small for gestational age (SGA). The chorionicity was determined according to standard ultrasound criteria between 11 and 14 weeks of gestation. Briefly, a monochorionic placenta (MC) was sonographically defined as single placental mass with typical T-sign. On the other hand, a single placental mass with a λ -sign or two separate placentas were considered dichorionic (DC). In addition, to ensure dizygosity, only sex discordant twins were included.

Placental weight was assessed on the delivery ward following removal of fetal membranes, the umbilical cord, and blood clots. The placentas were weighed by midwives using an accurate electronic bench scale (PBA655-A6, Mettler Toledo, Switzerland). For dichorionic placentas total placental weight represents the sum of the two individual placentas. The total placental weights were compared with reference values for singletons [9]. In order to correct for gestational age and to compare total placental weights of MC with those of DC twins, ratios between the observed (O) and the expected (E) birth weight for the given gestational age in singletons were calculated. Pinar et al. [9] have published placental weight reference values in singleton pregnancies allowing to calculate the expected (E) placental weight for a given gestational age: the polynomial regression equations that best fitted the mean placental weight (y)

for singletons at a given gestational age (x) was derived from Pinar et al. [6] and yielded $y = -531.3 + 33.22x - 0.1623x^2$. Analogous calculations were performed regarding the total birth weight. The expected mean birth weight (x') for a determined gestational age (y') was derived from a third order polynomial regression ($y' = 27,789 - 2790x' + 91.49x'^2 - 0.9235x'^3$) based on published reference values for singletons by Yudkin et al. [10] A similar procedure was used to investigate the association between the placental weight and birth weight.

To analyze the relationship between total placental and total birth weights in twin pregnancies the metabolic scaling equation was applied and fitted as described by Salafia et al. [8] Briefly, Aherne's power function relationship, i.e. total placental weight = $\alpha(\text{total birth weight})^\beta$ was recast into its logarithmic form. The data were then fitted by ordinary linear least-square regression using the curve fitting tool of MATLAB (The MathWorks, Natick, MA). Other functions ranging from linear to second/third order polynomial equations were tested to identify the best fitting curve.

Statistical analysis was performed with GraphPad Prism version 5.0 for Windows, (GraphPad Software, San Diego CA, USA). Independent sample student's t-test was used to compare continuous variables. Proportions were analyzed by using Fisher's exact test. Spearman rank correlation and linear logistic regression was used to assess the relationship between gestational age, birth weights, and total placental weights. A p-value of <0.05 was considered significant. This study was approved by the local ethical committee (Kantonale Ethikkommission Bern, date of approval: 11/18/2013).

3. Results

During the study period a total of 146 twin pregnancies were delivered at our institution. Of those, 83 cases (40 MC and 43 DC) fulfilled the inclusion criteria. The clinical characteristics of the study population are presented in Table 1. The two groups showed significant differences comparing maternal age, parity, and incidence of hypertensive complications of pregnancy. However, the proportion of IUGR was not different between groups. Over 80% of all pregnancies were delivered by caesarean section, and a relevant proportion of the neonates had to be transferred to the neonatal intensive care unit (NICU), mainly due to prematurity. In three cases with vaginal delivery of the first twin a caesarean section was performed for the second twin because of non-reassuring fetal heart rate trace.

The individual birth weights interposed on the reference ranges for singletons are depicted in Fig. 1a. Mean birth weights were not different between the two groups (Table 1). Similarly, although the incidence of individual birth weights below the 5th gestational age-specific percentile of singleton pregnancies was higher in the MC than in the DC group, this difference was not significant (MC: 23/80 [28.8%] vs. DC: 14/86 [16.3%]; $p = 0.06$). There were no differences in birth weight discordancy (DC versus MC: 315 ± 219 g [$15.7 \pm 10.9\%$] versus 358 ± 243 g [$14.4 \pm 9.1\%$]; $p = 0.52$ [$p = 0.71$]), nor in the prevalence of birth weight discordancy >20% (DC versus MC: 30.2% (13/43) versus 37.5% (15/40); $p = 0.49$) between the two groups. The O/E-ratio for the estimated birth weight was also not different (MC: 0.82 ± 0.15 vs. DC: 0.84 ± 0.12 ; $p = 0.39$). Total birth weights are shown in Fig. 1b. Almost all cases (except one MC twin) were above the 95th percentile for gestational age for singletons. Between MC and DC no significant differences were found regarding the total birth weights (MC: 4085 ± 1272 gr vs. DC: 4458 ± 661 gr; $p = 0.13$) and the total birth weight O/E-ratios (MC: 1.64 ± 0.24 vs. DC: 1.69 ± 0.18 ; $p = 0.28$).

Forty-three placentas of the 83 twin pregnancies were weighed in the delivery ward and available for analysis, whereas the others were sent directly to histopathologic examinations and

Table 1
Demographics and clinical characteristics of the study population.

| | Monochorionic twins (n = 40) | Dichorionic twins (n = 43) | p-value |
|-------------------------------------|------------------------------|----------------------------|----------|
| Age, year (mean ± SD) | 28.7 ± 5.1 | 30.7 ± 4.4 | <0.01 |
| Nulliparity (n, %) | 15 (37.5%) | 25 (58.1%) | <0.05 |
| GA, weeks (mean ± SD) | 34.5 ± 3.5 | 35.3 ± 3.2 | 0.2, NS |
| Cesarean section (n, %) | 34 (85%) | 36 (83.7%) | NS |
| Hypertensive disorders (n, %) | 4 (9.5%) | 0 | <0.05 |
| Birth weight, grams (mean ± SD) | 2042 ± 662 | 2239 ± 584 | 0.06, NS |
| Growth discordance (mean of % ± SD) | 15.7 ± 12.1 | 14.4 ± 9.1 | 0.88, NS |
| IUGR single/double | 14 (35%)/2 (5%) | 13 (30.2%)/2 (5%) | NS |
| Apgar value at 5 min (mean ± SD) | 8.4 ± 1.5 | 8.9 ± 1.3 | <0.01 |
| pH _{UA} (mean ± SD) | 7.17 ± 0.9 | 7.27 ± 0.1 | 0.4, NS |
| NICU (n, %) | 32/80 (40%) | 37/86 (43%) | 0.8, NS |
| Neonatal mortality (n, %) | 4/80 (5%) | 2/86 (2.32%) | 0.4, NS |

GA, gestational age at delivery; NICU, neonatal intensive care unit; pH_{UA}, umbilical artery pH.

unfortunately were weighed following formaldehyde fixation. Therefore, these cases could not be included in the analysis. All total placental weights were above the 90th percentile of those of singleton placentas (Fig. 2). Mean total placental weights between the groups were not different (MC: 887 ± 237 gr vs. DC: 815 ± 237 gr; $p = 0.33$). However, placental O/E-ratios were higher in MC compared to DC pregnancies (MC: 2.25 ± 0.85 vs. DC: 1.66 ± 0.61; $p < 0.05$). Statistical analysis showed a highly significant correlation between total placental weights and gestational age in DC ($r = 0.74$, $p = 0.0003$) but not in MC pregnancies ($r = 0.43$,

$p = 0.07$) (Fig. 3). The differences in the slopes of the best fitting curves manifest the differences in placental growth patterns in monochorionic and dichorionic pregnancies. Fig. 4 depicts the total birth weights plotted against placental weights. DC twins showed a strong correlation with placental weight ($r = 0.94$; $p < 0.0001$). In contrast, no correlation was found in MC twin pregnancies

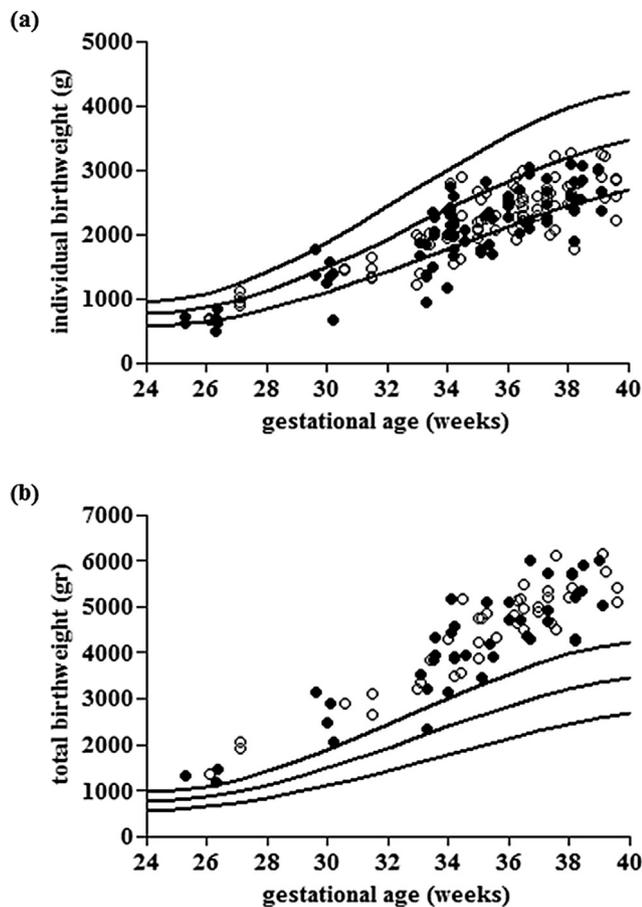


Fig. 1. Individual and total birth weights of the twins. Individual (a) and total birth weights (b) of monochorionic (filled circles) and dichorionic (empty circles) pregnancies plotted on reference ranges for singleton (Yudkin et al. [10]). The lines represent the 5th, 50th, and 95th percentile for gestational age.

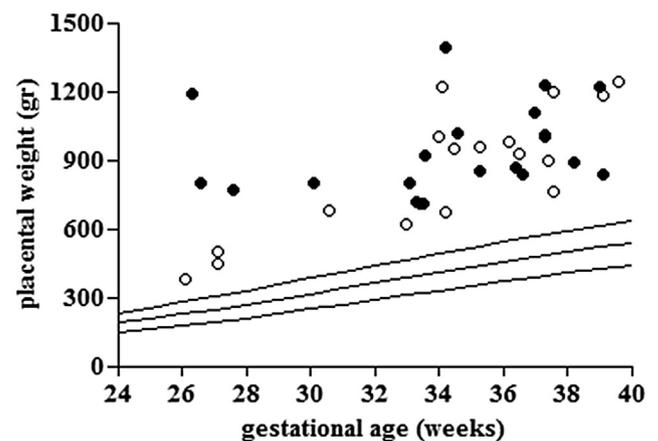


Fig. 2. Total placental weights. Total placental weights of monochorionic (filled circles) and dichorionic pregnancies (empty circles) plotted on reference ranges for singleton placental weights (Pinar et al. [9]). The lines represent the 10th, 50th, and 90th percentile for placental weight.

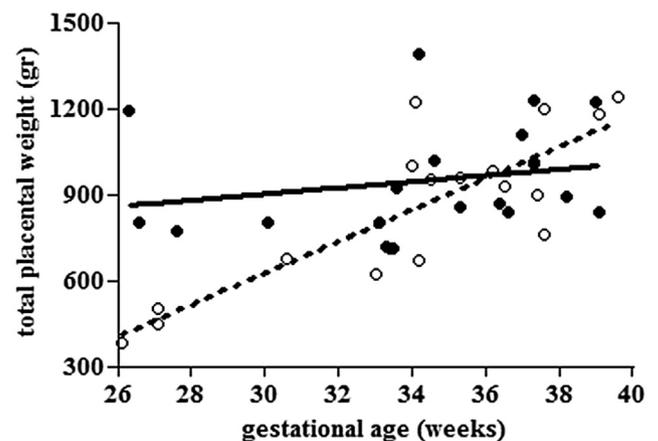


Fig. 3. Correlation between gestational age and total placental weight. Significant correlation between gestational age and total placental weight in dichorionic twin pregnancies (dashed line) but not in monochorionic (straight line).

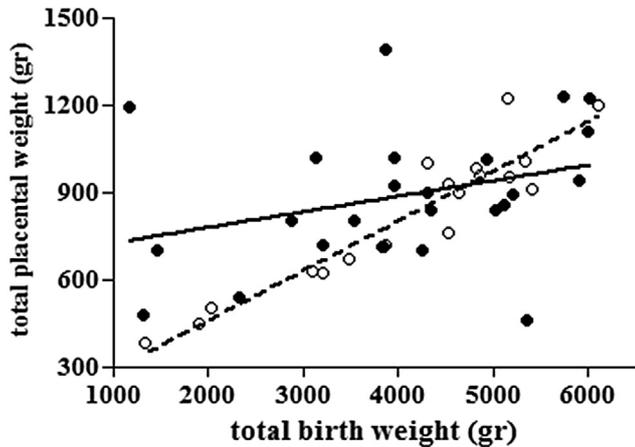


Fig. 4. Correlation between total placental weight to birth weight. Correlation between the total placental weight to birth weight of monochorionic (full circles, straight line) and dichorionic pregnancies (empty circles, dashed line).

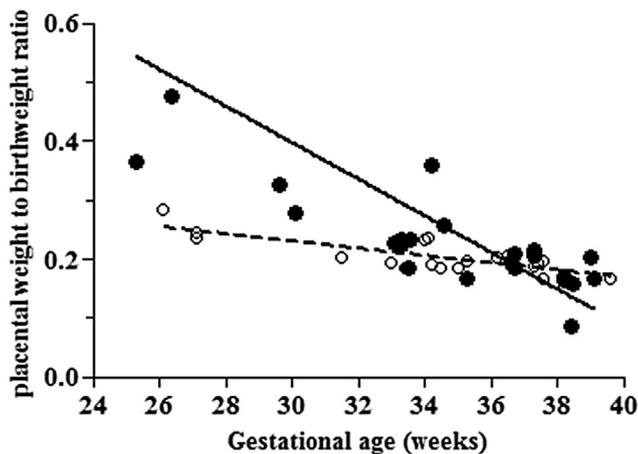


Fig. 5. Correlation between placental weight to birth weight ratio and gestational age. Correlation between placental weight to birth weight ratio of monochorionic (full circles) and dichorionic pregnancies (empty circles).

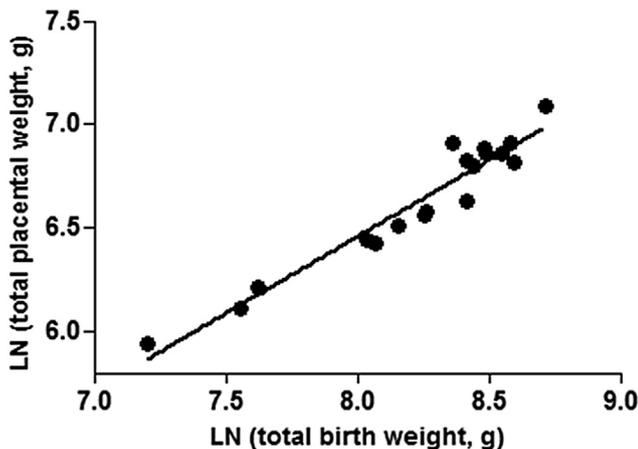


Fig. 6. Allometric metabolic scaling of total placental weight and birth weight of dichorionic pregnancies. Plot of the total placental weight (g) against birth weight (g) on a natural logarithmic (LN) scale. The slope of the best straight-line fit is 0.74.

($r = 0.33$; $p = 0.11$). Moreover, a highly significant correlation was found between the placenta to birth weight ratio and gestational age in both types of twins (MC: $r = -0.82$; $p < 0.0001$ and DC: $r = -0.59$; $p = 0.008$) (Fig. 5). Although, mean placenta to birth weight ratios were higher in MC twins, this difference did not reach significance over the entire observed gestational age period (MC: 0.26 ± 0.18 vs. 0.21 ± 0.03 ; $p = 0.18$). However, looking at cases ≤ 32 weeks, this difference was significant (MC $n = 4$: 0.49 ± 0.3 vs. DC $n = 4$: 0.24 ± 0.03 ; $p = 0.03$).

In order to investigate how the total placental weight of twins scales with their combined birth weight, we analyzed a variety of curves that fitted our data. A simple power function relationship as formulated by Kleiber and Aherne, i.e. placental weight = $\alpha(\text{birth weight})^\beta$, fitted best for the dichorionic placentas ($r = 0.95$). In dichorionic pregnancies the mean (exponentiated) α and β were 1.0036 ± 0.0106 (mean and SD; range 0.98–1.03) and 0.7412 ± 0.046 (range 0.64–0.85), respectively. The calculated value for β was 101.3% of the allometric exponent of 0.75 predicted by a supply limited fractal system [18–20]. Fig. 6 depicts the plot of the total placental weight (g) against birth weight (g) on a natural logarithmic (LN) scale. In monochorionic pregnancies, the mean (exponentiated) α and β were 3.1900 ± 0.0253 (range 3.13–3.25) and 0.4365 ± 0.068 (range 0.27–0.61), respectively, and the curve fit correlation coefficient (r) was 0.77. The calculated value for β was 141.3% of the allometric exponent of 0.75 predicted by a supply limited fractal system.

4. Discussion

Our results based on twins delivered beyond 25 weeks of gestation, show that the birth weight sum of MC as well as DC twins is higher than that of singletons, but not twice as high. These findings are in line with several other studies [3,11,12]. However, in contrast to these studies our data show no differences in birth weights depending on chorionicity [3,5]. Monochorionic placentas, which are intrinsically intended to supply only one fetus, support twins with total birth weights exceeding the birth weights of singletons. This is particularly interesting since the current study shows a different growth pattern of monochorionic placentas compared to dichorionic placentas.

A limiting factor compromising fetal growth in multiple pregnancies is the restricted intra-uterine environment. An inverse relationship between fetal number and birth weight has previously reported; a phenomenon, which is even more pronounced when trichorionic triplets were compared with dichorionic twins [3,12]. Besides the fetal number, monochorionic placentation *per se* also seems to play an independent role in fetal growth [3]. Gielen et al. found no difference in placental weights comparing monochorionic and dizygotic-dichorionic placentas [13]. Similar to this observation, we did not find a difference in placental weights between the two types of placentation without considering the important role of gestational age. Indeed, one of the most interesting observations of our study is that monochorionic placentas seem to have already reached their growth potential at the beginning of the third trimester while dichorionic placentas show continuous growth beyond 32 weeks of gestation. We speculate that monochorionic placentas start increasing their mass in order to adapt to the acquired circumstances of having to support two embryos instead of one as determined during the conception. This assumption is supported by the finding of distinct gestational age dependent changes in free β -human chorionic gonadotropin (β -hCG) and pregnancy-associated plasma protein-A (PAPP-A) maternal serum levels in monochorionic pregnancies [14]. While the median level of both biochemical markers are not different in monochorionic twin pregnancies at 8–9 weeks, when compared to singletons,

these values increase to 2.0 MoM for β -hCG and 1.5 MoM for PAPP-A of singleton pregnancies at 13–14 weeks. Moreover, in monochorionic pregnancies free β -hCG values are similar or even higher than those measured in dichorionic pregnancies after 12 weeks of gestation [14]. As shown in Fig. 5, monochorionic twins are characterized by a higher placental weight to birth weight ratio indicating a sort of adaptive process to an increased fetal demand particularly <32 weeks. However, this finding should be interpreted with caution due to the limited number of cases <32 gestational weeks. Similar findings have been reported also in placentas from small-for-gestational age infants representing an adaptive mechanism to maintain or even increase fetal supply by placental hypertrophy [15].

Monochorionic placentation seems to follow a “two step” growth pattern with an initial stage characterized by a rapid increase in mass followed by a second plateau-like phase. Indeed, according to our findings no substantial growth is detectable in monochorionic placentas after 26 weeks of gestation while dichorionic placentas still continue to show a gestational age dependent growth behavior. This finding is further corroborated by a higher placental weight to birth weight ratio of monochorionic twin pregnancies below 32 weeks of gestation compared to dichorionic pregnancies. Compared to the dichorionic situation in monochorionic pregnancies there is an excess of placental mass compared to fetal weight at least before 32 weeks of gestation (Fig. 5). These findings are in line with those recently observed by Paepe et al. [16] However, the driving force for the initial rapid growth in monochorionic pregnancies remains to be elucidated. Fetal signaling by growth factors, steroids, interleukins and altered perfusion might play a role.

Inclusion of IUGR fetuses could be considered as a limitation of our study. However, it is unlikely to affect our results since we compare the total placental mass and sum of neonatal birth weights between groups. Moreover, the proportion of single and double IUGR was not different between the groups.

To investigate whether the combined placental weight scales to combined fetal weight in twin pregnancies, the Aherne's equation was applied and fitted to our data sets. Analyzing a power function as proposed by Kleiber and Aherne yielded the best fit [6,7]. In order to increase the robustness of our predictions it is desirable to express the relationship between two entities with as less parameters as possible (Occam's razor [17]). It is fascinating that the underlying law describing the mutual dependence between placental and birth weight in such a complex system as twin pregnancies follow a simple power function relationship. The calculated allometric metabolic scaling parameters for dichorionic (twin) pregnancies were very similar to those for singletons presented by Salafia and co-workers [8]. This suggests that dichorionic placentation follows the general law of metabolic scaling as many other fundamental biological processes. [18] [19] [20] Moreover the value of the exponent β , 0.74, was congruent with the value predicted by the Kleiber's law [6]. However, the allometric scaling parameters in monochorionic twin pregnancies were substantially different compared to dichorionic pregnancies. This corroborates our postulation that placental growth and function deviates from the general metabolic scaling principle when a single placenta has to supply two fetuses. The deviance from this scaling could then reflect abnormal fetal–placental development. Indeed monochorionic pregnancies are associated with higher incidence of placental histologic abnormalities [21] as well as adverse pregnancy outcomes [4].

In summary, this study demonstrates that monochorionic and dichorionic placentas have distinctly different growth patterns. In monochorionic twin pregnancies, early placental adaptive mechanisms needed to ensure adequate growth of the fetuses leads

initially to an accelerated placental growth, while dichorionic placental growth is continuous and stable throughout the gestation. This difference in placental behavior may be explained by our finding that dichorionic placentas scale with birth weight, while monochorionic placentas do not. The monochorionic twins do not appear to follow allometric metabolic scaling principle, which makes them more vulnerable to placental compromise.

Funding sources of this study

None.

Disclosures

None declared.

Bullet statement

What's already known about this topic?

In contrast to dichorionic, monochorionic twin pregnancies have a shorter gestational duration and are at increased risk of placental insufficiency.

What does this study add?

In monochorionic twin pregnancies the single placenta responds to the demands of two fetuses with initially accelerated growth followed by a plateau in the late third trimester, whereas the dichorionic placentas grow continuously throughout the gestation. The monochorionic twins do not follow general metabolic scaling principle making them more vulnerable to placental compromise.

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