OBSTETRICS

Gestational diabetes mellitus and COVID-19: results from the COVID-19–Related Obstetric and Neonatal Outcome Study (CRONOS)

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BACKGROUND: Gestational diabetes mellitus is one of the most frequent pregnancy complications with a global prevalence of 13.4% in 2021. Pregnant women with COVID-19 and gestational diabetes mellitus are 3.3 times more likely to be admitted to an intensive care unit than women without gestational diabetes mellitus. Data on the association of gestational diabetes mellitus with maternal and neonatal pregnancy outcomes in pregnant women with SARS-CoV-2 infection are lacking.

OBJECTIVE: This study aimed to investigate whether gestational diabetes mellitus is an independent risk factor for adverse maternal and fetal and neonatal outcomes in pregnant women with COVID-19.

STUDY DESIGN: The COVID-19-Related Obstetric and Neonatal Outcome Study is a registry-based multicentric prospective observational study from Germany and Linz, Austria. Pregnant women with clinically confirmed COVID-19 were enrolled between April 3, 2020, and August 24, 2021, at any stage of pregnancy. Obstetricians and neonatologists of 115 hospitals actively provided data to the COVID-19-Related Obstetric and Neonatal Outcome Study. For collecting data, a cloud-based electronic data platform was developed. Women and neonates were observed until hospital discharge. Information on demographic characteristics, comorbidities, medical history, COVID-19–associated symptoms and treatments, pregnancy, and birth outcomes were entered by the local sites. Information on the periconceptional body mass index was collected. A primary combined maternal endpoint was defined as (1) admission to an intensive care unit (including maternal mortality), (2) viral pneumonia, and/or (3) oxygen supplementation. A primary combined fetal and neonatal endpoint was defined as (1) stillbirth at $\geq$24 0/7 weeks of gestation, (2) neonatal death $\leq$7 days after delivery, and/or (3) transfer to a neonatal intensive care unit. Multivariable logistic regression analysis was performed to evaluate the modulating effect of gestational diabetes mellitus on the defined endpoints.

RESULTS: Of the 1490 women with COVID-19 (mean age, 31.0±5.2 years; 40.7% nulliparous), 140 (9.4%) were diagnosed with gestational diabetes mellitus; of these, 42.9% were treated with insulin. Overall, gestational diabetes mellitus was not associated with an adverse maternal outcome (odds ratio, 1.50; 95% confidence interval, 0.88–2.57). However, in women who were overweight or obese, gestational diabetes mellitus was independently associated with the primary maternal outcome (adjusted odds ratio, 2.69; 95% confidence interval, 1.43–5.07). Women who were overweight or obese with gestational diabetes mellitus requiring insulin treatment were found to have an increased risk of a severe course of COVID-19 (adjusted odds ratio, 3.05; 95% confidence interval, 1.38–6.73). Adverse maternal outcomes were more common when COVID-19 was diagnosed with or shortly after gestational diabetes mellitus diagnosis than COVID-19 diagnosis before gestational diabetes mellitus diagnosis (19.6% vs 5.6%; $P<.05$). Maternal gestational diabetes mellitus and maternal preconception body mass index of $\geq$25 kg/m^2 increased the risk of adverse fetal and neonatal outcomes (adjusted odds ratio, 1.83; 95% confidence interval, 1.05–3.18). Furthermore, overweight and obesity (irrespective of gestational diabetes mellitus status) were influential factors for the maternal (adjusted odds ratio, 1.87; 95% confidence interval, 1.26–2.75) and neonatal (adjusted odds ratio, 1.81; 95% confidence interval, 1.32–2.48) primary endpoints compared with underweight or normal weight.

CONCLUSION: Gestational diabetes mellitus, combined with periconceptional overweight or obesity, was independently associated with a severe maternal course of COVID-19, especially when the mother required insulin and COVID-19 was diagnosed with or after gestational diabetes mellitus diagnosis. These combined factors exhibited a moderate effect on neonatal outcomes. Women with gestational diabetes mellitus and a body mass index of $\geq$25 kg/m^2 were a particularly vulnerable group in the case of COVID-19.

Key words: diabetes mellitus, invasive ventilation, large for gestational age, maternal pregnancy outcomes, morbidity, obesity, pregnancy, SARS-CoV-2

Introduction

Pregnancy is considered an independent risk factor for severe COVID-19,[1] and pregnancy outcomes are negatively influenced by preexisting comorbidities, such as cardiovascular disease, obesity, and diabetes mellitus (DM).[2] Obesity is

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AJOG at a Glance

Why was this study conducted?

This study aimed to quantify independent associations between gestational diabetes mellitus (GDM) and severe COVID-19 in pregnancy.

Key findings

After adjusting for confounders, GDM was independently associated with a more severe course of COVID-19 in women who were overweight (adjusted odds ratio [aOR], 2.90; 95% confidence interval [CI], 1.21−6.95) or obese (aOR, 2.54; 95% CI, 1.13−5.67), but not in women with normal weight. Women who were overweight or obese with insulin-treated GDM experienced a further increased risk of adverse outcomes (aOR, 3.05; 95% CI, 1.38−6.73). Adverse maternal outcomes were more common when COVID-19 was diagnosed with or shortly after GDM diagnosis than COVID-19 diagnosis before GDM diagnosis (19.6% vs 5.6%; $P<.05$). Neonatal adverse outcomes were associated with GDM and body mass index of $\geq$25 kg/m^2 in their mothers (aOR, 1.83; 95% CI, 1.05−3.18).

What does this add to what is known?

Pregnant women who are overweight or obese before or at the beginning of pregnancy with combined GDM and COVID-19 represented a vulnerable group.

associated with an unfavorable outcome in pregnant women, and its combination with abnormal glucose metabolism further enhances this effect.[3] Hyperglycemia in pregnancy is a continuum. Preexisting DM is at 1 end of the spectrum as a chronic disease, whereas gestational DM (GDM) represents the low end, first detected in pregnancy and usually resolving after delivery. GDM requiring insulin is regarded as a more severe form of the disorder.

Entry of SARS-CoV-2 into the body is mediated by its binding to the angiotensin-converting enzyme 2 (ACE2) receptor.[4] In DM, the entry of the virus may be facilitated by an increase of ACE2 receptor expression by hyperinsulinemia, which is further enhanced by the surface glycoprotein dipeptidyl peptidase-4.[5] DM may be associated with complement defects, immunodeficiency, and increased inflammatory activity. In nonpregnant individuals with COVID-19 inhospital hyperglycemia and inflammation are independently associated with a severe course.[6] In addition, it has been shown that SARS-CoV-2 may damage pancreatic beta cells, resulting in an increased incidence of newly diagnosed DM.[7,8]

Little is known about the modulatory role of GDM in pregnant women with COVID-19. GDM is one of the most frequent pregnancy complications with a global prevalence of 13.4% and a Europe prevalence of 7.8%.[9,10] Although GDM is a milder form of hyperglycemia, pregnant women with COVID-19 and GDM are 3.3 times more likely to be admitted to an intensive care unit (ICU) than women without DM; however, here, severe disease and invasive ventilation in women with GDM were not increased.[2] Analysis of data from registries can be skewed, either lacking specific information about GDM and its differentiation from DM or the data extraction is solely based on International Classification of Diseases codes.[11−13]

For the current study, data from the "COVID-19−Related Obstetric and Neonatal Outcome Study" (CRONOS), a hospital-based registry study in Germany and Linz, Austria, were used to evaluate data on the diagnosis and treatment of GDM. The aim of this subgroup analysis of the CRONOS registry was to investigate whether GDM represents an independent risk factor for adverse maternal and neonatal outcomes in pregnant women with COVID-19.

Material and Methods

CRONOS is a multicentric prospective observational study established by the German Society of Perinatal Medicine in April 2020 to offer a timely and fact-based extension of the counseling of pregnant women. Parts of the study results have been published.[14−16] Ethics approval was obtained (University Hospital Schleswig-Holstein, Kiel, Germany; file number D 451/20). Inpatient women with confirmed COVID-19 were included. No woman in our cohort was vaccinated against COVID-19 before their SARS-CoV-2 infection.

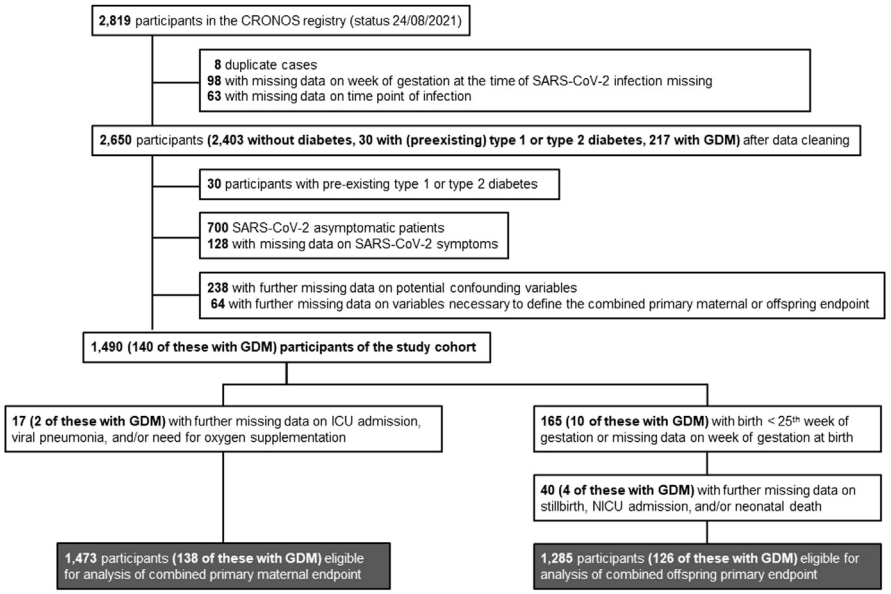
Data management

For collecting data, a reporting form was developed using the cloud-based electronic data capture platform of the service provider castoredc.com (Amsterdam, Netherlands). According to the study protocol, all women were prospectively enrolled in the study at first presentation in the maternity hospitals. Informed consent was either obtained in the antepartum period or waived in the postpartum period if presented with former COVID-19 in the current pregnancy. Information on demographic characteristics, comorbidities, previous and current pregnancy characteristics, COVID-19−associated symptoms and treatments, pregnancy and birth-specific events, and neonatal outcomes were entered for each pregnant woman.

Study cohort

At the time point of data extraction, obstetricians and neonatologists from 115 maternity hospitals had actively provided data to CRONOS. A total of 2819 extracted cases from April 3, 2020, to August 24, 2021, underwent review and plausibility check (Figure 1). Patients who tested positive for SARS-CoV-2 but did not have COVID-19−associated symptoms were excluded from the final analysis. The final study cohort was composed of 1490 women. Of these, the diagnosis of COVID-19 was confirmed by a real-time polymerase chain reaction (PCR) test in 1319 (88.5%), by a positive antigen test result in 40 (2.7%), and by positive

FIGURE 1
Flowchart showing the CRONOS participants being eligible for analysis



CRONOS, COVID-19—Related Obstetric and Neonatal Outcome Study; *GDM*, gestational diabetes mellitus; *ICU*, intensive care unit; *NICU*, neonatal intensive care unit.

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SARS-CoV-2 antibodies in 37 (2.5%). In 92 cases (6.2%), the type of positive test result was unknown, and in 2 cases (0.1%), the diagnosis was clinically based on the presence of COVID-19 symptoms. The data extraction was performed 2 months after the Delta variant became dominant in Germany.

Definition of gestational diabetes mellitus, gestational diabetes mellitus therapy, data acquisition

GDM was defined according to the International Diabetes in Pregnancy Study Groups criteria[17] In Germany, a 2-step approach is required.[18] First, a 50-g nonfasting 1-hour screen is performed between 24 and 28 weeks of gestation. Women with a test result of ≥135 mg/dL complete a 75-g oral glucose tolerance test (OGTT). GDM is confirmed if any of the following venous plasma glucose values are met or exceeded: fasting, 92 mg/dL; 1 hour, 180 mg/dL; and 2 hours, 153 mg/dL. The diagnosis can be made without OGTT if the screening plasma glucose value exceeds 200 mg/dL. Furthermore, GDM was assumed to be confirmed in 7 women who were classified as GDM by their resident gynecologist according to OGTT results, but the quantitative plasma glucose results were not documented in their maternal health records. GDM was treated according to the German guidelines.[18] Specific data regarding GDM were entered online by each hospital on site. Quality and completeness checks were performed by the central study organization. GDM data, OGTT values, and treatment of GDM were validated.

Definition of body mass index categories

Body mass index (BMI) was classified according to the World Health Organization: underweight, <18.5 kg/m^2; normal weight, 18.5 to 24.9 kg/m^2; overweight, ≥25 kg/m^2; and obesity, ≥30 kg/m^2. For clarity, overweight or obesity in this article refers to a BMI of ≥25 kg/m^2.

Outcomes and endpoint definition

We conducted a subgroup analysis on pregnant women with COVID-19, defining GDM as cases (exposure) and pregnant women with COVID-19 without GDM or DM as controls. We defined the combined primary maternal endpoint as (1) admission to an ICU (including maternal mortality), (2) diagnosis of viral pneumonia, and/or (3) need for oxygen supplementation. The combined primary fetal and neonatal endpoint was defined as the presence of (1) stillbirth at ≥24 0/7 weeks of gestation, (2) neonatal death ≤7 days after delivery, and/or (3) neonatal admission to the neonatal ICU (NICU). We prespecified secondary endpoints: maternal admission to an ICU (including maternal mortality), viral pneumonia, need for oxygen supplementation, neonatal transfer to the NICU, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, and preexisting hypertensive diseases), cesarean delivery, small and large for gestational age (SGA of <10th percentile and LGA of >90th percentile for gestational age and sex). Power calculation was done on preliminary data through November 2020, estimating that 119 cases, 1190 controls, and 110 cases, 1100 controls (1:10), would be sufficient to detect a difference of at least 10% with an alpha level of.05 and power of 80% in the maternal and fetal and neonatal combined primary endpoints, respectively.

Statistical methodology

Model 1

We examined the association of GDM (as exposure, reference group: women without any type of DM) with the defined primary maternal endpoint and with the primary fetal and neonatal endpoint, respectively, using logistic regression models adjusted for BMI (modeled as a 2- or 3-level variable) only. The multivariable-adjusted model included BMI, week of gestation at the onset of COVID-19 symptoms (or at PCR-positive test result), multiples (yes or no), maternal age at the time of positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥1), and hypertensive disorders in pregnancy (yes or no).

Model 2

We examined the association of GDM and BMI category in 4 subgroups of women, that is, (1) no GDM or DM, BMI of <25 kg/m^2 (reference group); (2) no GDM or DM, BMI of ≥ 25 kg/m^2; (3) GDM, BMI of <25 kg/m^2; and (4) GDM, BMI of ≥ 25 kg/m^2 with the primary maternal and fetal and neonatal endpoints using logistic regression models. In a sensitivity analysis, a 3-level stratification of BMI was performed, thus comparing 6 subgroups. For the multivariable-adjusted model, the aforementioned covariates were considered.

Model 3

In addition, individuals were stratified by the requirement for insulin treatment, thus comparing 6 subgroups: (1) no GDM or DM, BMI of <25 kg/m^2 (reference group); (2) no GDM of DM, BMI of ≥ 25 kg/m^2; (3) GDM without insulin, BMI of <25 kg/m^2; (4) GDM without insulin, BMI of ≥ 25 kg/m^2; (5) GDM with insulin, BMI of <25 kg/m^2; and (6) GDM with insulin, BMI of ≥ 25 kg/m^2.

In a subgroup analysis, we included only women with GDM and complete documentation of 75-g OGTT values at the time of GDM diagnosis and information on GDM treatment. The association between venous plasma glucose concentrations from OGTT (continuous variables, all included in the same model) and the combined primary endpoints (dependent variable) was assessed using logistic regression analysis, adjusted for potential confounders as defined above, including GDM treatment (basic management or insulin). The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to develop the combined primary endpoint per 1 mg/dL increase in plasma glucose concentrations are presented.

Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). P values of $<.05$ were considered statistically significant.

Results

Among the 1490 symptomatic women in the study cohort, 140 (9.4%) had GDM (Figure 1). Moreover, 74% of women with COVID-19 were diagnosed simultaneously with or shortly after GDM diagnosis. Most women with GDM showed abnormal fasting glucose concentrations during OGTT, either isolated or in combination with 1 pathologic postprandial glucose concentration value. GDM was treated with insulin in 43% of women (Table 1). Overall, 41% of women in the study cohort were nulliparous. Low language competency, a surrogate parameter in our cohort for low socioeconomic status, was found in 25% of women. Women with GDM were older and more likely to be overweight or obese than women without GDM or DM (Table 1).

Associations of diabetes status with combined primary maternal endpoint

In the overall sample, the odds to develop the combined primary maternal endpoint were comparable between women with GDM and those without any type of DM (model 1) (Table 2). Women with a BMI above the normal range (≥ 25 kg/m^2, including further stratification in overweight and obesity) had significantly higher odds for the maternal endpoint than women who were underweight or who had normal weight (models 1) (Table 2 and Supplemental Table 1). After stratifying the sample according to BMI categories, we observed that GDM was associated with 2.69 times higher odds for the combined maternal endpoint after multivariable adjustment in women who were overweight and obese (reference group: no GDM or DM, BMI of <25 kg/m^2) (model 2) (Table 2). The highest odds associated with GDM was observed in women who were overweight or obese requiring insulin therapy (model 3) (Table 2). Women with COVID-19 diagnosis with or after GDM diagnosis had a statistically significant higher frequency of the combined maternal endpoint than women with COVID-19 diagnosis before GDM diagnosis (19.6% vs 5.6%; $P<.05$) (Supplemental Table 2). In women who were underweight or had normal weight, the risk to develop the combined maternal endpoint was not different between women with GDM, irrespective of insulin use, and women without any type of DM (models 2 and 3) (Table 2).

Associations of diabetes status with combined primary fetal and neonatal endpoint

In the multivariable-adjusted model, the odds of developing the combined primary fetal and neonatal endpoint were not different among the offspring of women with GDM and those without any DM in the overall sample (model 1) (Table 3). Contrastingly, increased maternal BMI was associated with an approximately 80% higher risk to develop the combined endpoint (models 1) (Table 3 and Supplemental Table 3). In stratified analyses, we observed a risk increment of 83% and 91% for offspring of mothers who were overweight or obese with and without GDM, respectively, for the combined fetal and neonatal endpoint, compared with offspring of mothers of the reference group (model 2) (Table 3). There was no statistically significant difference in the primary fetal and neonatal endpoint depending on the time of COVID-19 diagnosis before or with or after GDM diagnosis (24.2% vs 21.5%) (Supplemental Table 2). Unlike the findings for the combined maternal endpoint, offspring of mothers using insulin seemed to already have an increased risk of developing the combined fetal and neonatal endpoint with a maternal BMI of <25 kg/m^2 (model 3) (Table 3).

Associations of diabetes status with secondary endpoints

Analysis of maternal admission to an ICU (including maternal mortality), oxygen supplementation, viral pneumonia, NICU admission (as single endpoints), and cesarean delivery confirmed that the vulnerable subgroups at increased risk of adverse outcomes were women who were overweight or obese and their offspring. Excluding cesarean delivery, the risk further increased if the mothers additionally had GDM (models 2) (Supplemental Table 4). The risk for hypertensive disorders in pregnancy was

TABLE 1
General characteristics of the total study cohort and according to DM status

Characteristic	n (no GDM or DM/GDM)	Total	No GDM or preexisting DM	GDM
5 most commonly reported COVID-19–related symptoms in symptomatic cases	1260/131	Malaise (60%), cough (60%), fatigue (53%), loss of sense of smell or taste (51%), nasal obstructions (41%)	Malaise (60%), cough (59%), fatigue (53%), loss of sense of smell or taste (51%), nasal obstructions (41%)	Cough (66%), malaise (57%), fatigue (53%), loss of sense of smell or taste (47%), nasal obstructions (46%)
Week of gestation at the onset of COVID-19 symptoms (OR at PCR-positive test result)	1350/140	28.2±9.8	28.1±9.9	28.9±8.9
Week of gestation of gestational diabetes mellitus diagnosis	0/140	—	—	25.3±4.3
Glucose-lowering therapy				
Basic management	0/140	—	—	80 (57.1)
Conventional insulin therapy				43 (30.7)
Intensified insulin therapy				17 (12.1)
Fasting venous plasma glucose concentration (mg/dL)[a]	0/130	—	—	96.6±9.7
Venous plasma glucose concentration after 1 h during OGTT (mg/dL)[a]	0/124	—	—	175.7±31.7
Venous plasma glucose concentration after 2 h during OGTT (mg/dL)[a]	0/121	—	—	135.1±29.3
Pathologic venous plasma glucose concentration during OGTT				
Only at fasting	0/120	—	—	44 (36.7)
Only after 1 h				13 (10.8)
Only after 2 h				10 (8.3)
At fasting and after 1 or 2 h				33 (27.5)
After 1 and 2 h				6 (5.0)
At all 3 time points				14 (11.7)
Maternal age at positive COVID-19 test result (y)	1350/140	31.0±5.2	30.9±5.2[b]	32.0±5.0[b]
Maternal BMI before or at the beginning of pregnancy (kg/m^2)				
Underweight or normal weight	1350/140	803 (53.9)	768 (56.9)[c]	35 (25.0)[c]
Overweight		387 (26.0)	340 (25.2)[c]	47 (33.6)[c]
Obese		300 (20.1)	242 (17.9)[c]	58 (41.4)[c]
Language competence (communication possible without any problems)	1350/140	1269 (85.2)	1153 (85.4)	116 (82.9)
Continent of birth				
Europe	1334/139	1015 (68.9)	936 (70.2)	79 (56.8)[b]
North and South America		13 (0.9)	12 (0.9)	1 (0.7)
Africa		50 (3.4)	43 (3.2)	7 (5.0)
Asia		394 (26.8)	342 (25.6)	52 (37.4)
Australia		1 (0.07)	1 (0.07)	0 (0.0)
Nicotine or smoking during pregnancy (yes)	1350/140	47 (3.2)	39 (2.9)	8 (5.7)
Nulliparous (yes)	1350/140	606 (40.7)	557 (41.3)	49 (35.0)
Hypertensive disorders in pregnancy (yes)	1350/140	94 (6.3)	76 (5.6)[c]	18 (12.9)[c]
Mother in ICU (yes)	1334/137	68 (4.6)	54 (4.1)[d]	14 (10.2)[d]
Maternal intubation (yes)	1334/137	29 (2.0)	24 (1.8)	5 (3.7)
Maternal oxygen supplementation (yes)	1335/138	119 (8.1)	100 (7.5)[b]	19 (13.8)[b]
Maternal viral pneumonia (yes)	1323/136	91 (6.2)	76 (5.7)[b]	15 (11.0)[b]
Mother deceased (yes)	1333/137	4 (0.3)	4 (0.3)	0 (0.0)

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TABLE 1
General characteristics of the total study cohort and according to DM status *(continued)*

Characteristic	n (no GDM or DM/GDM)	Total	No GDM or preexisting DM	GDM
Combined primary maternal endpoint (yes)	1335/138	139 (9.4)	117 (8.8)[d]	22 (15.9)[d]
Multiples (yes)	1350/140	44 (3.0)	37 (2.7)	7 (5.0)
Premature rupture of membranes or spontaneous preterm delivery (yes)	1159/126	187 (14.6)	168 (14.5)	19 (15.1)
Stillbirth (yes)	1159/126	13 (1.01)	11 (0.95)	2 (1.59)
Umbilical cord arterial pH<7.1 (yes)	1126/123	46 (3.7)	40 (3.6)	6 (4.9)
Apgar score of <7 at 5 min (yes)	1126/123	29 (2.3)	24 (2.1)	5 (4.1)
Child in neonatal ICU (yes)	1148/124	203 (16.0)	177 (15.4)	26 (21.0)
Child deceased after delivery (yes)	1147/126	4 (0.3)	3 (0.3)	1 (0.8)
Combined primary offspring endpoint (yes)	1159/126	217 (16.9)	189 (16.3)	28 (22.2)
Mode of delivery (cesarean delivery)	1192/130	495 (37.4)	438 (36.7)	57 (43.9)
Small for gestational age (yes)	1021/113	79 (7.0)	70 (6.9)	9 (8.0)
Large for gestational age (yes)	1021/113	103 (9.1)	77 (7.5)[c]	26 (23.0)[c]

Data are presented as number/total number (percentage) or mean±standard deviation, unless otherwise specified. $P<.05$, $P<.001$, and $P<.01$ are for comparison between no GDM or preexisting DM and GDM based on the chi-squared test or Fisher exact test (categorical variables) or Student *t* test (continuous normally distributed variables).

DM, diabetes mellitus; *GDM*, gestational diabetes mellitus; *ICU*, intensive care unit; *OGTT*, oral glucose tolerance test; *OR*, odds ratio; *PCR*, polymerase chain reaction.

[a] To convert to mmol/L multiply mg/dL with 0.055; [b] $P<.05$; [c] $P<.001$; [d] $P<.01$.

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increased in women with GDM compared with their counterparts without DM (model 1) (Supplemental Table 4). Although the offspring of women with GDM did not differ in their risk to be born SGA compared with the offspring of women without any type of DM, the offspring of women with GDM were approximately 3 times more likely to be born LGA (models 1). After additional stratification, the offspring of women with GDM and who were overweight or obese had increased odds for LGA compared with the offspring of women without any type of DM and who were underweight or had normal weight (models 2 and 3) (Supplemental Table 4).

Associations of plasma glucose concentrations with combined primary endpoints

We performed a subgroup analysis of women with GDM to assess the association of venous plasma glucose concentrations from OGTT at the time of GDM diagnosis with the combined primary endpoints. Higher glucose concentrations after 2 hours were independently associated with higher odds to develop the combined primary maternal endpoint. Fasting glucose concentrations were independently and directly associated with the combined primary fetal and neonatal endpoint (Figure 2).

Comment

Principal findings

Pregnant women with GDM and COVID-19 undergo a more severe course of the infection if they are overweight or obese periconceptionally or require insulin in association with a periconceptional BMI of $\geq$25 kg/m^2. Adverse maternal outcomes were more common when COVID-19 was diagnosed with or shortly after GDM diagnosis than COVID-19 diagnosis before GDM diagnosis. These combined factors had a moderate influence on adverse neonatal outcomes. In women with a BMI of <25 kg/m^2 and COVID-19, GDM (with or without insulin) had no adverse effect on the severity of the maternal course.

Hypothesized mechanism of action and further research

COVID-19 may interact with the course of GDM[19] and vice versa. Here, 74% of women with COVID-19 that occurred simultaneously with or shortly after GDM diagnosis experienced a more severe course than women with COVID-19 that occurred before GDM diagnosis. Of note, 43% of women were treated with insulin, supporting previous studies that inflammation may worsen hyperglycemia. In large randomized trials, the insulin rates were 7% and 20%, respectively.[20,21] The INTERCOVID study reported an increased risk ratio for COVID-19 in women with insulin-treated GDM regardless of their BMI.[22]

On their first consultation with their obstetrician, pregnant women should be informed of the measures to reduce the risk of GDM, for example, increasing exercise, cessation of smoking, switching to a healthy diet, and weight gain control

TABLE 2
Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight or obese), and combined primary maternal endpoint

	Combined primary maternal endpoint				
Variable	n (column %)	Yes (n [row %])	No (n [row %])	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Model 1					
GDM					
No GDM or preexisting DM	1335 (90.6)	117 (8.8)	1218 (91.2)	Ref	Ref
GDM, no DM	138 (9.4)	22 (15.9)	116 (84.1)	1.56 (0.94–2.59)	1.50 (0.88–2.57)
BMI[c]					
Underweight or normal weight (<25 kg/m^2)	796 (54.0)	48 (6.0)	748 (94.0)	Ref	Ref
Overweight or obese (≥ 25 kg/m^2)	677 (46.0)	91 (13.4)	586 (86.6)	2.29 (1.58–3.33)[d]	1.87 (1.26–2.75)[d]
Model 2					
No GDM or DM, underweight or normal weight	761 (51.7)	44 (5.9)	717 (94.2)	Ref	Ref
No GDM or DM, overweight or obese	574 (39.0)	73 (12.7)	501 (87.3)	2.37 (1.61–3.51)[d]	1.93 (1.28–2.90)[d]
GDM, underweight or normal weight	35 (2.4)	4 (11.4)	31 (88.6)	2.10 (0.71–6.22)	2.01 (0.65–6.25)
GDM, overweight or obese	103 (7.0)	18 (17.5)	85 (82.5)	3.45 (1.91–6.24)[d]	2.69 (1.43–5.07)[d]
Model 3					
No GDM or DM, underweight or normal weight	761 (51.7)	44 (5.8)	717 (94.2)	Ref	Ref
No GDM or DM, overweight or obese	574 (39.0)	73 (12.7)	501 (37.6)	2.37 (1.61–3.51)[d]	1.93 (1.28–2.90)[d]
GDM without insulin, underweight or normal weight	26 (1.8)	3 (11.5)	23 (88.5)	2.13 (0.61–7.35)	1.98 (0.53–7.34)
GDM without insulin, overweight or obese	54 (3.7)	7 (13.0)	47 (87.0)	2.43 (1.04–5.68)[d]	2.30 (0.94–5.63)
GDM with insulin, underweight or normal weight	9 (0.6)	1 (11.1)	8 (88.9)	2.04 (0.25–16.65)	2.09 (0.24–18.01)
GDM with insulin, overweight or obese	49 (3.3)	11 (22.4)	38 (77.6)	4.72 (2.26–9.86)[d]	3.05 (1.38–6.73)[d]

Data are presented as aOR (95% CI) using logistic regression analyses with combined primary maternal endpoint (yes or no) as the dependent variable.

aOR, odds ratio; *BMI*, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *Ref*, reference interval.

[a] Model 1 adjusted for BMI only and models 2 and 3 unadjusted; [b] Additionally adjusted for week of gestation at the onset of COVID-19 symptoms (or at a positive polymerase chain reaction test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥ 1), and hypertensive disorders in pregnancy (yes or no); [c] Maternal BMI before or at the beginning of pregnancy (kg/m^2); [d] $P<.05$.

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according to the US National Academy of Medicine guidelines, which are the same in Germany. For example, women with obesity should gain weight not more than 9 kg until delivery. All women with GDM diagnosis should receive individual counseling on diet, undergo education, and start self-measurement of capillary blood glucose. The aforementioned measures for prevention are recommended to be intensified after GDM diagnosis to reduce the frequency of insulin use; monitoring visits to discuss the progress should be more frequent. In addition, fetal growth should be monitored regularly by ultrasound examination to detect fetal macrosomia, which is following the German national guidelines on the management of GDM.[18]

Here, the severe course of COVID-19 only affected women who were overweight or obese (with or without GDM), allowing us to conclude that BMI is a relevant factor in the course of the disease. Obesity is associated with an unfavorable outcome in pregnant women, and its combination with abnormal glucose metabolism further enhances this effect.[3] Although we had no information on the quality of metabolic control after GDM diagnosis, the 3-fold increased rate of LGA in women with GDM compared with women without any type of DM (23% vs 7.5%) was indicative of the challenge

TABLE 3
Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight or obese), and combined primary fetal and neonatal endpoint

	Combined primary fetal and neonatal endpoint				
Variable	n (column %)	Yes (n [row %])	No (n [row %])	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Model 1					
GDM					
No GDM or preexisting DM	126 (9.8)	189 (16.3)	970 (83.7)	Ref	Ref
GDM, no DM	1159 (90.2)	28 (2.2)	98 (77.8)	1.20 (0.76–1.90)	1.11 (0.69–1.79)
BMI[c]					
Underweight or normal weight (<25 kg/m^2)	690 (53.7)	87 (12.6)	603 (87.4)	Ref	Ref
Overweight or obese (≥ 25 kg/m^2)	595 (46.3)	120 (21.9)	465 (78.2)	1.89 (1.40–2.56)[d]	1.81 (1.32–2.48)[d]
Model 2					
No GDM or DM, underweight or normal weight	660 (51.4)	81 (12.3)	579 (87.7)	Ref	Ref
No GDM or DM, overweight or obese	499 (38.8)	108 (21.6)	391 (78.4)	1.97 (1.44–2.71)[d]	1.91 (1.37–2.65)[d]
GDM, underweight or normal weight	30 (2.3)	6 (20.0)	24 (80.0)	1.79 (0.71–4.50)	1.90 (0.75–4.82)
GDM, overweight or obese	96 (7.5)	22 (22.9)	74 (77.1)	2.13 (1.25–3.61)[d]	1.83 (1.05–3.18)[d]
Model 3					
No GDM or DM, underweight or normal weight	660 (51.4)	81 (12.3)	579 (87.7)	Ref	Ref
No GDM or DM, overweight or obese	499 (38.8)	108 (21.6)	391 (78.4)	1.97 (1.44–2.71)[d]	1.91 (1.37–2.65)[d]
GDM without insulin, underweight or normal weight	22 (1.7)	3 (13.6)	19 (86.4)	1.13 (0.33–3.90)	1.17 (0.33–4.09)
GDM without insulin, overweight or obese	52 (4.1)	11 (21.2)	41 (78.9)	1.92 (0.95–3.88)	1.65 (0.79–3.46)
GDM with insulin, underweight or normal weight	8 (0.6)	3 (37.5)	5 (62.5)	4.29 (1.01–18.29)[d]	4.76 (1.11–20.41)[d]
GDM with insulin, overweight or obese	44 (3.4)	11 (25.0)	33 (75.0)	2.38 (1.16–4.90)[d]	2.03 (0.96–4.32)

Data are presented as aOR (95% CI) using logistic regression analyses with combined primary offspring endpoint (yes or no) as the dependent variable.

aOR, odds ratio; *BMI*, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *Ref*, reference interval.

[a] Model 1 adjusted for BMI only and models 2 and 3 unadjusted; [b] Additionally adjusted for week of gestation at the onset of COVID-19 symptoms (or at a positive polymerase chain reaction test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥ 1), and hypertensive disorders in pregnancy (yes or no); [c] Maternal BMI before or at the beginning of pregnancy (kg/m^2); [d] $P<.05$.

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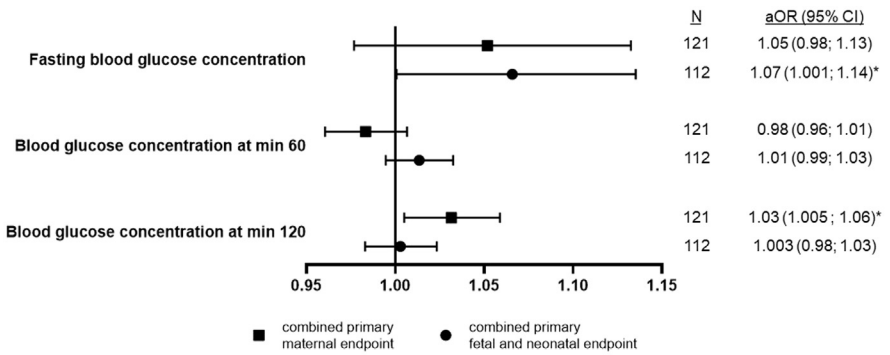
in achieving normoglycemia in COVID-19. In the trials mentioned above, the LGA rate was 13% at most; moreover, in randomized screening trials, the LGA rate was even <10%.[23,24] Our data did not confirm an increased rate of stillbirth in GDM as reported in the analysis from the Premier Healthcare Database.[13] Independent of GDM status, the US Centers for Disease Control and Prevention reported a 47% overall increased risk of stillbirth with COVID-19, increasing further when the Delta virus variant was dominant.[12]

The coexistence of GDM and overweight or obesity is common and has been seen in 75% of pregnancies in our GDM subgroup vs 43.1% of pregnancies without DM. Typical for insulin resistance in the cases of GDM, we saw an isolated elevated fasting plasma glucose, the only abnormal result in 36.7% of pregnancies and an additional 39.2% of pregnancies in combination with abnormal results of the 1-hour or 2-hour OGTT value.[25] All 3 OGTT values were elevated in 11.7% of pregnancies. According to the literature and based on these results, we can presume that women with GDM and COVID-19 in our cohort are at high risk of developing type 2 DM during the next 5 to 10 years.[26]

GDM prevalence seems to be increasing during the pandemic.[13,27–29]

FIGURE 2
Associations between plasma glucose concentrations from OGTT and primary endpoints



Data are presented as aOR (95% CI) using logistic regression analyses for combined primary maternal and fetal and neonatal endpoints (yes or no) as the dependent variable (separate model for each) per 1 mg/dL increase in venous plasma glucose concentrations from OGTT (continuous variables, all included in the same model). Adjusted for week of gestation at the onset of COVID-19 symptoms (or at PCR-positive test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), parity (0 or $\geq$1), maternal BMI category before or at the beginning of pregnancy (BMI, $<$25 or $\geq$25 kg/m^2), hypertensive disorders in pregnancy (yes or no), and type of GDM therapy (diet or insulin). The model with combined primary fetal and neonatal endpoint was additionally adjusted for nicotine or smoking during pregnancy (yes or no) as a quasi-complete separation of data points was observed with this potential confounding variable. The *asterisk* represents $P<.05$.

aOR, adjusted odds ratio; *BMI*, body mass index; *CI*, confidence interval; *OGTT*, oral glucose tolerance test; *PCR*, polymerase chain reaction.

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The 30% increased risk of GDM observed in the United States may be explained by a change in women's lifestyles under the conditions of the pandemic.[29] Unfavorable lifestyle modification is known to increase the risk of developing impaired glucose tolerance during pregnancy. Our data have shown that only 1 of 3 values of OGTT was associated with a severe course in the mother and offspring, respectively. Thus, OGTT results seem to have a limited predictive value on adverse pregnancy outcomes in COVID-19. Further research is needed to evaluate the relationship between the quality of GDM therapy and the course and outcome of COVID-19. Because pregnant women may have a higher proportion of asymptomatic infections,[30] further research is required on asymptomatic pregnant women with SARS-CoV-2 infection and GDM.

Clinical implications

Large studies of hospitalized pregnant women with COVID-19 have reported increased maternal morbidity and mortality compared with nonpregnant women.[1,2,31] Physiological associations of GDM (ie, hyperinsulinemia) may enhance ACE2 receptor expression followed by facilitated SARS-CoV-2 entry. In addition, GDM may affect the damage of pancreatic beta cells in more severe cases on insulin therapy, followed by an excess incidence of type 2 DM. Therefore, measures are needed to detect GDM as early as possible, recommending lifestyle changes (eg, a healthy diet or regular exercise) and encouraging women to take part in regular follow-up examinations, for example, OGTT, fasting plasma glucose, and Hba1c testing for diabetes diagnosis. Vaccination with an mRNA vaccine has the potential to substantially reduce COVID-19–associated inflammation, which may further decrease hyperglycemia in pregnancy.

Our data have provided additional information for caregivers of pregnant women. GDM is a common complication in pregnancy. Women with GDM, combined with periconceptional overweight or obesity, should be considered a vulnerable group in COVID-19, especially if they require insulin. The analysis of the CRONOS subgroup of patients with COVID-19 with admission to the ICU showed that GDM was the most common comorbidity.[15] Despite high LGA frequency, GDM seemed to have little effect on neonatal outcomes. The decision between conservative management in pregnant patients with COVID-19 and the risk of iatrogenic preterm delivery requires interdisciplinary monitoring and consultation. Vaccination with an mRNA vaccine combined with hygiene protection measures is an important option for preventing or mitigating the severe course of COVID-19 in pregnancy.[32,33] The pandemic should not discourage women from undergoing GDM screening or planning their birth in a hospital to receive the full benefits of adequate care.[34]

Strengths and limitations of the study

Here, we used data from a homogeneous cohort and rigorous data monitoring concerning the confirmation of COVID-19, GDM, and its therapy and adverse maternal and offspring outcomes. Diligent data monitoring and recalls and plausibility tests of reported cases and laboratory test results allowed us to detect and eliminate discrepancies.[35]

Some limitations should be mentioned. First, the hospitals reporting data only represent 30% of all births in Germany. Second, we cannot exclude that residual confounders remained unconsidered in the analysis; for example, it is unclear whether or not all hospitals reported all their pregnant women with COVID-19 during the study period. Small numbers in model 3 led to limited interpretation because of large CI intervals. Here, we used LGA as a surrogate for blood glucose control and quality of

DM management but with limited validity as exact data are not available. Moreover, our study did not include women with asymptomatic SARS-CoV-2 infection or a cohort without COVID-19. This limited the generalization of data to those women with COVID-19 during their pregnancy. Third, we had no information on monogenic DM, but we presumed from our data that the incidence is low. Lastly, some diagnostic and treatment decisions may have been influenced by uncertainties during the pandemic and high workloads.

Conclusions

GDM, combined with periconceptional overweight or obesity, was independently associated with a severe maternal course of COVID-19, especially when insulin was required for treatment. Adverse maternal outcomes were more common when COVID-19 was diagnosed with or shortly after GDM diagnosis than COVID-19 diagnosis before GDM diagnosis. These combined factors had a moderate adverse effect on neonatal outcomes. Caregivers for women with GDM and COVID-19 should be aware of the additional risks that GDM poses. ■

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Appendix

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- University Hospital, Rostock, Germany: J.S.
- St. Juergen Hospital, Bremen, Germany: K.L.
- District Hospital, Ebersberg, Germany: Stephan Hasmueller
- City Hospital, Zittau, Germany: Bettina Hollenbach
- Saalfeld Hospital, Saalfeld, Germany: Dietrich Hager
- University Hospital, Lübeck, Germany: Julia Rothe
- Diakonissen Hospital, Flensburg, Germany: Barabara Fleig
- Marien Hospital, Bottrop, Germany: Katharina Freienstein
- Fürstenfeldbruck Hospital, Fürstenfeldbruck, Germany: Kerstin Brettschneider
- Eggenfelden Hospital, Rottal-Inn, Germany: Irmgard Drost
- Sophien and Hufeland Hospital, Weimar, Germany: Cathleen Heinemann
- District Hospital, Freiberg, Germany: Martina Sperling
- Hospital Bad Salzungen, Bad Salzungen, Germany: Ines Tonndorf

- University Hospital, Duesseldorf, Germany: Melva Baum
- Neuwerk Hospital, Mönchengladbach, Germany: Vanessa Nikolai
- Heart-Jesu-Hospital, Muenster, Germany: Joachim Zucker-Reimann
- Neuwied Hospital, Neuwied, Germany: Richard Berger
- University Hospital, Tuebingen, Germany: Harald Abele
- Heidenheim Hospital, Heidenheim, Germany: Annika Knesebeck
- Caritas Maria Heimsuchung Hospital Pankow, Berlin, Germany: Jens Rohne
- Dietrich-Bonhoeffer Hospital, Neubrandenburg, Germany: Konstanze Kissing-Pahl
- Imland Hospital, Rendsburg, Germany: Annika Ertel
- Itzehoe Hospital, Itzehoe, Germany: Laura Pohlmann
- Ubbo-Emmius Hospital, Aurich, Germany: Kathrin Meyer-Eckle
- Protestant Hospital of Bethel Foundation, Bielefeld, Germany: C.B.J.
- Kalk Hospital, Koeln, Germany: Martin Dambowy
- LAKUMED Hospital, Landsberg, Germany: Mirjam Ulrich
- District Hospital, Erding, Germany: I.B.
- St. Theresien Hospital, Nuremberg, Germany: Ulf Dammer
- Caritas Hospital, Bad Mergentheim, Germany: Sönke Ebert
- KMG Hospital, Sömmerda, Germany: Katharina Feistner
- University Hospital, Leipzig, Germany: Holger Stepan
- Sana Hanse Hospital, Wismar, Germany: J.S.
- City Hospital, Solingen, Germany: Elina Voigthaus
- EUREGIO Hospital, Nordhorn, Germany: Susanne Beckmann
- Christophorus Hospital, Coesfeld, Germany: Elisabeth Edeler
- Medius Hospital, Nürtingen, Germany: Tanja Scheufele-Klein
- University Hospital, Wuerzburg, Germany: Catharina Bartmann
- Diakonissen Hospital, Dresden, Germany: A.T.
- Westcoast Hospital, Heide, Germany: S.E.H.
- City Hospital, Karlsruhe, Germany: Magdalena Tackenberg

SUPPLEMENTAL TABLE 1

Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight vs obese), and combined primary maternal endpoint

Variable	Combined primary maternal endpoint		
	n (column %)	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Model 1			
GDM			
No GDM or preexisting DM	1335 (90.6)	Ref	Ref
GDM, no DM	138 (9.4)	1.56 (0.94–2.59)	1.50 (0.87–2.56)
BMI[c]			
Underweight or normal weight (<25 kg/m^2)	796 (54.0)	Ref	Ref
Overweight (≥ 25 kg/m^2)	380 (25.8)	2.28 (1.50–3.46)[d]	1.84 (1.19–2.85)[d]
Obese (≥ 30 kg/m^2)	297 (20.2)	2.32 (1.48–3.64)[d]	1.90 (1.17–3.07)[d]
Model 2			
No GDM or DM, underweight or normal weight	761 (51.7)	Ref	Ref
No GDM or DM, overweight	335 (22.7)	2.34 (1.5–3.64)[d]	1.87 (1.18–2.97)[d]
No GDM or DM, obese	239 (16.2)	2.43 (1.5–3.94)[d]	2.01 (1.21–3.37)[d]
GDM, underweight or normal weight	35 (2.4)	2.10 (0.71–6.22)	2.01 (0.65–6.25)
GDM, overweight	45 (3.1)	3.52 (1.55–8.02)[d]	2.90 (1.21–6.95)[d]
GDM, obese	58 (3.9)	3.40 (1.61–7.16)[d]	2.54 (1.13–5.67)[d]

Data are presented as aOR (CI) using logistic regression analyses with combined primary maternal endpoint (yes or no) as the dependent variable.

aOR, odds ratio; *BMI*, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *Ref*, reference interval.

[a] Model 1 adjusted for BMI only and model 2 unadjusted; [b] Additionally adjusted for week of gestation at the onset of COVID-19 symptoms (or at a positive polymerase chain reaction test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥ 1), and hypertensive disorders in pregnancy (yes or no); [c] Maternal BMI before or at the beginning of pregnancy (kg/m^2); [d] $P<.05$.

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SUPPLEMENTAL TABLE 2

Comparison of timing of COVID-19 with prevalence of primary and secondary endpoints among the subgroup of women with gestational diabetes mellitus

Variable	n (GDM)	Diagnosis of COVID-19 before the diagnosis of GDM	Diagnosis of COVID-19 with or after the diagnosis of GDM
Combined primary maternal endpoint (yes)	138	2 (5.6)	20 (19.6) [a]
Combined primary fetal and neonatal endpoint (yes)	126	8 (24.2)	20 (21.5)
Mother in ICU (yes)	137	1 (2.8)	13 (12.9)
Maternal oxygen supplementation (yes)	138	2 (5.6)	17 (16.7)
Maternal viral pneumonia (yes)	136	2 (5.6)	13 (13.0)
Cesarean delivery (yes)	130	17 (50.0)	40 (41.7)
Child in neonatal ICU (yes)	124	25 (78.1)	73 (79.4)
Small for gestational age (yes)	113	3 (9.7)	6 (7.3)
Large for gestational age (yes)	113	7 (22.6)	19 (23.2)

Data are presented as number (percentage).

GDM, gestational diabetes mellitus; *ICU*, intensive care unit.

[a] $P<.05$ for comparison between the diagnosis of COVID-19 before the diagnosis of GDM and the diagnosis of COVID-19 with or after the diagnosis of GDM based on the chi-squared test or Fisher exact test.

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SUPPLEMENTAL TABLE 3

Associations between diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight vs obese), and combined primary fetal and neonatal endpoint

	Combined primary fetal and neonatal endpoint		
Variable	n (column %)	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Model 1			
GDM)			
No GDM or preexisting DM	126 (9.8)	Ref	Ref
GDM, no DM	1159 (90.2)	1.21 (0.76–1.92)	1.12 (0.70–1.81)
BMI[c]			
Underweight or normal weight (<25 kg/m^2)	690 (53.7)	Ref	Ref
Overweight (≥ 25 kg/m^2)	336 (26.2)	1.96 (1.39–2.76)[d]	1.87 (1.31–2.67)[d]
Obese (≥ 30 kg/m^2)	259 (20.2)	1.81 (1.24–2.65)[d]	1.72 (1.15–2.56)[d]
Model 2			
No GDM or DM, underweight or normal weight	660 (51.4)	Ref	Ref
No GDM or DM, overweight	292 (22.7)	2.01 (1.40–2.88)[d]	1.92 (1.32–2.80)[d]
No GDM or DM, obese	207 (16.1)	1.93 (1.29–2.90)[d]	1.88 (1.23–2.87)[d]
GDM, underweight or normal weight	30 (2.3)	1.79 (0.71–4.50)	1.90 (0.75–4.83)
GDM, overweight	44 (3.4)	2.38 (1.16–4.90)[d]	2.16 (1.01–4.59)[d]
GDM, obese	52 (4.1)	1.92 (0.95–3.88)	1.57 (0.75–3.30)

Data are presented as aOR (95% CI) using logistic regression analyses with combined primary offspring endpoint (yes or no) as the dependent variable.

aOR, odds ratio; *BMI*, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *Ref*, reference interval.

[a] Model 1 adjusted for BMI only and model 2 unadjusted; [b] Additionally adjusted for week of gestation at the onset of COVID-19 symptoms (or at a positive polymerase chain reaction test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥ 1), and hypertensive disorders in pregnancy (yes or no); [c] Maternal BMI before or at the beginning of pregnancy (kg/m^2); [d] $P<.05$.

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SUPPLEMENTAL TABLE 4

Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight vs obese), and secondary endpoints

Variable	n (column %)	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Mother in ICU			
Model 1			
GDM			
No GDM or preexisting DM	1334 (90.7)	Ref	Ref
GDM, no DM	137 (9.3)	2.00 (1.07–3.76)[c]	1.84 (0.95–3.56)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	795 (54.0)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	676 (46.0)	3.15 (1.80–5.50)[c]	2.41 (1.36–4.30)[c]
Model 2			
No GDM or DM, underweight or normal weight	760 (51.7)	Ref	Ref
No GDM or DM, overweight or obese	575 (39.0)	3.30 (1.82–5.97)[c]	2.54 (1.37–4.68)[c]
GDM, underweight or normal weight	25 (2.4)	2.82 (0.62–12.77)	2.64 (0.56–12.53)
GDM, overweight or obese	102 (6.9)	6.20 (2.84–13.52)[c]	4.34 (1.91–9.87)[c]
Oxygen supplementation (mother)			
Model 1			
GDM			
No GDM or preexisting DM	1335 (90.6)	Ref	Ref
GDM, no DM	138 (9.4)	1.58 (0.92–2.70)	1.49 (0.85–2.62)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	796 (54.0)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	677 (46.0)	2.18 (1.46–3.24)[c]	1.74 (1.15–2.64)[c]
Model 2			
No GDM or DM, underweight or normal weight	761 (51.7)	Ref	Ref
No GDM or DM, overweight or obese	574 (39.0)	2.30 (1.51–3.50)[c]	1.85 (1.20–2.87)[c]
GDM, underweight or normal weight	35 (2.4)	2.45 (0.82–7.31)	2.42 (0.77–7.57)
GDM, overweight or obese	103 (7.0)	3.24 (1.71–6.13)[c]	2.42 (1.23–4.76)[c]
Viral pneumonia (mother)			
Model 1			
GDM			
No GDM or preexisting DM	1323 (90.7)	Ref	Ref
GDM, no DM	136 (9.3)	1.63 (0.89–2.95)	1.54 (0.82–2.88)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	792 (54.3)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	667 (45.7)	2.17 (1.38–3.40)[c]	1.68 (1.05–2.69)[c]
Model 2			
No GDM or DM, underweight or normal weight	758 (52.0)	Ref	Ref
No GDM or DM, overweight or obese	565 (38.7)	2.28 (1.42–3.67)[c]	1.77 (1.08–2.90)[c]
GDM, underweight or normal weight	34 (2.3)	2.43 (0.70–8.42)	2.31 (0.63–8.41)
GDM, overweight or obese	102 (7.0)	3.35 (1.65–6.8)[c]	2.46 (1.17–5.18)[c]

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SUPPLEMENTAL TABLE 4

Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight vs obese), and secondary endpoints *(continued)*

Variable	n (column %)	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
Hypertensive disorders in pregnancy			
Model 1			
GDM			
No GDM or preexisting DM	1335 (90.6)	Ref	Ref
GDM, no DM	138 (9.4)	1.85 (1.06–3.24)[c]	1.78 (1.01–3.15)[c]
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	796 (54.0)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	677 (46.0)	3.06 (1.91–4.9)[c]	3.14 (1.94–5.08)[c]
Model 2			
No GDM or DM, underweight or normal weight	761 (51.7)	Ref	Ref
No GDM or DM, overweight or obese	574 (39.0)	2.87 (1.76–4.69)[c]	2.97 (1.8–4.89)[c]
GDM, underweight or normal weight	35 (2.4)	0.87 (0.11–6.58)	0.89 (0.12–6.81)
GDM, overweight or obese	103 (7.0)	5.82 (3.02–11.21)[c]	5.74 (2.92–11.29)[c]
Cesarean delivery			
Model 1			
GDM			
No GDM or preexisting DM	1192 (90.2)	Ref	Ref
GDM, no DM	130 (9.8)	1.13 (0.78–1.65)	1.06 (0.73–1.56)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	709 (53.6)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	613 (46.4)	1.71 (1.36–2.15)[c]	1.68 (1.32–2.13)[c]
Model 2			
No GDM or DM, underweight or normal weight	678 (51.3)	Ref	Ref
No GDM or DM, overweight or obese	514 (38.9)	1.75 (1.38–2.22)[c]	1.73 (1.35–2.21)[c]
GDM, underweight or normal weight	31 (2.3)	1.40 (0.67–2.93)	1.43 (0.68–3.03)
GDM, overweight or obese	99 (7.5)	1.84 (1.20–2.83)[c]	1.67 (1.07–2.59)[c]
Neonatal ICU admission			
Model 1			
GDM			
No GDM or preexisting DM	1148 (90.3)	Ref	Ref
GDM, no DM	124 (9.8)	1.19 (0.74–1.90)	1.12 (0.68–1.82)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	683 (53.7)	Ref	Ref
Overweight or obese (≥25 kg/m^2)	589 (46.3)	1.95 (1.43–2.66)[c]	1.86 (1.34–2.58)[c]
Model 2			
No GDM or DM, underweight or normal weight	653 (51.3)	Ref	Ref
No GDM or DM, overweight or obese	495 (38.9)	2.06 (1.49–2.85)[c]	1.99 (1.42–2.80)[c]

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SUPPLEMENTAL TABLE 4

Associations among diabetes mellitus status (gestational diabetes mellitus vs no diabetes mellitus), body mass index (underweight or normal weight vs overweight vs obese), and secondary endpoints *(continued)*

Variable	n (column %)	Crude or only BMI (aOR [95% CI])[a]	Multivariable (aOR [95% CI])[b]
GDM, underweight or normal weight	30 (2.4)	1.96 (0.77–4.94)	2.12 (0.83–5.41)
GDM, overweight or obese	94 (7.4)	2.11 (1.22–3.67)[c]	1.85 (1.04–3.29)[c]
Small for gestational age			
Model 1			
GDM			
No GDM or preexisting DM	1021 (90.0)	Ref	Ref
GDM, no DM	113 (10.0)	1.54 (0.73–3.25)	1.50 (0.70–3.19)
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	619 (54.6)	Ref	Ref
Overweight or obese (≥ 25 kg/m^2)	515 (45.4)	0.44 (0.26–0.74)[c]	0.45 (0.27–0.77)[c]
Model 2			
No GDM or DM, underweight or normal weight	590 (52.0)	Ref	Ref
No GDM or DM, overweight or obese	431 (38.0)	0.45 (0.26–0.78)[c]	0.47 (0.27–0.82)[c]
GDM, underweight or normal weight	29 (2.6)	1.66 (0.56–4.94)	1.68 (0.55–5.07)
GDM, overweight or obese	84 (7.4)	0.65 (0.25–1.69)	0.64 (0.24–1.68)
Large for gestational age			
Model 1			
GDM			
No GDM or preexisting DM	1021 (90.0)	Ref	Ref
GDM, no DM	113 (10.0)	3.10 (1.86–5.16)[c]	3.13 (1.87–5.26)[c]
BMI[d]			
Underweight or normal weight (<25 kg/m^2)	619 (54.6)	Ref	Ref
Overweight/obese (≥ 25 kg/m^2)	515 (45.4)	1.78 (1.16–2.73)[c]	1.71 (1.10–2.66)[c]
Model 2			
No GDM or DM, underweight or normal weight	590 (52.0)	Ref	Ref
No GDM or DM, overweight or obese	431 (38.0)	1.71 (1.07–2.73)[c]	1.66 (1.03–2.67)[c]
GDM, underweight or normal weight	29 (2.6)	2.54 (0.84–7.69)[c]	2.66 (0.87–8.13)
GDM, overweight or obese	84 (7.4)	5.63 (3.11–10.19)[c]	5.46 (2.96–10.07)[c]
Model 3			
No GDM or DM, underweight or normal weight	590 (52.0)	Ref	Ref
No GDM or DM, overweight or obese	431 (38.0)	1.71 (1.07–2.73)[c]	1.66 (1.03–2.66)[c]
GDM without insulin, underweight or normal weight	21 (1.9)	2.64 (0.74–9.40)	2.84 (0.79–10.28)
GDM without insulin, overweight or obese	40 (3.5)	6.01 (2.78–13.04)[c]	6.16 (2.79–13.59)[c]
GDM with insulin, underweight or normal weight	8 (0.7)	2.27 (0.27–18.93)	2.20 (0.26–18.76)
GDM with insulin, overweight or obese	44 (3.9)	5.29 (2.46–11.34)[c]	4.89 (2.23–10.72)[c]

Data are presented as aOR (95% CI) using logistic regression analyses with secondary endpoints (yes or no) as the dependent variable (separate model for each).

aOR, odds ratio; *BMI*, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *ICU*, intensive care unit; *Ref*, reference interval.

[a] Model 1 adjusted for BMI only and models 2 and 3 unadjusted; [b] Additionally adjusted for week of gestation at the onset of COVID-19 symptoms (or at a positive polymerase chain reaction test result), multiples (yes or no), maternal age at positive COVID-19 test result, language competence (communication possible with or without problems), nicotine or smoking during pregnancy (yes or no), parity (0 or ≥ 1), and hypertensive disorders in pregnancy (yes or no). Models with viral pneumonia as the dependent variable were not adjusted for nicotine or smoking during pregnancy as a quasi-complete separation of data points was observed; [c] $P<.05$; [d] Maternal BMI before or at the beginning of pregnancy (kg/m^2).

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