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

Anda-Petronela Radan, MD, David Baud, MD, Guillaume Favre, MD, Andrea Papadia, MD, PhD, Daniel Surbek, MD, Marc Baumann, MD, Luigi Raio, MD

PII: S1198-743X(22)00076-3

DOI: https://doi.org/10.1016/j.cmi.2022.02.003

Reference: CMI 2829

To appear in: Clinical Microbiology and Infection

Received Date: 8 November 2021

Revised Date: 31 January 2022

Accepted Date: 1 February 2022

Please cite this article as: Radan A-P, Baud D, Favre G, Papadia A, Surbek D, Baumann M, Raio L, Low placental weight and altered metabolic scaling after severe acute respiratory syndrome coronavirus type 2 infection during pregnancy: a prospective multicentric study, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.02.003.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.



1	Low placental weight and altered metabolic scaling after severe acute respiratory
2	syndrome coronavirus type 2 infection during pregnancy: a prospective
3	multicentric study
4	Anda-Petronela RADAN, MD*, David BAUD, MD **, Guillaume FAVRE, MD **,
5	Andrea PAPADIA, MD, PhD***, Daniel SURBEK, MD*, Marc BAUMANN, MD*,
6	Luigi RAIO, MD*
7 8	*Department of Obstetrics and feto-maternal Medicine, University Hospital of Bern, University of Bern, Switzerland
9	**Women – Mother – Child Department, Lausanne University Hospital, Lausanne,
10	Switzerland
11	***Department of Obstetrics and Gynecology, Ente Ospedaliero Cantonale (EOC),
12	Lugano, Switzerland
13	
14	Corresponding Author: Anda-Petronela Radan, MD
15	Department of Obstetrics and feto-maternal Medicine
16	University Hospital of Bern
17	University of Bern, Switzerland
18	Friedbühlstrasse 19, CH-3010 Bern, Switzerland
19	Tel +41316321010/ Fax: +41316321646
20	Email: anda-petronela.radan@insel.ch

22 Abstract

23 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 β, an
indicator of a normal fetal-placental growth, in order to analyze the placental
function.

30 <u>Methods</u>

31 We included 153 singleton pregnancies with SARS-CoV-2 positive PCR in our study, 32 who delivered at three referring hospitals in Switzerland. Placental weight and b/p ratio 33 were compared to published reference charts. Logistic regression analysis investigated 34 the role of time of infection and other confounding factors on placental weight. The 35 scaling exponent β was compared to the reference value of ³/₄.

36 Results

Placental weight was inferior or equal to the 10th centile in 42.5%(65/153) and to the 3rd 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 >50th 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 (R²=0.56).

43 <u>Conclusion</u>

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.

- hund

64 Introduction

65 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 66 since¹. In its severe forms, SARS-CoV-2 infection can trigger a hyper-inflammatory 67 response, leading to a complex, immune-mediated disorder². It is rational to believe 68 69 that COVID-19 as highly immunogenic viral infection may interfere with the regular 70 course of pregnancy, and that pregnant women could be highly susceptible to a more severe course of the disease². Indeed, recent systematic reviews report more severe 71 72 outcomes in pregnant women with symptomatic SARS-CoV-2 infection and a higher 73 risk to be admitted to the intensive care unit (ICU) and to require invasive 74 ventilation³. The risk for adverse neonatal outcome also seems to be elevated⁵. Moreover, the risk of stillbirth seems to be increased, as reported by a British study 75 including more than 340.000 women⁵. 76

77 To date, it is still unclear to which extent placental damage could be responsible for 78 adverse maternal and neonatal outcome in these pregnancies. Although a fair amount 79 of attention focused on this topic, reports are yet inconclusive. Several studies report histopathological alterations such as presence of intervillous thrombi and placental 80 81 infarcts as an expression of maternal vascular malperfusion after SARS-CoV-2 infection⁶⁻⁹. Presence of a robust inflammatory response at the maternal-fetal 82 83 interface and possible associations with long-term neurocognitive impairment in children after immune activation in the placenta have also been discussed¹⁰. 84

Nevertheless, histopathological findings are still conflicting, since several studies
report no differences between placentas originating from SARS-CoV-2 infected
mothers, as compared to controls¹¹⁻¹².

88 Maternal viral infection can be associated with placental alterations, such as 89 lymphoplasmacytic villitis following cytomegalovirus infection, as well as 90 intervillositis after Zika or Dengue virus infections⁶. Expression of angiotensin-91 converting enzyme 2 (ACE2) in the placenta offers a potential entry mechanism for SARS-CoV-2, yet vertical transmission seems to be exceptionally rare⁷⁻⁹. Beyond the 92 93 inconsistency of data lies one certainty: no histopathological `footprint` in association 94 with SARS-CoV-2 has yet been found, and the described changes can be associated with other pregnancy related pathologies such as hypertensive complications $^{13-14}$. 95

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 fetus¹⁵.

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 hyperbilirubinemia¹⁶⁻¹⁷. In mice, small placentas have been shown to upregulate placental transport systems in order to prevent fetal growth restriction¹⁶⁻¹⁷. 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 placenta¹⁶⁻¹⁷.

107 A similar approach to assess placental efficacy is to calculate the metabolic scaling 108 exponent β , which reflects the fractal structure of the placental vasculature¹⁸. This model 109 proposes an explanation on how the placenta `translates` into fetal mass, thus 110 metabolism into organism¹⁸.

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

113 assessing placental function by assessing its weight, calculating the b/p ratio and 114 analyzing whether the scaling exponent β in our population is close to ³/₄ which would 115 be congruent with an optimal placental metabolic efficiency.

116 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.

128 Statistical analysis was performed with GraphPad Prism version 8.0 for Windows, 129 (GraphPad Software, San Diego CA, USA). Independent sample student's t-test was 130 used to compare continuous variables. Proportions were analyzed by using Fisher's 131 exact test or Chi² test where appropriate. Spearman rank correlation and linear logistic 132 regression were used to assess the relationship between gestational age, birth weight, 133 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 134 135 weight was performed, considering low placental weight as inferior or equal to the 3rd and to the 10th percentile, respectively. A p-value of <0.05 was considered significant. 136

137 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-β, the metabolic scaling equation was
 applied and fitted as described by Salafia et al ¹⁸.

141 Since human neonatal birthweight does not scale linearly with the placental weight but

142 this interconnection follows the rules of allometric metabolic scaling model described

by Keiber's law and Ahern's adaptation for the feto-placental unit¹⁹⁻²⁰, we considered

144 following formula:

145 placental weight = α (birthweight)^{β}

146 which reveals the relationship between placental weight and birth weight, under the hypothesis that the placenta and the fetus interact like a fractal supply system¹⁸. We 147 148 considered as reference the β -value close to the value of $\frac{3}{4}$, which has been previously described as normal in allometric metabolic studies in singleton pregnancies¹⁸⁻²¹. 149 Briefly, Ahern's power function relationship, i.e. placental weight (PW) = α (birth 150 weight)^{β} was transformed in a linear form by applying the natural logarithm to both 151 sides: $Ln(PW)=Ln\alpha+\beta*LnBW$. The data were then fitted by ordinary linear least-152 153 square regression using the curve-fitting tool of the statistical software.

154 **Results**

155 During the study period, 153 placentas following pregnancies affected by SARS-CoV-

156 2 infection were included. Description of baseline characteristics is depicted in Table 1.

157 Placental weight was inferior or equal to the 10^{th} centile in 42.5% (65/153) and inferior 158 or equal to the 3^{rd} centile in 19% (29/153) of the cases (Fig. 1). B/p ratio was > 50th 159 centile in 80.4% (123/153) of the cases and > 90th centile in 31.37% (48/153) of the 160 cases (Fig. 2). Linear regression modelling of the analysed population revealed a 161 metabolic scaling exponent β of 0.871±0.064 (R²=0.56) and LnPW= -0.786 + 0.871*LnBW (Fig 3).

163 Trimester 1, 2 and 3 were defined as conception up to 11 + 6 weeks, between 12 to 23 164 + 6 weeks and more than 24 weeks of gestation, respectively. In 62.1% (95/153) of the 165 cases, infection occurred in the third trimester of gestation. In 29.41% (45/153) and in 166 4.58%; (7/153) of the cases, infection occurred in the second and first trimester, 167 respectively. In 3.92% (6/153) cases, the time-point of infection was unknown. 168 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 169 and for the 10th centile, adjusted for trimester of infection and multiparty status. 170

171 In multivariate logistic regression analysis considering adjusted OR on available co-172 variates: BMI >35 kg/m2, ethnicity, tobacco consumption, multiparty, gestational 173 diabetes, pregestational diabetes and preeclampsia, multiparty was the only significant 174 factor negatively associated with low placental weight defined as inferior or equal to 175 10^{th} 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.

184 Discussion

185 The main finding of our study was the increased incidence of low placental weight after 186 SARS-CoV-2 infection during pregnancy. This finding contrasts with the 187 predominantly normal birthweight of the corresponding neonates and leads to an 188 elevated b/p ratio in our cohort. Furthermore, we found a distinctively higher value of 189 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 low¹⁷. 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.

196 One of the largest studies investigating the meaning of the b/p ratio relies on data from over 500.000 singleton deliveries in Norway²³. The authors analyzed the relative risk of 197 198 fetal death in the lowest and highest b/p ratio quartiles for both preterm and term 199 deliveries in their population. In the preterm group, in both lowest and highest b/p ratio 200 quartiles, odds ratio for fetal death was increased, whereas at term, an elevated risk for 201 fetal demise was found in the highest quartile. This finding is highly relevant and 202 suggests that a small placenta as related to fetal size could be a risk factor for fetal death 203 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.

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

report documents a rate of 66.7% placentas $< 10^{\text{th}}$ centile (n=20), which is in line with 209 our findings, nevertheless associated with an accordingly high prevalence of FGR¹². 210

211 As previously mentioned, there is preliminary data linking fetal death to SARS-CoV-2 212 infection during pregnancy. The mechanism behind these findings is not yet elucidated, 213 and so far, placental inflammation and/or generic consequence of maternal illness in 214 pregnancy were invoked as a potential cause⁵. Our data cannot fully explain the 215 underlying mechanism either, but raise further concerns regarding these insights. Given 216 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 217 218 COVID-19 disease during pregnancy.

We used as reference placental weight charts for singleton pregnancies published by 219 220 Thomson et al. in 2007, which are based on data originating from 231.806 deliveries from Norway²². To our knowledge, these are the largest published placental weight 221 222 reference charts originating from a population similar to ours in terms of ethnical 223 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 224 225 population, 85.7% of the women were born in Norway, thus the ethnicity can be 226 extrapolated to our Swiss, predominantly Caucasian population, as opposed to other placental weight curves available, where an important percent of the population was of 227 African (>80%) or Asian (>95%) ethnicity²⁴⁻²⁵. Furthermore, the reference values were 228 229 generated by using outcomes from pregnancies between 24 and 44 weeks of gestation, 230 identical to our cohort. All though Swiss reference curves for placental weight are also 231 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 232 curves^{22,26}. Given the size and characteristics of the available references, we consciously 233

234 decided against a case-control approach. We are aware that some may regard this as a 235 weak point of our analysis, thus we intended to counterbalance it with the calculation of 236 the scaling exponent β in our population.

237 On this note, we found a distinctively higher value of the scaling exponent β than 238 expected in normal singleton pregnancies. A higher value of β correlates with a newborn 239 weight lower than that predicted by Kleiber's metabolic scaling law¹⁸. It is assumed that 240 a deviation from a $\beta \approx 0.75$ may reflect a decreased metabolic efficiency of the placenta, 241 as β reflects the fractal structure of the placental vasculature¹⁸. This correlates with the 242 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 birth²⁷⁻²⁸. 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 basis²⁸.

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 pregnancy²⁹. 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.

260 Our study is the only one to date describing a relevant association between low placental 261 weight as well as an altered metabolic scaling value in pregnancies complicated by 262 SARS-CoV-2 infection, without cofounding factors such as FGR. The main strengths 263 of the study are its prospective and multicentric nature. For the moment, it is still 264 speculative to assert that SARS-CoV-2 alone may be responsible for these findings, the 265 size of the cohort being the main limitation of our study. A further limitation is not being 266 able to assess severity of disease in all patients, because of data inconsistency, thus not 267 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-β 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 offspring²⁷⁻²⁸. 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 cases³⁰.

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

279 **<u>Disclosure statement:</u>** The author(s) report(s) no conflict of interest.

280 **Financial support:** No funding.

281 <u>Authors` contributions:</u>

- 282 Anda-Petronela RADAN: conception and design of the study, acquisition of data,
- analysis and interpretation of data, drafting the article
- 284 David BAUD: acquisition of data, analysis and interpretation of data, revising the
- article critically for important intellectual content
- 286 Guillaume FAVRE: acquisition of data, analysis and interpretation of data
- 287 Andrea PAPADIA: acquisition of data, revising the article critically for important
- 288 intellectual content
- 289 Daniel SURBEK: acquisition of data, revising the article critically for important
- 290 intellectual content
- 291 Marc BAUMANN: analysis and interpretation of data
- 292 Luigi RAIO: conception and design of the study, analysis and interpretation of data,
- 293 revising the article critically for important intellectual content

294 References

- Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global
 emergency. A review of the 2019 novel coronavirus (COVID- 19). Int J Surg
 2020; 76: 71–76.
- Mor G., Aldo P, Alvero A. The unique immunological and microbial aspects of
 pregnancy. Nat Rev Immunol 17, 469–482 (2017).
 https://doi.org/10.1038/nri.2017.64
- 301 3. Elsaddig M., Khalil A. Effects of the COVID pandemic on pregnancy outcomes.
 302 Best Practice & Research Clinical Obstetrics & Gynaecology, Volume 73, 2021,
- 303 125-136, https://doi.org/10.1016/j.bpobgyn.2021.03.004.

α_1	1111	m	а I	116	in T	~ 1
					ν.	

304	4.	Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and
305		maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy:
306		living systematic review and meta-analysis. BMJ. 2020 Sep 1;370:m3320. doi:
307		10.1136/bmj.m3320. PMID: 32873575; PMCID: PMC7459193.

- 308 5. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of
 309 pregnant women with SARS-CoV-2 infection at the time of birth in England:
 310 national cohort study. American Journal of Obstetrics and Gynecology. 2021
 311 May. DOI: 10.1016/j.ajog.2021.05.016. PMID: 34023315; PMCID:
 312 PMC8135190.
- 313 6. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental
 314 Pathology in COVID-19. Am J Clin Pathol. 2020;154(1):23-32.
 315 doi:10.1093/ajcp/aqaa089
- 316 7. Gengler C, Dubruc E, Favre G, Greub G, de Leval L, Baud D. SARS-CoV-2
 317 ACE-receptor detection in the placenta throughout pregnancy. *Clin Microbiol*318 *Infect.* 2021;27(3):489-490. doi:10.1016/j.cmi.2020.09.049
- Jaiswal N, Puri M, Agarwal K, et al. COVID-19 as an independent risk factor for subclinical placental dysfunction. Eur J Obstet Gynecol Reprod Biol. 2021 Jan 29;259:7-11. doi: 10.1016/j.ejogrb.2021.01.049. Epub ahead of print.
 PMID: 33556768; PMCID: PMC7845516.
- 323 9. Hecht JL, Quade B, Deshpande V, et al. SARS-CoV-2 can infect the placenta 324 and is not associated with specific placental histopathology: a series of 19 325 placentas from COVID-19-positive mothers. Mod Pathol. 2020 Nov;33(11):2092-2103. doi: 10.1038/s41379-020-0639-4. Epub 2020 Aug 2. 326 327 PMID: 32741970; PMCID: PMC7395938.

nirn	D		nr	$\sim f$
Jurn			$\mathcal{D}\mathcal{I}$	U I

328	10. Lu-Culligan A, Chavan AR, Vijayakumar P, et al. SARS-CoV-2 infection in
329	pregnancy is associated with robust inflammatory response at the maternal-
330	fetal interface. medRxiv [Preprint]. 2021 Jan 26:2021.01.25.21250452. doi:
331	10.1101/2021.01.25.21250452. PMID: 33532791; PMCID: PMC7852242.

- 332 11. Gao L, Ren J, Xu L, et al. Placental pathology of the third trimester pregnant
 333 women from COVID-19. Diagn Pathol. 2021 Jan 14;16(1):8. doi:
 334 10.1186/s13000-021-01067-6. PMID: 33441152; PMCID: PMC7806280.
- 12. HE M, Skaria P, Kreutz K et al. Histopathology of Third Trimester Placenta
 from SARS-CoV-2-Positive Women, Fetal and Pediatric Pathology, DOI:
 10.1080/15513815.2020.1828517
- 338 13. Bustamante Helfrich B, Chilukuri N, He H, et al. Maternal vascular
 339 malperfusion of the placental bed associated with hypertensive disorders in
 340 the Boston Birth Cohort. Placenta. 2017;52:106-113.
- 341 14. Weiner E, Feldstein O, Tamayev L, et al. Placental histopathological lesions
 342 in correlation with neonatal outcome in preeclampsia with and without severe
 343 features. Pregnancy Hypertens. 2018;12:6-10.
- 344 15. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental
 345 growth and metabolism. Biochim Biophys Acta Mol Basis Dis. 2020 Feb
 346 1;1866(2):165359. doi: 10.1016/j.bbadis.2018.12.010. Epub 2018 Dec 26.
 347 PMID: 30593896; PMCID: PMC6594918.
- 348 16. Salavati N, SGordijn SJ, USovio U, et al. Birth weight to placenta weight ratio
 349 and its relationship to ultrasonic measurements, maternal and neonatal
 350 morbidity: A prospective cohort study of nulliparous women. Placenta. 2017.
 351 DOI: 10.1016/j.placenta.2017.11.008

\sim	1112	n		D		nr	\sim	~ 1
U	ull.		aı		Ц.	$\mathcal{D}\mathcal{I}$	U	U.

352	17. Hayward CE, Lean S, Sibley CP, et al. Placental Adaptation: What Can We
353	Learn from Birthweight: Placental Weight Ratio? Front Physiol. 2016; 7: 28.
354	Published online 2016 Feb 5. doi: 10.3389/fphys.2016.00028

- 355 **18.** Salafia CM, Misra DP, Yampolsky M, Charles AK, Miller RK. Allometric
- 356 metabolic scaling and fetal and placental weight. Placenta. 2009 Apr;30(4):355-
- 357 60. doi: 10.1016/j.placenta.2009.01.006. Epub 2009 Mar 4. PMID: 19264357;
 358 PMCID: PMC3779882.
- **19.** Kleiber M. Body size and metabolism. Hilgardia 1932;6:315–353
- 360 20. Gruenwald P. The placenta and its maternal supply line: Effects of insufficiency
 361 on the fetus. Baltimore: University Park Press; 1975
- 362 21. Baumann MU, Marti M, Durrer L, et al. Placental plasticity in monochorionic
 363 twins: Impact on birth weight and placental weight. Placenta. 2015
 364 Sep;36(9):1018-23. doi: 10.1016/j.placenta.2015.07.120. Epub 2015 Jul 14.
 365 PMID: 26215381.
- 366 22. Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. Placenta weight
 367 percentile curves for singleton deliveries. BJOG. 2007 Jun;114(6):715-20. doi:
 368 10.1111/j.1471-0528.2007.01327.x. PMID: 17516963.
- 369 23. Haavaldsen C., Samuelsen S. O., Eskild A. (2013). Fetal death and placental
 370 weight/birthweight ratio: a population study. Acta Obstet. Gynecol. Scand. 92,
 371 583–590. 10.1111/aogs.12105
- 24. Dombrowski MP, Berry SM, Johnson MP, Saleh AA, Sokol RJ. Birth weightlength ratios, ponderal indexes, placental weights, and birth weight-placenta
 ratios in a large population. Arch Pediatr AdolescMed. 1994;148:508–12.
- 375 25. Ogawa M, Matsuda Y, Nakai A, Hayashi M, Sato S, Matsubara S. Standard
 376 curves of placental weight and fetal/placental weight ratio in Japanese

377	population: difference according to the delivery mode, fetal sex, or maternal
378	parity. Eur J Obstet Gynecol Reprod Biol. 2016 Nov;206:225-231. doi:
379	10.1016/j.ejogrb.2016.09.004. Epub 2016 Oct 5. PMID: 27750181.
380	26. Burkhardt T, Schäffer L, Schneider C, Zimmermann R, Kurmanavicius J.
381	Reference values for the weight of freshly delivered term placentas and for
382	placental weight-birth weight ratios. Eur J Obstet Gynecol Reprod Biol. 2006
383	Sep-Oct;128(1-2):248-52. doi: 10.1016/j.ejogrb.2005.10.032. Epub 2005 Dec
384	27. PMID: 16377060.
385	27. Barker DJ. In utero programming of chronic disease. Clin Sci (Lond).
386	1998;95(2):115–28.
387	28. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk
388	of hypertension in adult life. BMJ 1990;301(6746)
389	29. Bloise E, Zhang J, Nakpu J et al. Expression of severe acute respiratory
390	syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and
391	transmembrane protease serine 2, in the placenta across gestation and at the
392	maternal-fetal interface in pregnancies complicated by preterm birth or
393	preeclampsia. Am J Obstet Gynecol. 2021 Mar;224(3):298.e1-298.e8. doi:
394	10.1016/j.ajog.2020.08.055. Epub 2020 Aug 25. PMID: 32853537; PMCID:
395	PMC7445125.
396	30. Vouga M., Favre G., Martinez-Perez O., et al. Maternal outcomes and risk
397	factors for COVID-19 severity among pregnant women. Sci Rep 11, 13898
398	(2021). https://doi.org/10.1038/s41598-021-92357-y

402		
403		
404		
405		
406	Tables and Figures	

407 <u>Tables</u>

408 **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 ±	38.8 ± 2.71
SD)	
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)	$320\overline{6.57 \pm 637.49}$
Placental weight (grams \pm SD)	520.42 ± 124.81

409

410 Values are shown as median (range), number and % or mean \pm standard deviation (SD) where

411 appropriate; ¹*preterm delivery:* <37 0/7 weeks of gestation; ²*FGR:* Fetal growth restriction

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

414



- **Table 2**: Clinical characteristics of the study population dichotomized between
- 417 placental weight $\leq 10^{th}$ and $> 10^{th}$ centile for gestational age

Characteristics	Placent	Placental weight		
	$\leq 10^{\text{th}}$ centile	> 10 th centile		
	[n = 65 (42.5%)]	[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	

⁴¹⁹ Values are shown as median (range) or number and % where appropriate; *ns*, not significant

428 <u>Figure legends</u>

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

432

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

436

437 Figure 3. Relationship between birth weight and placental mass. Fitted straight line to438 natural logarithms (LN) of birth weight (BW) and placental weight (PW).

439





