Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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reported hypoglycemic episodes, which, confirmed by self-blood glucose monitoring, were all mild episodes (level 1, glycemia 60–70 mg/dL). The dose of metformin in patients who did have hypoglycemia in this group was 1487±355 mg/d compared with 1341±566 mg/d among those who did not experience hypoglycemia (P=0.382). Therefore, we could not relate hypoglycemia to the dose of metformin.

Women in the metformin-only subgroup who had any hypoglycemic event did not show any difference in the level of pregestational body mass index or in weight or weight gain at any period during the study.

The time of drug exposure was 84.6±45.6 days in the metformin group. This allowed us to calculate the incidence of hypoglycemia (event/person/year) and to compare it with the data from Dunkley et al. In the mentioned study, the incidence of hypoglycemia in patients treated with metformin was 0.76/patient/year vs 1.18/patient/year in our trial (metformin-only subgroup).

The glucose values we used to record hypoglycemia were those defined by the American Diabetes Association, adding an intermediate glucose category (glucose between 60 and 70 mg/dL). Perhaps the definition of hypoglycemia during pregnancy should not be the same as for other categories of diabetes, because we know that the glucose levels in pregnant women are physiologically lower than those in the general population. It is possible that level 1 hypoglycemia is reflective, in some cases (biochemical but not clinical events), of lower physiological glucose values rather than pharmacologic iatrogenic events.

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TO THE EDITORS: We read with much interest the published article “Coronavirus disease 2019 infection and placental histopathology in women delivering at term” by Patberg et al. We wish to share our scientific views on this article.

It was a comprehensive case-control study with a good sample size. Multivariable analysis was used to exclude the confounding bias. In addition, inclusion of other reports helped provide solid evidence for comparison in the study.

However, there are a few issues that may be highlighted. Irrespective of symptoms, only women with a positive COVID-19 test result were considered for compulsory screening. Clinically, we cannot differentiate an asymptomatic “carrier” from a healthy person with a false-positive result given that both are asymptomatic. Thus, not surprisingly, in the published paper, only 10% of women experienced symptoms. Most studies reported similar screening tests. Thus, we feel that this study could have repeated the screening after 48–72 hours to confirm the validity of the positive test result or repeated it at term before the delivery to correlate the COVID-19 infection with placenta morphology.

The risk of meconium aspiration syndrome (MAS) was found to be higher in the COVID-19 cohort. However, the incidence of MAS is multifactorial compared with COVID-19 alone. As this is just an observation, we believe that this warrants a detailed discussion, with more emphasis on the multifactorial causes.

Vasculitis of unknown origin or chronic intervillositis was also one of the findings in the COVID-19 cohort. However, it was also considered multifactorial because all COVID-19 cohorts in this study were tested only once. A higher correlation can be assumed if the COVID-19 test is positive within 72 hours before delivery. This is because of the nonspecific changes of placental histology, which can be caused by inflammation or the intrapartum event itself in an otherwise normal pregnancy.

It would be interesting to observe the long-term maternal and fetal follow-up to this study. We applaud the work by the authors and thank the editor for publishing such an interesting article.
Reply to the Letter to the Editors regarding COVID-19 infection and placental histopathology in women delivering at term

Thank you for your comments regarding our publication, “Coronavirus disease 2019 infection and placental histopathology in women delivering at term.” The authors bring up several issues that we wish to address.

First, in response to the comments regarding the possibility of false positive COVID-19 polymerase chain reaction (PCR) testing and the suggestion to repeat screening within 48 to 72 hours, we acknowledge that false positive results are possible; however, this was a retrospective cohort study and, therefore, repeat testing was not feasible. Another publication from our institution using the same PCR methodology estimated a test specificity of 96%, and thus we feel it unlikely that a high false positive rate contributed substantially to our findings.

Second, we did not assess for meconium aspiration syndrome in our study. We assume that the authors were referring to our report of more frequent placental histopathologic findings of meconium in the COVID-19 cohort. We agree that the presence of meconium on histopathologic examinations is a nonspecific finding, and we do not make the argument that this should be attributed to COVID-19. In fact, we acknowledge in the discussion section of the article that this finding was likely attributable to a higher rate of vaginal delivery in the COVID-19 group and of little clinical significance.

Third, the authors state that “vasculitis of unknown origin, chronic intervillositis, can also be stated as one of the findings in the COVID-19 cohort.” We believe that they are referring to our finding of villitis of unknown etiology (sometimes referred to as chronic villitis) that was 3-fold more common in the COVID-19 cohort than in the negative controls. In response to their comment that these changes can be caused by inflammation, we agree. However, we disagree that it can be caused by an intrapartum event, because these histopathologic changes are caused by chronic cellular inflammation of villous stroma, which does not manifest in such a short period. We acknowledge that the etiology of villitis of unknown etiology can be multifactorial, but hypothesize that it may have been a direct consequence of infection of the placenta or caused by an altered immune response to increased levels of cytokines, which can occur following other respiratory viral infections. In addition, the rate of villitis of unknown etiology in our COVID-19 cohort (20.7%) was higher than expected in term placentas (5%–15%), further suggesting that it is unlikely to be a spurious finding.

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