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Gestational diabetes is associated with SARS-CoV-2 infection during pregnancy: A case-control study

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Short title: Gestational diabetes and SARS-CoV-2

Abstract

Aim

Individuals with SARS-CoV-2 infection and (pre-existing) diabetes, including pregnant women, present with more severe morbidity, as compared to non-diabetic subjects. To date, evidence is limited concerning the role of gestational diabetes (GDM) in severity of SARS-CoV-2 infection during pregnancy, or vice versa. The aim of our study was to investigate the prevalence of GDM in a SARS-CoV-2 infected pregnant population and evaluate risk factors for and from severe infection in these patients.

Methods

A case-control study with prospective data collection for the case group and 1:2 matching with historical controls based on parity, BMI and ethnicity was conducted (n=224). GDM screening was performed at 26 weeks' gestation. Multivariate binary logistic regression analysis was performed to assess risk factors for GDM and inpatient COVID-19 management.

Results

34.6% of the patients in the case group suffered from GDM, vs. 16.1% in the control group (p=0.002). 35.7% patients were diagnosed with GDM after, vs. 33.3% before SARS-CoV-2 infection (OR (95%CI) 1.11(0.40-3.08), p=0.84), with no correlation between time point of infection and GDM diagnosis. SARS-CoV-2 (OR (95%CI) 2.79 (1.42, 5.47), p=0.003) and BMI (OR (95%CI) 1.12 (1.05, 1.19), p=0.001) were significant independent risk factors for GDM.

Conclusion

Data suggests that GDM increases the risk of infection in SARS-CoV-2 infected pregnant women. Meanwhile, SARS-CoV-2 during pregnancy might increase the risk of developing GDM.

Vaccination and caution in using protective measures should be recommended to pregnant women, particularly when suffering from GDM.

Keywords: SARS-CoV-2, gestational diabetes, COVID-19

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Introduction

Diabetes mellitus (DM) is one of the most frequent comorbidities in individuals with SARS-CoV-2 infection [1-2]. Evidence shows that individuals suffering from diabetes present higher morbidity and mortality as compared to non-diabetic subjects [1].

Analogue to the general population, pregnant women suffering from preexisting diabetes seem to present with a higher severity degree of SARS-CoV-2 infection [3, 4]. An international case control analysis comparing data stratified by the severity of maternal disease identified pulmonary comorbidities, hypertensive disease and DM as risk factors associated with a severe form of SARS-CoV-2 infection in pregnancy [5]. Furthermore, it has been previously suggested that hyperglycemia generally increases viral replication and decreases anti-viral response, making a causal relationship between diabetes and SARS-CoV-2 biologically plausible [1,2]. However, there is limited data so far whether these elaborations also apply to gestational diabetes (GDM).

GDM is a major public health issue, with an abrupt increase in prevalence in the last decade, and international committees report a so-called `metabolic pandemic` [6]. According to The Hyperglycemia and Adverse Pregnancy Outcome Study, the level of glycaemia during pregnancy is directly linked to the presence of adverse obstetrical outcomes [7-8].

Prevalence of GDM lies worldwide between 9,3% and 25,5% [8]. A British study described a 33.8% increase in GDM since the onset of the pandemic, attributing this mainly to reduced exercise levels and psychical stress [9].

SARS-CoV mediated pancreatic islet cell damage is not a newly described phenomenon, as earlier experiences with MERS and SARS teach us [10]. DM is a multifactorial disease, and its development is linked to genetic and environmental influences. Indeed, a causal relationship between viral infections and acute glycemic decompensation with onset of Type I diabetes has been previously described [11].

In this context, increasing evidence shows that SARS-CoV-2 can trigger severe diabetic ketoacidosis in persons with new-onset Type I diabetes, most probably due to high angiotensin converting enzyme 2

(ACE2) expression in the endocrine part of the pancreas. The mechanism seems to involve cell apoptosis with decreased pancreatic insulin secretion [11].

The aim of our study was to investigate the prevalence of GDM in a SARS-CoV-2 infected pregnant population and evaluate risk factors for and from severe infection in these patients.

Methods

We included 224 pregnant women in our case-control study. The case group consisted of 75 women with SARS-CoV-2 infection during pregnancy, irrespective of the severity of the symptoms. We included all SARS-CoV-2 positive women who were managed at our tertiary hospital between May 2020 and July 2021. Data from these individuals were collected prospectively within the international COVI-Preg register. Cases were matched 1:2 with a historical cohort of women who delivered before the SARS-CoV-2 pandemic between 01.01.2016 and 31.10.2019, based on parity, body mass index (BMI) and ethnicity. In one woman, only one matching control was found, so that the control group consisted of 149 individuals. Screening for GDM by 75mg oral glucose tolerance test (OGTT) was performed at 26 weeks' gestation in all 224 women. Normal blood sugar values were defined as follows: fasting < 5,1mmol/l, one hour after glucose ingestion < 10mmol/l, two hours after glucose ingestion < 8,5mmol/l. All women where OGTT was not available were previously excluded.

First trimester was defined as conception to 13 + 6 weeks, second trimester from 14 + 0 to 26 + 6 weeks and third trimester as more than 27 + 0 weeks of gestation.

Diagnosis of COVID-19 infection in the case group was made by identification of SARS-CoV-2-PCR in a nasopharyngeal swab.

Written informed consent was obtained, institutional review board approval was provided by the Ethical Committee of Berne (2020-00832). The study was performed in accordance with the principles of the Declaration of Helsinki. No external funding was received.

Statistical Analysis

Mean values and SD were calculated for continuous variables and percentages for the qualitative variables. A student t-test and Fisher's exact test was used to compare continuous parametric variables and binary variables between the two groups, respectively. Possible risk factors for gestational diabetes and inpatient COVID-19 management were determined with multivariate binary logistic regression analysis. A logistic regression analysis was also performed to identify if the time of COVID-19 infection during pregnancy was associated with GDM. Missing data were excluded from the analysis. Significance was set at $p<0.05$. Statistical analysis was carried out with SPSS 25.0 software (SPSS, USA).

Results

Baseline characteristics of the study population and delivery outcomes are depicted in Table 1. Altogether, 26/75 (34.66%) of the patients in the case group suffered from gestational diabetes vs. 24/149 (16.1%) in the control group (p=0.002). The rate of preterm delivery was 17.3% in the case group vs. 7.6% in the control group (p=0.04).

Multivariate logistic regression analysis revealed that SARS-CoV-2 (OR (95%CI) 2.79 (1.42, 5.47), p=0.003) and BMI (OR (95%CI) 1.12 (1.05, 1.19), p=0.001) were significant independent risk factors for GDM.

In 11/75 (14.66%) patients, SARS-CoV-2 infection occurred in the first trimester of gestation, in 19/75 (25.33%) in the second and in 37/75 (49.33%) in the third trimester. In eight patients, time-point of infection was unknown (10.66%). Of these, three suffered from GDM.

Out of 28 patients infected with COVID-19 ≤ 26 week of pregnancy, 10 (35.7%) had a positive OGTT (GDM diagnosis) afterwards. This is similar to the 13/39 (33.3%) of patients with positive OGTT before infected with COVID (OR (95%CI) 1.11 (0.40, 3.08, Chi-Square = 0.84).

89.33% of the patients (67/75) in the case group suffered from asymptomatic, mild or moderate SARS-CoV-2 infection, according to the National Institutes of Health **(**NIH) criteria for severity of the disease [12]. 12% (9/75) of the patients had severe or critical illness with inpatient management. Of these, 5.33% (4/75) required intensive care unit (ICU) admission and ventilation. These four patients underwent an emergency delivery because of SARS-CoV-2 infection. No patient deaths were recorded.

Of the nine patients with inpatient management, four (44.44%) suffered from GDM. Of the four patients who required admission at the ICU, two suffered from GDM (50%). Of the 66 patients with outpatient management, 22 suffered from GDM (33.33%). This difference was not significant in chi-square test (p=0.51). Regression analysis of factors associated with inpatient COVID-19 management (inpatient vs. outpatient) showed no significance for GDM (OR (95%CI) 1.14 (0.22, 5.80, p= 0.88), time-point of infection (OR (95%CI) 1.08 (0.98, 1.20), p=0.12) or BMI (OR (95%CI) 1.07 (0.91, 1.25), 0.41). .

Discussion

The main finding of our study is a significantly higher incidence of GDM in a SARS-CoV-2 infected pregnant population, as compared to historical controls. All though no statistical correlation was found between the time point of infection in regards to OGTT, previous data concerning DM and COVID-19 during pregnancy would support in a first line that those patients with GDM are more prone to SARS-CoV-2 infection. Meanwhile, multivariate regression analysis revealed that BMI and COVID-19 were independent risk factors for GDM in our cohort, thus supporting the theory of the virus-triggered diabetes onset.

A recently published multicentric study also reported an association between insulin dependent GDM and COVID-19 diagnosis in pregnancy, yet over 80% of the participants were SARS-CoV-2 positive at the time-point of delivery, thus chronologically after diagnosis of GDM [13]. Our report is to our knowledge the first case-control study providing evidence, even if limited, for a possible causal relationship between COVID-19 and onset of GDM.

As stated before, the hyperglycemic level directly correlates with adverse obstetrical outcome [7, 8]. Incidence of GDM was higher in the SARS-CoV-2 hospitalized patients (44.44% vs. 33.33% in those with outpatient management), yet this difference was marginally not statistically significant (p=0.51). Meanwhile, 50% of the women requiring ICU admission in our cohort suffered from GDM, which is alarming. On a deeper analysis, BMI, GDM and time point of infection none correlated with inpatient management of SARS-CoV-2 infection, thus with the degree of severity. Since previous large reports could clearly show a correlation between high BMI and severity of infection, we believe that our results are a consequence of the small number of women with inpatient management and ICU admission, thus lack of statistical power to demonstrate a possible association [5].

With an European rate of GDM of 16.3% and worldwide of up to 25.5%, these results are of concern and call for consequences in the management of pregnant patients suffering from GDM or at risk for GDM in the context of the pandemic [7-8].

Higher exposition to hospital visits in women suffering from GDM could be cofounding factor for SARS-CoV-2 infection in pregnancy. We mention that patient management was adapted in our center during the major SARS-CoV-2 pandemic surges, mostly by conversion to teleconsultations. Diabetes testing protocols remained unaltered.

In both our study groups, GDM rate was higher than in the general pregnant population in Switzerland, which could be explained by the higher proportion of high-risk pregnancies as well as by the high number of women of South Asian ethnicity being followed at our institution [8].

The rate of hospital admission in SARS-CoV-2 infection in our population was in line with previous reports [5]. We noted a significantly higher incidence of premature delivery in the case group, whereas in the control group, incidence was similar to that of the general pregnant population in our country [14]. The 17.33% rate of preterm delivery in the SARS-CoV-2 infected women in our cohort is in line with results from a large previous meta-analysis [15].

One major strength of our report is the prospective data assessment in the case group and the case-control approach. Homogeneity of testing is another major strength, since standard OGTT was carried out in each patient in both groups, which distinguishes us from previous publications. The ability to classify the COVID-19 infection in respect to the symptoms is a further strength of our study. The major limitation is the cohort size as well as not having matched for further comorbidities or lower socioeconomic status, which is a known risk factor for both GDM as well as SARS-CoV-2 infection, because of incomplete records.

Conclusion

The significantly higher rate of GDM among women with SARS-CoV-2 infection during pregnancy, as compared to corresponding controls, suggests that GDM increases the risk of infection. Meanwhile, SARS-CoV-2 during pregnancy might increase the risk of developing GDM. Vaccination and caution in using protective measures should be recommended to pregnant women, particularly those with co-morbidities.

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Author's contribution:

APR: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article

MF: acquisition of data, analysis and interpretation of data

KN: analysis and interpretation of data, statistics, revising the article

BM: acquisition of data, revising the article critically for important intellectual content

BS: acquisition of data

LR: analysis and interpretation of data, revising the article critically for important intellectual content

DS: conception and design of the study, revising the article critically for important intellectual content

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Characteristics	Cases n= 75	Controls n= 149	P value

Tables and Figures

Age		30.76 ± 4.63	30.62 ± 4.48	ns
BMI (kg/m^2)		26.27 ± 5.08	25.91 ± 5.03	ns
Parity		1 (0-7)	1 (0-5)	ns
Ethnicity	Caucasian	60 (80)	120 (80)	ns
	African	11 (14.7)	21 (14.1)	
	South Asia	2 (2.7)	4 (2.7)	
	East Asia	1 (1.3)	2 (1.3)	
	Mixed	1 (1.3)	2 (1.3)	
Twins		1 (1.3)	4 (2.7)	ns
GDM		26/75 (34.7)	24/149 (16.1)	0.002
SGA/IUGR		9/70 (12.9)	13/139 (9.4)	ns
Preterm delivery		13/75 (17.3)	11/144 (7.6)	0.04
Mode of delivery	Spontaneous vaginal delivery	31/66 (47)	69/140 (49.3)	ns
	Operative vaginal delivery	6/66 (9.1)	15/140 (10.7)	
	Primary cesarean section	19/66 (28.8)	29/140 (20.7)	
	Secondary cesarean section	10/66 (15.2)	27/140 (19.3)	
pHa		7.25 ± 0.078	7.18 ± 0.683	ns
5Min. Apgar score		8.91 ± 1.01	8.82 ± 1.40	ns
Fetal transfer to the ICU		7/66 (10.6)	8/136 (5.9)	ns

Table 1. Comparison of baseline characteristics and pregnancy outcomes between the two groups

* missing values were excluded from the analysis