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

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15 Short title: Gestational diabetes and SARS-CoV-2

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21 Abstract22 Aim

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

29 Methods

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

34 Results

35 34.6% of the patients in the case group suffered from GDM, vs. 16.1% in the control group ( $p=0.002$ ).  
36 35.7% patients were diagnosed with GDM after, vs. 33.3% before SARS-CoV-2 infection (OR (95%CI)  
37 1.11(0.40-3.08),  $p=0.84$ ), with no correlation between time point of infection and GDM diagnosis.  
38 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),  $p=0.001$ )  
39 were significant independent risk factors for GDM.

40 Conclusion

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

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

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

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61 Introduction

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

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

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

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

80 SARS-CoV mediated pancreatic islet cell damage is not a newly described phenomenon, as earlier  
81 experiences with MERS and SARS teach us [10]. DM is a multifactorial disease, and its development is  
82 linked to genetic and environmental influences. Indeed, a causal relationship between viral infections  
83 and acute glycemic decompensation with onset of Type I diabetes has been previously described  
84 [11].

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

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

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

## 91 Methods

92 We included 224 pregnant women in our case-control study. The case group consisted of 75 women  
93 with SARS-CoV-2 infection during pregnancy, irrespective of the severity of the symptoms. We  
94 included all SARS-CoV-2 positive women who were managed at our tertiary hospital between May  
95 2020 and July 2021. Data from these individuals were collected prospectively within the international  
96 COVI-Preg register. Cases were matched 1:2 with a historical cohort of women who delivered before  
97 the SARS-CoV-2 pandemic between 01.01.2016 and 31.10.2019, based on parity, body mass index  
98 (BMI) and ethnicity. In one woman, only one matching control was found, so that the control group  
99 consisted of 149 individuals. Screening for GDM by 75mg oral glucose tolerance test (OGTT) was  
100 performed at 26 weeks' gestation in all 224 women. Normal blood sugar values were defined as  
101 follows: fasting < 5,1mmol/l, one hour after glucose ingestion < 10mmol/l, two hours after glucose  
102 ingestion < 8,5mmol/l. All women where OGTT was not available were previously excluded.

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

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

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

## 110 *Statistical Analysis*

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

## 119 Results

120 Baseline characteristics of the study population and delivery outcomes are depicted in Table 1.  
121 Altogether, 26/75 (34.66%) of the patients in the case group suffered from gestational diabetes vs.  
122 24/149 (16.1%) in the control group ( $p = 0.002$ ). The rate of preterm delivery was 17.3% in the case  
123 group vs. 7.6% in the control group ( $p = 0.04$ ).

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

127 In 11/75 (14.66%) patients, SARS-CoV-2 infection occurred in the first trimester of gestation, in 19/75  
128 (25.33%) in the second and in 37/75 (49.33%) in the third trimester. In eight patients, time-point of  
129 infection was unknown (10.66%). Of these, three suffered from GDM.

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

133 89.33% of the patients (67/75) in the case group suffered from asymptomatic, mild or moderate  
134 SARS-CoV-2 infection, according to the National Institutes of Health (NIH) criteria for severity of the  
135 disease [12]. 12% (9/75) of the patients had severe or critical illness with inpatient management. Of

136 these, 5.33% (4/75) required intensive care unit (ICU) admission and ventilation. These four patients  
137 underwent an emergency delivery because of SARS-CoV-2 infection. No patient deaths were  
138 recorded.

139 Of the nine patients with inpatient management, four (44.44%) suffered from GDM. Of the four  
140 patients who required admission at the ICU, two suffered from GDM (50%). Of the 66 patients with  
141 outpatient management, 22 suffered from GDM (33.33%). This difference was not significant in chi-  
142 square test ( $p=0.51$ ). Regression analysis of factors associated with inpatient COVID-19 management  
143 (inpatient vs. outpatient) showed no significance for GDM (OR (95%CI) 1.14 (0.22, 5.80,  $p= 0.88$ ),  
144 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),  
145 0.41). .

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#### 147 Discussion

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

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



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

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

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

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

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

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

## 191 Conclusion

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

197 Disclosure statement: The author(s) report(s) no conflict of interest.

## 198 Author's contribution:

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

201 MF: acquisition of data, analysis and interpretation of data

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

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

204 BS: acquisition of data

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

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

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Characteristics	Cases n= 75	Controls n= 149	P value
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259 Tables and Figures

Age		30.76 ± 4.63	30.62 ± 4.48	ns
BMI (kg/m <sup>2</sup> )		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

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

261 \* missing values were excluded from the analysis

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