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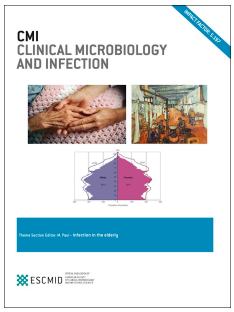

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Low placental weight and altered metabolic scaling after severe acute respiratory syndrome coronavirus type 2 infection during pregnancy: a prospective multicentric study

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Abstract

Objectives

A higher risk for adverse pregnancy outcome is associated with SARS-CoV-2 infection, which could be partially explained by an altered placental function. Since histopathology is often unspecific, we aimed to assess placental weight, birthweight/placental-weight (b/p) ratio and the metabolic scaling exponent ß, an indicator of a normal fetal-placental growth, in order to analyze the placental function.

Methods

We included 153 singleton pregnancies with SARS-CoV-2 positive PCR in our study, who delivered at three referring hospitals in Switzerland. Placental weight and b/p ratio were compared to published reference charts. Logistic regression analysis investigated the role of time of infection and other confounding factors on placental weight. The scaling exponent β was compared to the reference value of ¾.

Results

Placental weight was inferior or equal to the 10^{th} centile in 42.5%(65/153) and to the 3^{rd} centile in 19%(29/153) of the cases. The risk of low placental weight was not influenced by the trimester of infection. B/p ratio was $>50^{th}$ centile in 80.4%(123/153) of the cases. Incidence of fetal growth restriction, preeclampsia and gestational diabetes was 11.8%(18/153), 3.3%(5/153) and 19.6%(30/153). Linear regression modelling revealed a pathologic metabolic scaling exponent β of 0.871±0.064 (R^2=0.56).

Conclusion

SARS-CoV-2 during pregnancy was associated with a higher incidence of low placental weight, an increased b/p ratio and an abnormal scaling exponent β in our cohort. This could be particularly relevant for the yet controversial issue of increased stillbirth rate in SARS-CoV-2 infection during pregnancy. In this regard, intensified fetal surveillance should be mandatory in these pregnancies.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019, and has caused a major global health crisis ever since[1]. In its severe forms, SARS-CoV-2 infection can trigger a hyper-inflammatory response, leading to a complex, immune-mediated disorder[2]. It is rational to believe that COVID-19 as highly immunogenic viral infection may interfere with the regular course of pregnancy, and that pregnant women could be highly susceptible to a more severe course of the disease[2]. Indeed, recent systematic reviews report more severe outcomes in pregnant women with symptomatic SARS-CoV-2 infection and a higher risk to be admitted to the intensive care unit (ICU) and to require invasive ventilation[3].The risk for adverse neonatal outcome also seems to be elevated[5]. Moreover, the risk of stillbirth seems to be increased, as reported by a British study including more than 340.000 women[5].

To date, it is still unclear to which extent placental damage could be responsible for adverse maternal and neonatal outcome in these pregnancies. Although a fair amount of attention focused on this topic, reports are yet inconclusive. Several studies report histopathological alterations such as presence of intervillous thrombi and placental infarcts as an expression of maternal vascular malperfusion after SARS-CoV-2 infection[6-9]. Presence of a robust inflammatory response at the maternal-fetal interface and possible associations with long-term neurocognitive impairment in children after immune activation in the placenta have also been discussed[10].

Nevertheless, histopathological findings are still conflicting, since several studies report no differences between placentas originating from SARS-CoV-2 infected mothers, as compared to controls[11-12].

Maternal viral infection can be associated with placental alterations, such as lymphoplasmacytic villitis following cytomegalovirus infection, as well as intervillositis after Zika or Dengue virus infections[6]. Expression of angiotensin-converting enzyme 2 (ACE2) in the placenta offers a potential entry mechanism for SARS-CoV-2, yet vertical transmission seems to be exceptionally rare[7-9]. Beyond the inconsistency of data lies one certainty: no histopathological `footprint` in association with SARS-CoV-2 has yet been found, and the described changes can be associated with other pregnancy related pathologies such as hypertensive complications[13-14].

A healthy placenta is a prerequisite for appropriate fetal growth and development, and alterations at its level may cause hypoxia and impairment of various transport systems such as glucose and amino acids transport, which may have short- and longtime consequences for the fetus[15].

Birthweight/placental weight ratio (b/p ratio), also defined as gram fetus per gram placenta, reflects a marker of placental efficiency. A high b/p ratio seems to be associated with adverse obstetrical outcome such as fetal distress, meconium-stained amniotic fluid or hyperbilirubinemia[16-17]. In mice, small placentas have been shown to upregulate placental transport systems in order to prevent fetal growth restriction[16-17]. An elevated b/p ratio could be a marker for increased nutrient transfer to the fetus, who despite its `normal` weight, seems to be at risk by `outgrowing` its placenta[16-17].

A similar approach to assess placental efficacy is to calculate the metabolic scaling exponent ß, which reflects the fractal structure of the placental vasculature[18]. This model proposes an explanation on how the placenta `translates` into fetal mass, thus metabolism into organism[18].

Given the inconsistency of data regarding placental histopathology after SARS-CoV-2 infection during pregnancy, we aimed to further follow the more basic approach of

assessing placental function by assessing its weight, calculating the b/p ratio and analyzing whether the scaling exponent β in our population is close to ¾ which would be congruent with an optimal placental metabolic efficiency.

Methods:

We included in our study prospective data originating from singleton pregnancies between 24 and 44 weeks of gestation affected by SARS-CoV-2 infection who delivered between May 2020 and July 2021 at three referring hospitals in Switzerland, irrespective of maternal symptoms. Diagnosis of infection was performed by evidence of SARS-CoV-2-RNA in real time polymerase chain reaction test (RT-PCR) in nasopharyngeal swab in all women. Weight of wet, untrimmed placentas was assessed in a standard manner within minutes after delivery, after removal of blood clots.

Written consent was obtained from all women for use of COVID-19 related data. Institutional review board (IRB) approval from the Cantonal Ethical Committees of Bern, Lausanne and Lugano was obtained. The study was performed in accordance with the principles of the Declaration of Helsinki.

Statistical analysis was performed with GraphPad Prism version 8.0 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 or Chi^2 test where appropriate. Spearman rank correlation and linear logistic regression were used to assess the relationship between gestational age, birth weight, and placental weight. Placental weight scale and percentiles were calculated according to Thompson JM et al. [22]. A case-control analysis comparing low to normal placental weight was performed, considering low placental weight as inferior or equal to the 3^{rd} and to the 10^{th} percentile, respectively. A p-value of <0.05 was considered significant.

For multivariate analysis, co-variates will be considered into the regression model if the univariate analysis shows a difference between groups with a p value $p<0.25$.

To verify the fetal-placental scaling exponent-ß, the metabolic scaling equation was applied and fitted as described by Salafia et al [18].

Since human neonatal birthweight does not scale linearly with the placental weight but this interconnection follows the rules of allometric metabolic scaling model described by Keiber's law and Ahern's adaptation for the feto-placental unit[19-20], we considered following formula:

$$\text{placental weight} = \alpha\ (\text{birthweight})^{\beta}$$

which reveals the relationship between placental weight and birth weight, under the hypothesis that the placenta and the fetus interact like a fractal supply system[18]. We considered as reference the β-value close to the value of ¾, which has been previously described as normal in allometric metabolic studies in singleton pregnancies[18-21]. Briefly, Ahern's power function relationship, i.e. placental weight (PW) = α(birth weight)$^{\beta}$ was transformed in a linear form by applying the natural logarithm to both sides: Ln(PW)=Lnα+ß*LnBW. The data were then fitted by ordinary linear least-square regression using the curve-fitting tool of the statistical software.

Results

During the study period, 153 placentas following pregnancies affected by SARS-CoV-2 infection were included. Description of baseline characteristics is depicted in Table 1. Placental weight was inferior or equal to the 10th centile in 42.5% (65/153) and inferior or equal to the 3rd centile in 19% (29/153) of the cases (Fig. 1). B/p ratio was > 50th centile in 80.4% (123/153) of the cases and > 90th centile in 31.37% (48/153) of the cases (Fig. 2). Linear regression modelling of the analysed population revealed a

metabolic scaling exponent β of 0.871±0.064 (R^2=0.56) and LnPW= -0.786 + 0.871*LnBW (Fig 3).

Trimester 1, 2 and 3 were defined as conception up to 11 + 6 weeks, between 12 to 23 + 6 weeks and more than 24 weeks of gestation, respectively. In 62.1% (95/153) of the cases, infection occurred in the third trimester of gestation. In 29.41% (45/153) and in 4.58%; (7/153) of the cases, infection occurred in the second and first trimester, respectively. In 3.92% (6/153) cases, the time-point of infection was unknown. Univariate logistic regression revealed that the risk of low placental weight was not significantly different between each trimester of infection after OR analysis for the 3rd and for the 10th centile, adjusted for trimester of infection and multiparty status.

In multivariate logistic regression analysis considering adjusted OR on available co-variates: BMI >35 kg/m2, ethnicity, tobacco consumption, multiparty, gestational diabetes, pregestational diabetes and preeclampsia, multiparty was the only significant factor negatively associated with low placental weight defined as inferior or equal to 10th percentile (OR 0.49 [95% CI [0.25 – 0.97]; p=0.034) (Table 2).

The incidence of fetal growth restriction (FGR), defined as a fetal weight <10th centile for gestational age, was 11.8% (18/153), whereas 3.3% (5/153) of cases were complicated by preeclampsia. Gestational diabetes was present in 19.6% (30/153) of the cases. (Table 1)

After infection in the first trimester, no pregnancy was complicated by FGR (0/7). Of the pregnancies where infection occurred in the second trimester, 13.33%(6/45) resulted in FGR, vs. 9.5%(9/95) after infection in the third trimester. In three cases of FGR (3/153, 2%), the time point of infection was unknown.

Discussion

The main finding of our study was the increased incidence of low placental weight after SARS-CoV-2 infection during pregnancy. This finding contrasts with the predominantly normal birthweight of the corresponding neonates and leads to an elevated b/p ratio in our cohort. Furthermore, we found a distinctively higher value of the metabolic scaling exponent β than expected in normal singleton pregnancies.

Understanding the possible implications of a pathologically altered b/p ratio is important for further interpretation of these findings. A low b/p ratio is commonly found in FGR fetuses, where both placental and fetal weight are low[17]. In contrast, the combination small placenta/normal sized fetus seems to be a sign of upregulated nutrient transfer capacity in an apparently normal pregnancy, where the resulting `normal` fetal weight possibly masks an altered placenta/fetus-dyad.

One of the largest studies investigating the meaning of the b/p ratio relies on data from over 500.000 singleton deliveries in Norway[23]. The authors analyzed the relative risk of fetal death in the lowest and highest b/p ratio quartiles for both preterm and term deliveries in their population. In the preterm group, in both lowest and highest b/p ratio quartiles, odds ratio for fetal death was increased, whereas at term, an elevated risk for fetal demise was found in the highest quartile. This finding is highly relevant and suggests that a small placenta as related to fetal size could be a risk factor for fetal death at term.

By relating these findings to our cohort, this could indicate that presumably low-risk fetuses are actually at high risk, and that SARS-CoV-2 could act as a `promoter` for the destabilisation of the placental-fetal dyad in these pregnancies.

Data on placental weight after maternal SARS-CoV-2 infection is limited, as most publications focus on histopathological and immunhistochemical examinations. One

report documents a rate of 66.7% placentas < 10th centile (n=20), which is in line with our findings, nevertheless associated with an accordingly high prevalence of FGR[12].

As previously mentioned, there is preliminary data linking fetal death to SARS-CoV-2 infection during pregnancy. The mechanism behind these findings is not yet elucidated, and so far, placental inflammation and/or generic consequence of maternal illness in pregnancy were invoked as a potential cause[5]. Our data cannot fully explain the underlying mechanism either, but raise further concerns regarding these insights. Given the scenario of increased risk for fetal demise in relation with elevated b/p ratio, we believe it is legitimate to be concerned about the "stability" of the placental function in COVID-19 disease during pregnancy.

We used as reference placental weight charts for singleton pregnancies published by Thomson et al. in 2007, which are based on data originating from 231.806 deliveries from Norway[22]. To our knowledge, these are the largest published placental weight reference charts originating from a population similar to ours in terms of ethnical distribution, gestational age and type of pregnancy (multiple pregnancies have been excluded from our analysis, in order to best fit the reference curves). In the reference population, 85.7% of the women were born in Norway, thus the ethnicity can be extrapolated to our Swiss, predominantly Caucasian population, as opposed to other placental weight curves available, where an important percent of the population was of African (>80%) or Asian (> 95%) ethnicity[24-25]. Furthermore, the reference values were generated by using outcomes from pregnancies between 24 and 44 weeks of gestation, identical to our cohort. All though Swiss reference curves for placental weight are also available, these are based on a population starting with 37 weeks of gestation and derive from a significantly lower cohort, thus our decision in favor of the Scandinavic curves[22,26]. Given the size and characteristics of the available references, we consciously

decided against a case-control approach. We are aware that some may regard this as a weak point of our analysis, thus we intended to counterbalance it with the calculation of the scaling exponent β in our population.

On this note, we found a distinctively higher value of the scaling exponent β than expected in normal singleton pregnancies. A higher value of β correlates with a newborn weight lower than that predicted by Kleiber's metabolic scaling law[18]. It is assumed that a deviation from a $\beta \approx 0.75$ may reflect a decreased metabolic efficiency of the placenta, as β reflects the fractal structure of the placental vasculature[18]. This correlates with the elevated b/p ratio.

Looking beyond the presumed risk for fetal death associated with an elevated b/p ratio, there is evidence linking placental growth and metabolism to development of chronic diseases in later life. Placental weight seems to play a critical role in fetal programming, without necessarily influencing size at birth[27-28]. This may occur due to developmental plasticity, where adaptation to a low trans-placental supply of nutrients can influence the long-term development of the offspring on an epigenetical basis[28].

Our study shows no significant difference in risk of low placenta weight in pregnant women infected by the SARS-CoV-2 between trimesters of infection. This finding of an apparently lack of association between early infection during pregnancy and the incidence of placental insufficiency is somewhat anticyclical, as the expression of ACE2 and transmembrane protease serine-2 receptors in the placenta are highest in the first trimester of pregnancy[29]. Given the absolute low number of cases with FGR in our cohort, we believe it is not possible to draw any solid conclusion relying on this data.

The incidence of preterm delivery and FGR in our cohort were both in line with the Swiss incidence of these adverse pregnancy outcomes (Table 1). In only four cases

(4/153, 2.61%), both FGR and premature delivery were present, so that an association between the two cannot be clearly stated.

Our study is the only one to date describing a relevant association between low placental weight as well as an altered metabolic scaling value in pregnancies complicated by SARS-CoV-2 infection, without cofounding factors such as FGR. The main strengths of the study are its prospective and multicentric nature. For the moment, it is still speculative to assert that SARS-CoV-2 alone may be responsible for these findings, the size of the cohort being the main limitation of our study. A further limitation is not being able to assess severity of disease in all patients, because of data inconsistency, thus not considering it in multivariate logistic regression.

It seems urgent to continue research on placental defensive and potentially altered adaptive mechanism during infection, in particular after SARS-CoV-2 viral infection. Analyzing placental weight, b/p ratio and the scaling exponent-ß may offer additional clues to understand the processes at the maternal-placental interface.

A healthy, normal sized and adequately functioning placenta is not only important for the direct outcome of the pregnancy, but is likely to provide lifetime benefits for the offspring[27-28]. Our study reveals that the maternal-fetal unit could be at risk for placental related impairment after SARS-CoV-2 infection during pregnancy, and we believe that intensified fetal surveillance should be mandatory in these cases[30].

Keywords: SARS-CoV-2, COVID-19, placental weight, birthweight/placental weight ratio, metabolic scaling exponent β, gestational diabetes

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Authors` contributions:

Anda-Petronela RADAN: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article

David BAUD: acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content

Guillaume FAVRE: acquisition of data, analysis and interpretation of data

Andrea PAPADIA: acquisition of data, revising the article critically for important intellectual content

Daniel SURBEK: acquisition of data, revising the article critically for important intellectual content

Marc BAUMANN: analysis and interpretation of data

Luigi RAIO: conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content

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Tables and Figures

Tables

Table 1. Clinical characteristics and outcomes of the study population

Characteristics	**values**
BMI (kg/m2)	24.8 [22.2 - 29.4]
Parity	2 [1-2]
Gestational age at delivery (weeks ± SD)	38.8 ± 2.71
Preterm delivery[1]	16 (10.45%)
Gestational diabetes (%)	30 (19.6%)
Preeclampsia (%)	5 (3.3%)
Fetal growth restriction[2]	18 (11.76%)
Gestational age at infection (weeks)	31 [26 - 37]
Birth weight (grams ± SD)	3206.57 ± 637.49
Placental weight (grams ± SD)	520.42 ± 124.81

Values are shown as median (range), number and % or mean ± standard deviation (SD) where appropriate; [1]*preterm delivery:* <37 0/7 weeks of gestation; [2]*FGR:* Fetal growth restriction

defined by abdominal circumference <5th percentile / fetal weight <10th percentile with altered hemodynamic or abnormal growth trajectory

Table 2: Clinical characteristics of the study population dichotomized between placental weight ≤ 10th and > 10th centile for gestational age

Characteristics	**Placental weight**		**p-value**
	≤ 10th centile [n = 65 (42.5%)]	**> 10th centile** [n = 88 (57.5%)]	
BMI (kg/m2)	24.0 [22 - 28.1]	25.6 [22.2 - 31.2]	ns
Tobacco consumption (%)	2 (3.1%)	4 (4.5%)	ns
Parity	2 [1-2]	2 [1-3]	ns
Gestational diabetes (%)	12 (18.5%)	18 (20.5%)	ns
Preeclampsia (%)	2 (3.1%)	3 (3.4%)	ns
Gestational age at infection (weeks)	31 [26 - 37]	30 [22 - 37]	ns
Gestational age at delivery (weeks)	39 [38 - 40]	39 [37 - 40]	ns

Values are shown as median (range) or number and % where appropriate; *ns*, not significant

Figure legends

Figure 1. Placental weights (black dots) plotted on reference ranges derived from Thompson et al [22]. The lines represent the 10th, 50th, and 90th percentile for gestational age.

Figure 2. Birth weight/placental weight ratio (b/p weight ratio). Placental weights (black dots) plotted on reference ranges derive from Thompson et al [22]. The lines represent the 10th, 50th, and 90th percentile for gestational age.

Figure 3. Relationship between birth weight and placental mass. Fitted straight line to natural logarithms (LN) of birth weight (BW) and placental weight (PW).