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

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Abstract

Objective: to investigate a possible bi-directional association between gestational diabetes (GDM) and the SARS-CoV-2 infection during pregnancy. Design: case-control study with prospective data collection for the case group and 1:2 matching with historical controls Setting: University Hospital of Bern, Switzerland Population: 224 pregnant women: 75 cases with SARS-CoV-2 infection during pregnancy, matched 1:2 with controls based on parity, BMI and ethnicity. Methods: SARS-CoV-2 infection was diagnosed by RT-PCR. Screening for GDM was performed by 75mg oral glucose tolerance test at 26 weeks' gestation in all women. Main Outcomes: Prevalence of GDM was calculated in both groups. 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 the SARS-CoV-2 infection, vs. 33.3% diagnosed before infection (OR(95%CI) 1.11(0.40-3.08), p=0.84), with no correlation between the 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. Conclusions: The significantly higher rate of GDM among women with SARS-CoV-2 infection during pregnancy, as compared to matching controls, suggests that GDM increases the risk of infection. On the other hand, 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. Funding: none Keywords: SARS-CoV-2, gestational diabetes, COVID-19

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 a higher rate of hospital admission and a higher mortality as compared to non-diabetic subjects [1, 3, 4].

Analogue to the general population, pregnant women suffering from preexisting diabetes seem to present with a higher severity degree of SARS-CoV-2 infection [5, 6]. 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 antiviral response, making a causal relationship between diabetes and SARS-CoV-2 biologically plausible [7,8]. 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, as international committees report a so-called 'metabolic pandemic' [9,10]. 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 [11].

Prevalence of GDM lies worldwide between 9,3% and 25,5% [11]. 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 [12].

SARS-CoV mediated pancreatic islet cell damage is not a newly described phenomenon, as earlier experiences with MERS and SARS teach us [9]. DM is a multifactorial disease, whose 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. To date, several viruses have been suggested as promoters for the development of Type I diabetes in humans, including Coronavirus [1, 10].

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 [9]. The mechanism seems to involve cell apoptosis with decreased pancreatic insulin secretion [13, 14].

The aim of our study was to investigate a possible bidirectional association between GDM and SARS-CoV-2 infection during pregnancy, as well as to evaluate the plausibility of a physiopathological background, by using a case-control approach.

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 referral hospital between May 2020 and July 2021. Data from these individuals were collected prospectively within the international COVI-Preg register [15]. 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.

At birth, clinical data on maternal and fetal outcomes were collected.

Written informed consent and institutional review board approval were obtained (2020-00832). The study was performed in accordance with the principles of the Declaration of Helsinki.

No external funding was received for performing this study.

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 the diagnosis of gestational diabetes. Missing data were excluded from the analysis. Significance was set at a p-value of $<$0.05. Statistical analysis was carried out with SPSS 25.0 software (SPSS, USA).

Results

Baseline characteristics of the study population 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). Neonatal outcomes were collected in all the other women and are also summarized in Table 1.

Multivariate logistic regression analysis showed 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 (Table 2).

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 (Chi-Square 0.84) (Table 3, Figure 1).

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 [14]. 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%). Regression analysis of factors associated with inpatient COVID-19 management (inpatient vs. outpatient) showed no significance for GDM, time-point of infection or BMI (Table 4).

Discussion

Main findings

The main finding of our study is a significantly higher rate of gestational diabetes in a SARS-CoV-2 infected pregnant population, when compared to historical controls, which raises concerns about the association between GDM and SARS-CoV-2 infection during pregnancy. All though no statistical correlation was found between the time point of infection in regards to OGTT, previous data on 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. On the other hand, multivariate regression analysis found BMI and COVID-19 to be independent risk factors for GDM in our cohort, supporting the theory of the virus-triggered diabetes onset. This 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 [9,10]. What the severity of infection is concerned, to date, only a clear association between previously existing diabetes and severe course of SARS-CoV-2 infection could be established [18, 19]. Being able to determine the severity of the SARS-CoV-2 infection based on the NIH classification is one of the strengths of our study. All though the size of our cohort does not allow us to make a statement regarding the severity of SARS-COV-2 in relation to GDM, 50% of the women requiring ICU admission in our cohort suffered from GDM, which is alarming. On a deeper analysis, body mass index, GDM and time point of infection none correlated with inpatient management of SARS-CoV-2 infection, thus with the degree of severity (Table 4). 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 [19].

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 [16].

A recently published multicentric study with similar design reports 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, making the assessment of a bi-directional association difficult [14]. Until larger case-control studies are available, it remains open if this association is uni- or bidirectional, meaning if SARS-CoV-2 also plays a pathophysiological role in the genesis of GDM. Possible mechanisms of SARS-CoV-2 induced metabolic decompensation with onset of diabetes were described in the introduction of this report and are, at least on a theoretical basis, conceivable [9,10]. Several epidemiological studies note a seasonal distribution of gestational diabetes, which reinforces the 'viral theory' of onset of diabetes, with extension to pregnant women [9,10].

In order to perform data analysis in our study, we matched the case population with historical controls based on parity, BMI and ethnicity. Since a high BMI and specific ethnicities are known risk factors for gestational diabetes, the rationale for choice of controls was to eliminate these cofounding factors from the analysis [10]. Furthermore, we decided for parity as a matching criterion with the intention to analyze presence of GDM in a previous pregnancy as a risk factor for the current GDM diagnosis (Table 2).

The rationale of choosing historical controls, i.e. pregnancies managed at our institution prior to the pandemic, was to secure that asymptomatic, not tested SARS-CoV-2 infected women were not included in the control group by accident. The timeline for control group was intentionally kept narrow (three years before the pandemic), in order to reduce bias that could possibly occur by fluctuations of GDM prevalence in time.

Although a further cofounding factor for SARS-CoV-2 infection in GDM affected women could be a higher exposition to hospital visits in these patients, we mention that management adaptation has been performed in our center during the major SARS-CoV-2 pandemic surges, i.e. reduction of consultations or conversion to telemedicine. Nevertheless, no alteration in diabetes testing regimens occurred, i.e. testing has been performed analogue to the pre-pandemic period. In both groups, women where OGTT was not available were excluded, in order to avoid possible diagnosis biasing. Homogeneity of testing is a major strength of our study, since standard OGTT was used in every single patient in both groups, which distinguishes us from previous publications.

In both our study groups, GDM rate was higher than in the general pregnant population in our country, which could be explained by the higher proportion of high-risk pregnancies as well as by the high number of South Asian immigrants being followed at our institution [16].

The rate of hospital admission in SARS-CoV-2 infection in our population was in line with previous reports [19]. We noted a significantly higher rate of premature delivery in the case group, as compared to the controls, where preterm delivery corresponds those of the general pregnant population [20]. The 17.33% rate of preterm delivery is in line with results from a large previous meta-analysis reporting 17% preterm delivery in SARS-CoV-2 infection during pregnancy [19].

Strengths and Limitations

One major strength of our study is the prospective data assessment in the case group and the case-control approach. As mentioned before, further strengths are represented by the homogeneity of GDM diagnosis in both groups, as well as the ability to classify the COVID-19 in respect to the symptoms. The major limitation is the cohort size as well as not having matched for further comorbidities or lower socioeconomic status because of incomplete records, which is a known risk factor for both GDM as well as SARS-CoV-2 infection [10,21].

Interpretation

According to CDC reports, only 31% of the pregnant US population has been vaccinated against SARS-CoV-

2 so far [22]. We believe it is safe to extrapolate these numbers to the majority of the developed economy countries, although recommendations for vaccination in pregnant women have been issued in a considerable proportion of states worldwide [23]. Taking a deeper look at the vaccination rate of the general population in low-income countries, incidences of 12% for Asian countries or even significantly lower in the majority of African states have been reported [24]. All though pregnant women are generally considered to build a young and healthy population, increasingly high BMI and gestational diabetes rates, as well as maternal age, the wide spread of the highly contagious variants and still low vaccination acceptance make SARS-CoV-2 to a highly relevant issue in obstetrics.

Therefore, pregnant women in general and those with GDM in particular should not only be recommended early vaccination, but also caution in using protective measures. Moreover, appropriate counseling should be offered to these patients at risk.

Conclusions: The significantly higher rate of GDM among women with SARS-CoV-2 infection during pregnancy, as compared to matching controls, suggests that GDM increases the risk of infection. On the other hand, 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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Tables and Figures

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

Characteristics	Characteristics	Cases n= 75	Controls n= 149	P value

Characteristics	Characteristics	Cases n= 75	Controls n= 149	P value
Age	Age	30.76 ± 4.63	30.62 ± 4.48	ns
BMI (kg/m^2)	BMI (kg/m^2)	26.27 ± 5.08	25.91 ± 5.03	ns
Parity	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	Twins	1 (1.3)	4 (2.7)	ns
GDM	GDM	26/75 (34.7)	24/149 (16.1)	0.002
SGA/IUGR	SGA/IUGR	9/70 (12.9)	13/139 (9.4)	ns
Preterm delivery	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	pHa	7.25 ± 0.078	7.18 ± 0.683	ns
5Min. Apgar score	5Min. Apgar score	8.91 ± 1.01	8.82 ± 1.40	ns
Fetal transfer to the ICU	Fetal transfer to the ICU	7/66 (10.6)	8/136 (5.9)	ns

* missing values were excluded from the analysis

Table 2. Regression analysis of factors associated with GDM

	OR (95%CI) 222 patients included in the model	p
Previous GDM	1.17 (0.18, 7.48)	0.87
BMI	1.12 (1.05, 1.19)	**0.001**
COVID-19 infection	2.79 (1.42, 5.47)	**0.003**

*Cox and Snell R2 = .088. Nagelkerke R2 = .135

Goodness-of-fit test Hosmer & Lemeshow: $\chi 2$= 6.500. df= 8. P= .586

Table 3. Regression analysis of association between time of COVID-19 infection and GDM diagnosis

	OR (95%CI) 67 patients included in the model	p
Time of COVID-19 infection ([?] 26 week of pregnancy vs >26 week of pregnancy)	1.11 (0.40, 3.08)	0.84

Table 4. Regression analysis of factors associated with inpatient COVID-19 management GDM

	OR (95%CI) 66 patients included in the model	p
BMI	1.07 (0.91, 1.25)	0.41
GDM	1.14 (0.22, 5.80)	0.88
Week of pregnancy with COVID-19 infection	1.08 (0.98, 1.20)	0.12

*Cox and Snell R2 = .066. Nagelkerke R2 = .121

Goodness-of-fit test Hosmer & Lemeshow: $\chi 2 = 5.197$. df= 7. P= .636

Figure 1. COVID-19 infection reported to the time-point of GDM diagnosis (OGTT)