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## Effects of SARS-CoV-2 on prenatal lung growth assessed by fetal MRI

The COVID-19 pandemic has resulted in a plethora of acute and long-term diseases, with lung health remaining an important focus. Even though reports of fetal viral transmission of SARS-CoV-2<sup>1</sup> and viral placental infection<sup>2</sup> have raised concerns, implications for longer-term lung health induced by a virus with high affinity to the respiratory epithelium<sup>3</sup> have not been addressed. Our study was designed to elucidate the effects of SARS-CoV-2 infection on the fetus, especially in light of ongoing discussions about the benefits of vaccination during pregnancy. Additionally, we aimed to inform

future studies on pulmonary health in children exposed to SARS-CoV-2 during pregnancy. We used fetal MRI to assess lung volume as a measure of pulmonary growth in the offspring of women with uncomplicated SARS-CoV-2 infection during pregnancy. This study was approved by the local institutional review board (ethical approval #LMU-207-33).

We analysed the MRI data of 34 pregnant women (median gestational age 33.5 weeks [range 24–40]; appendix p 3) with only mild symptoms of PCR-proven SARS-CoV-2 infection and no related hospital admissions. Fetal lung volume, normalised to estimated fetal weight, was described as a percentage of the respective 50th percentile reference values (appendix p 6).<sup>4</sup> The effects of gestational age at MRI scan, sex,

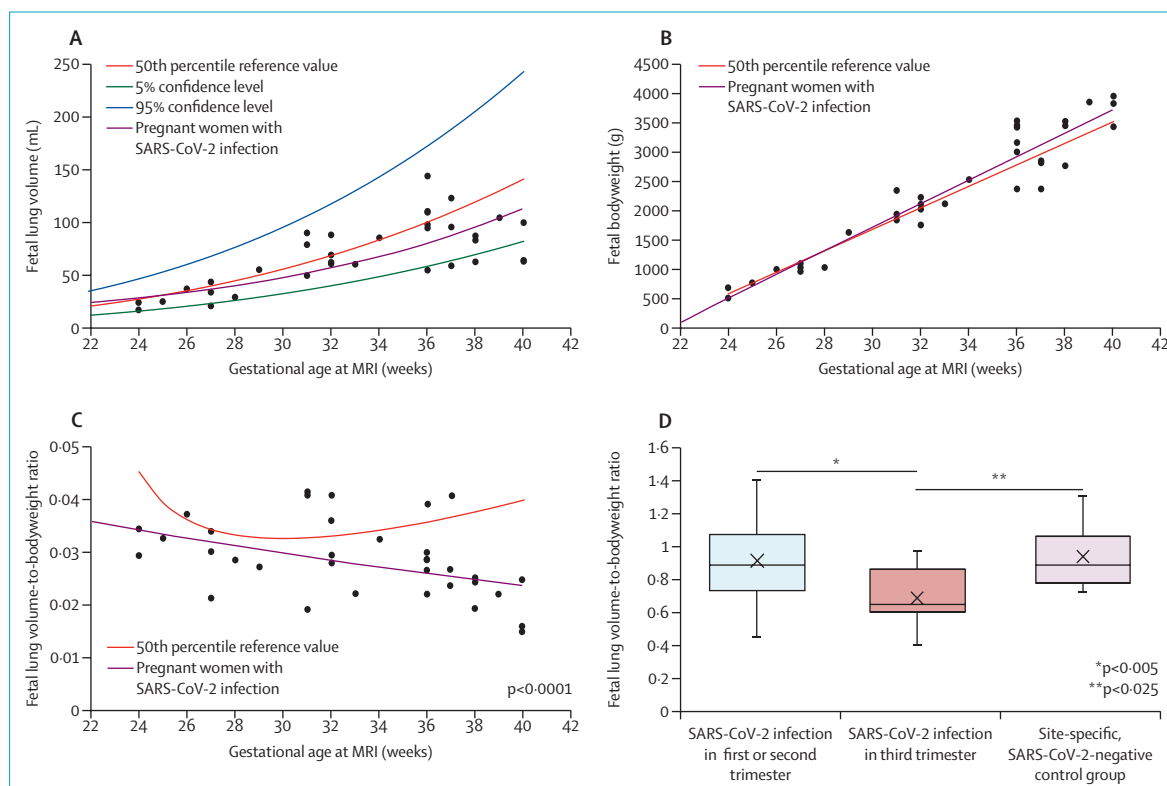
timepoint (trimester) of infection (confirmed by positive PCR), and duration of infection in days (PCR to MRI) on fetal lung volume were assessed by generalised linear modelling with identity link function for normal distribution. Placental heterogeneity and thrombosis were scored from 0 (none) to 4 (severe).

In pregnant women who tested positive for SARS-CoV-2, normalised fetal lung volume was significantly reduced compared with age-adjusted reference values,<sup>4</sup> in the absence of structural abnormalities or organ infarction, and was unexplained by differences in somatic growth (84% vs 24% of 50th percentile reference;  $p < 0.0001$ ; figure). The timepoint of infection showed significant effects on fetal lung growth, with reduced lung volumes



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See Online for appendix



**Figure: Effects of SARS-CoV-2 on fetal lung volume and bodyweight**

(A) 50th percentile values, 95% confidence level, and 5% confidence level of total fetal lung volume (mL) over gestational age (weeks at MRI), and the trend observed in pregnant women with SARS-CoV-2 infection. (B) 50th percentile reference values of estimated fetal bodyweight (g) over gestational age (weeks at MRI) and the trend observed in pregnant women with SARS-CoV-2 infection. (C) 50th percentile reference values of fetal lung volume-to-bodyweight ratio over gestational age (weeks at MRI) and the trend observed in pregnant women with SARS-CoV-2 infection. (D) Fetal lung volume normalised by fetal bodyweight (expressed as a percentage of 50th percentile reference value) with timepoint of infection in the third trimester vs timepoint of infection in the first or second trimester vs a site-specific, SARS-CoV-2-negative control group.

observed with SARS-CoV-2 infections acquired during the third trimester (69% vs 91% of 50th percentile reference in the first or second trimester;  $p=0.0249$ ; figure). Duration of infection ( $p=0.5657$ ), gestational age at MRI scan ( $p=0.5704$ ), and sex ( $p=0.3721$ ) did not show significant effects. The reduction in normalised lung volume was supported by the masked comparison to a site-specific, SARS-CoV-2-negative control group ( $n=15$ , 95% vs 69% of 50th percentile reference with infection in third trimester;  $p=0.0050$ ; appendix p 4), as well as a second reader study (appendix p 4). Compared with pregnant women who tested negative for SARS-CoV-2, pregnant women who tested positive for SARS-CoV-2 showed increased placental heterogeneity ( $p=0.0475$ ) and thrombotic changes ( $p=0.0230$ ); however, the association between placental changes and normalised lung volume was not significant when taking gestational age at MRI scan into account ( $p=0.4508$  and  $p=0.4004$ , respectively). Neonatal follow-up in 21 (62%) of 34 neonates at birth (gestational age 35–42 weeks) showed adequate birthweight for gestational age and no indication of acute postnatal respiratory distress (Apgar score 9–10; pulse oximetry 97–100%).

The effects of SARS-CoV-2 infection during pregnancy on fetal lung development have been largely understudied throughout the COVID-19 pandemic. To our knowledge, this is the first study showing reduced fetal lung volume in otherwise healthy pregnant women with SARS-CoV-2 infection. This reduction was dependent on the timepoint of infection, indicating that the most significant results occurred in the third trimester, thereby overlapping with the sacular stage of lung development dedicated to the expansion of (future) air spaces.<sup>5</sup> Despite equivocal findings on placental transmission,<sup>6</sup> predominant viral transmission in the third trimester,<sup>1</sup> and the significant correlation

between positive maternal PCR test and amniotic presence of SARS-CoV-2 near term<sup>7</sup> might enhance exposure of the developing lung parenchyma to the virus, facilitated through increased fetal breathing in the third trimester. Specifically, the high affinity of the virus to alveolar epithelial cells<sup>3</sup> could affect the so-called developmental sprint of these cells. The absence of postnatal respiratory distress in this cohort points to an important, subclinical phenotype related to prenatal exposure to SARS-CoV-2 that should be functionally and structurally addressed in follow-up studies under consideration of exposure to environmental hazards, including infections and toxins. Furthermore, recommendations of SARS-CoV-2 vaccination during pregnancy might be supported by our data.

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\*Sophia Stoecklein,  
Vanessa Koliogiannis, Tobias Prester,  
Thomas Kolben, Magdalena Jegen,  
Christoph Hübener, Uwe Hasbargen,  
Andreas Flemmer, Olaf Dietrich,  
Regina Schinner, Julien Dinkel,  
Nicola Fink, Maximilian Muenchhoff,  
Susan Hintz, Maria Delius,  
Sven Mahner, Jens Ricke,  
Anne Hilgendorff  
sophia.stoecklein@med.uni-muenchen.  
de

Department of Radiology (SS, VK, TP, OD, RS, JD, NF, JR) and Department of Obstetrics and Gynecology, Perinatal Center (TK, MJ, CH, UH, MD, SM), Ludwig Maximilian University Hospital, Munich 81377, Germany; Division of Neonatology and Perinatal Center (AF, AH) and Center for Comprehensive Developmental Care at iSPZ (AH), University Children's Hospital Dr von Hauner Children's Hospital, Munich, Germany; Max von Pettenkofer

Institute and Gene Center, National Reference Center for Retroviruses, Ludwig Maximilian University, Munich, Germany (MM); Department of Pediatrics–Neonatology, Stanford University, Palo Alto, CA, USA (SH); Institute for Lung Biology and Disease and Comprehensive Pneumology Center, German Center for Lung Research, Munich, Germany (AH)

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