as isolated treatment. Most obstetrical and perinatal results were similar between groups.

The study team collected and analyzed a large amount of data, leading to an interesting and important debate, and we do not have any critical remarks about the study. Nevertheless, we would like to ask 2 questions related to hypoglycemia in the metformin study group. Hypoglycemic episodes were far more common in the insulin group; however, some episodes with relatively low glycemic levels (<54 mg/dL) also occurred in the metformin group (55.9% with insulin vs 17.7% with metformin treatment; odds ratio, 6.118; 95% confidence interval, 3.134–11.944; P=.000).

Metformin, as a drug targeting mainly insulin resistance, is considered to have a very low risk of hypoglycemia in patients with type 2 diabetes with a risk ratio for nonsevere hypoglycemia in a model-based meta-analysis of ~2 when compared with placebo. A relatively recent “real-world” study among patients with type 2 diabetes showed a 2.5-fold increased risk for hypoglycemia in patients treated with insulin compared with those treated with metformin, with the incidence of hypoglycemia being 4.39 per person-year for insulin and 0.76 per person-year for metformin.

Unfortunately, the patient-level factors, such as reduced dietary intake, increased physical activity, or alcohol consumption, which may contribute to the metformin-related hypoglycemia risk, are unknown because these factors are not usually recorded during the studies.

Because the study of Picón-César et al was conducted with great care, we would like to ask if detailed information about the circumstances during hypoglycemic episodes in the metformin group are available and primarily if the risk of hypoglycemia was associated with the metformin dose. Such knowledge would enhance the understanding of the mechanism of metformin-related hypoglycemia and contribute to diminishing its risk.

Our second question is related to the mean duration of the treatment in the study because it was not clearly stated in the paper. This information would further enhance the study impact and enable the calculation of per person-year frequency of hypoglycemia and a comparison with such a number in patients with type 2 diabetes.

With great respect, we suggest considering these comments if study continuation is planned.

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Gestational diabetes, metformin, and risk of hypoglycemia

We appreciate the comments of Drs Jan Brož and Klára Brožová regarding our recent publication “Metformin versus insulin in gestational diabetes: glycemic control, and obstetrical and perinatal outcomes. Randomized prospective trial.”

Unfortunately, we did not record the exact circumstances in which the hypoglycemic episodes occurred, but, in both treatment groups, most hypoglycemic episodes happened in the period between breakfast and prelunch (Table 2 in the original article). By ruling out alcohol consumption and not having evaluated the factual carbohydrate intake (neither a possible concurrent emesis), we think that greater physical activity during these hours is the reason for this higher rate of hypoglycemia.

As you suggested, we have studied the possible relationship between the hypoglycemic episodes and the dose of metformin. At the prepartum visit (maximum metformin dose), patients who experienced any hypoglycemic episode had a mean metformin dose of 1540±316 mg/d compared with 1421±543 mg/d among women who did not experience hypoglycemia (P=.359). In the metformin-only group, 6 women
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 ($P$=.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 (met-
formin-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 pharmaco-
logic iatrogenic events.

TO THE EDITORS: We read with much interest the pub-
lished 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 re-
ports 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 pub-
lished 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 corre-
lation 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 inter-
esting article.