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Original Article

Impact of diabetes on the severity of COVID-19 infection in pregnant women - A single-center descriptive study

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ABSTRACT

Background and aims: Pregnant women have significant morbidity and mortality due to COVID-19 infection. Pregnancy and diabetes are known risk factors for severe COVID 19 infection. Understanding the interactions between COVID-19 and diabetes in pregnancy is crucial in developing appropriate therapeutic approaches. India, like many other countries, has a very high prevalence of diabetes and COVID-19 infected cases. Such studies are minimal worldwide and none from India to the best of our knowledge.

Materials and methods: We did a retrospective cross-sectional study. 856 COVID-19 infected pregnant women were included in the study. We estimated the impact of diabetes on the severity of COVID-19 infected pregnant women and compared the outcomes with the non-diabetic group.

Results: Prevalence of diabetes in pregnancy in the present study was 15.43%(n = 132/856). Prevalence of diabetes in non-severe infection was 14%(n = 115/818), severe infection was 44.73%(n = 17/38), and in maternal deaths was 75% (n = 6/8). The age-adjusted odds ratio for diabetes for severe infection was 4.492 (95% CI = 2.277–8.865, $p < 0.001$). COVID-19 infected pregnant women with diabetes were at higher risk for Cesarean section (78.3%) and ICU admission for newborns (14.81%)

Conclusion: Diabetes in pregnant women is strongly associated with the severity of COVID-19 infection. The prevalence of diabetes in pregnancy increases as the severity of COVID-19 infection increases. Diabetes is associated with more adverse outcomes in mothers and newborns. It is necessary to identify pregnant women with diabetes and prioritize them in public health interventions like vaccination.

1. Introduction

In the rapid outbreak of COVID 19 all around the world, pregnant women, like other people, are infected with the virus. Physiological respiratory and non-respiratory changes and immunological changes during pregnancy may predispose pregnant women to COVID 19 infection and worsen outcomes. Morbidity and mortality in COVID 19 infection are increased by comorbidities like Diabetes [1].

India is placed second worldwide with at least 77 million people (aged 20–79yrs.) living with diabetes [2]. India is also having one of the highest prevalence of COVID -19 infected cases [3].

It is necessary to determine the impact of diabetes on the severity of COVID-19 infection in pregnant women to modify the therapeutic strategies and reduce maternal morbidity and mortality. The vulnerable groups in pregnant women should be identified and prioritized in public health interventions like vaccination which is currently low due to safety concerns.

There are many studies on the risk of severity of COVID-19 infection in the general population with diabetes. Understanding the interactions between these two diseases is crucial in developing appropriate therapeutic approaches. However, to the best of our knowledge, there are very few studies worldwide and none from India to assess the impact of diabetes on the severity of COVID-19 infection in pregnant women. There is limited data on maternal and newborn outcomes of COVID -19 infected pregnant women with diabetes compared to those without diabetes. It was in this background that we conducted this study.

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2. Materials and methods

2.1. Design and objectives

We did a retrospective cross-sectional study with the primary objective to estimate the association of diabetes and the severity of Covid-19 infection in pregnant women. The secondary objective was to compare maternal and newborn outcomes among COVID-19 infected pregnant women with and without diabetes mellitus.

2.2. Ethics

After obtaining approval from the Institutional Ethics Committee, the study was registered with the Clinical Trials Registry-India under CTRI/2021/09/036831. A waiver of written informed consent was obtained due to the rapid emergence and highly infectious nature of the disease and being a record-based study with anonymized data.

2.3. Settings and sample

The study was conducted in a designated COVID-19 tertiary care hospital and teaching institute with 1300 beds in Kerala, India. The study period was one year, from 1 August 2020 to 31 July 2021. Pregnant women with laboratory-confirmed COVID-19 infection by Rapid Antigen Test or RT-PCR on the nasal/throat swab sample done as per the World Health Organization guidance and admitted during the study period were included. Patients transferred to other centres during treatment or discharged against medical advice were excluded. Data of patients were collected from the Hospital Medical Record section.

From the study population, those with diabetes were identified. Gestational diabetes was identified by the Oral Glucose Tolerance Test (after 75 g of oral glucose 2-h plasma glucose value > 140 mg %) as per DIPSI criteria [4] which is followed by our institution. Pre-gestational diabetes was identified from the history and old medical records. Severe COVID-19 infection, as per National Institute of health COVID-19 treatment guideline [5], was defined as lab-confirmed COVID-19 infection with respiratory distress and SpO2 < 94% on room air or respiratory rate >30/minute. Asymptomatic/symptomatic patients with SpO2 $\geq$ 94% and respiratory rate $\leq$30/minute were considered non-severe infections. At SpO2 < 94%, the patient was placed in a higher treatment category by state treatment guidelines [6], and steroids and oxygen supplementation were indicated.

The estimated maternal outcomes were severity of COVID-19 infection (non-severe/severe/death), antepartum complications like preeclampsia, preterm labor, mode of delivery (vaginal/cesarean), and postpartum complications. Newborn outcomes included prematurity, birth weight, Newborn Intensive Care Unit admission, neonatal COVID-19 infection and neonatal death.

2.4. Data abstraction

Data abstraction forms included socio-demographic details, clinical characteristics, obstetric/medical history, maternal and neonatal complications. Data retrieved from the medical records were reviewed and double-checked. The dataset for the study was frozen on 31 July 2021.

2.5. Statistical analysis

Continuous variables were described by mean ± standard deviation (SD) or median (interquartile range (IQR), considering the normality. Counts and percentages described categorical variables. For testing the association of factors with severity, the Chi-square test for association was used. Logistic regression analysis was done to find the risk factors of severity of COVID-19 infection. A p-value less than 0.05 was considered significant. The data were entered into MS Excel, and analysis was done using SPSS version 24.

3. Results

856 pregnant women who tested positive for SARS CoV-2 infection were enrolled in the study. There were 132 patients with diabetes with a prevalence of 15.42% (n = 132/856). Twelve patients (9%) among the people with diabetes had pre-gestational diabetes.

The diabetic status and COVID-19 infection severity in enrolled pregnant women are summarized in a flow chart in Fig. 1.

3.1. Socio-demographic and clinical characteristics

Table 1 summarizes the socio-demographic and clinical characteristics of pregnant women. Age: A significantly higher proportion of subjects aged more than 35 years who were diabetic compared to those aged less than or equal to 35 years, using the Chi-square test.

Gestational age: A significantly higher percentage of those between 28 and 37 weeks of gestation had diabetes than the other two gestational age groups (using the Chi-square test).

Symptoms: A more significant proportion of symptomatic had diabetes compared to asymptomatic (using Chi-square test). Among the symptomatic (n = 183), the most common symptom was fever (60%), followed by cough (48%) and breathlessness (17%).

The most common comorbidity, other than diabetes, was hypertension. Other comorbidities were bronchial asthma, hypothyroidism, structural heart diseases, hematological and immunological diseases.

3.2. Severity of Covid-19 infection

Severe COVID-19 infection were seen in 38 patients (4.43%, n = 38/856) and non-severe in 818 patients (95.56%, n = 818/856). There were eight maternal deaths during the study period, out of which six were diabetic. Fig. 2 shows the prevalence of diabetes in COVID-19 infection of varying severity in pregnant women.

Prevalence of diabetes in non -severe infection was 14% (n = 115/818), in severe infection was 44.73%(n = 17/38), and in maternal deaths was 75% (n = 6/8).

The association of different risk factors with severity of infection is given in Table 2.

3.3. Diabetes and severity of infection

Table 2a shows the association between diabetes and the severity of infection.

As given in Table 2a, the proportion of cases with severe infection was significantly higher among people with diabetes than non-diabetics (using the Chi-square test for association).

The proportion of pre-gestational diabetic cases with severe infection was significantly more than the proportion of gestational diabetes cases with severe infection (using Fisher's exact test), as shown in Table 2b.

The association of comorbidities like hypertension and bronchial asthma with the infection severity is given in Tables 2c and 2d, respectively. There were no cases with chronic kidney disease, chronic respiratory disease other than bronchial asthma, cardiovascular disease other than structural heart disease or active malignancy in the study group.

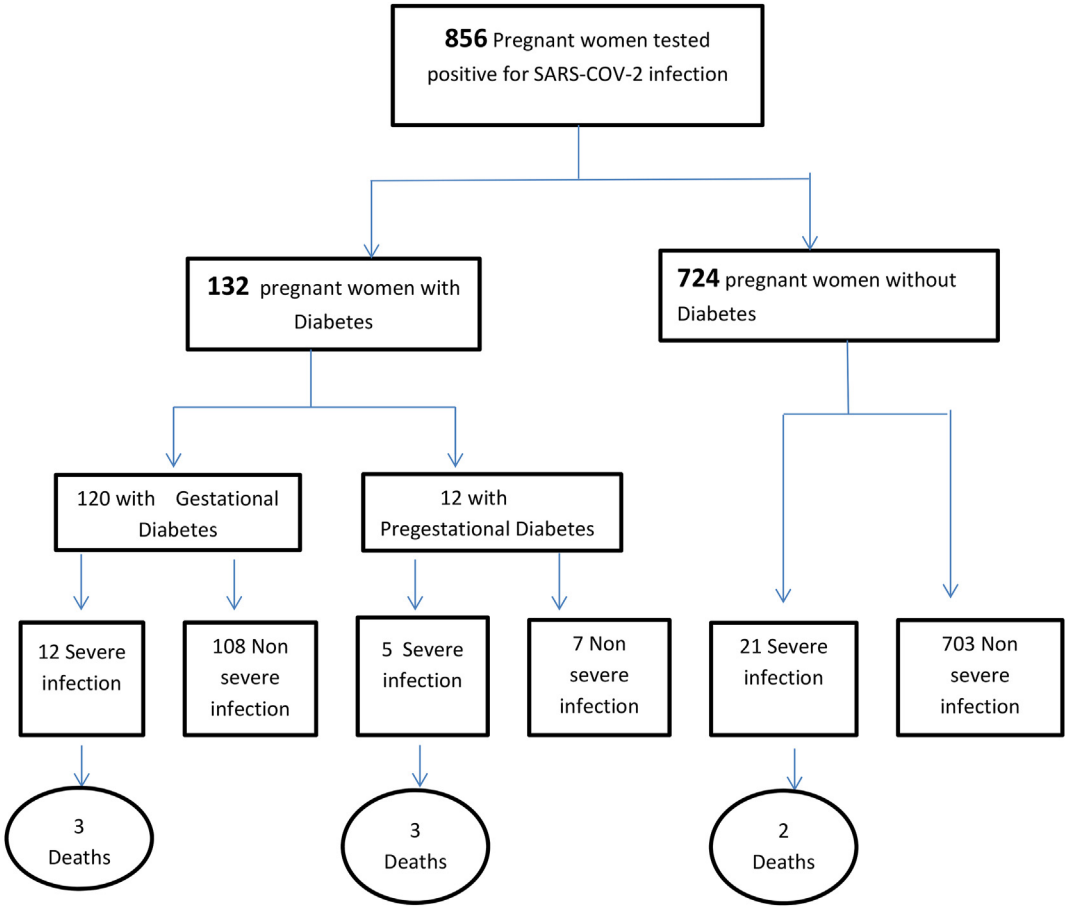

Fig. 1. Flow Chart of the pregnant women tested positive for SARS CoV-2 infection.

Table 1
The socio-demographic and clinical characteristics of pregnant women.

		Diabetic	Non-diabetic		
Risk factors		N(%)	N(%)	Total	P
Age in years	≤35	114(14.4)	680 (85.6)	794	<0.002
	>35	18(29)	44 (71)	62	
Parity	Primi	55(15.5)	298(84.4)	353	
	Multi	76(15.3)	420(84.6)	496	
	Grand multi	1(14.2)	6(85.7)	7	
Gestational age at time of exposure	<28 weeks	11(12)	80(87.9)	91	<0.006
	28-37,	59(21)	221(78.9)	280	
	>37 weeks	62(12.78)	423(87.21)	485	
Comorbidities	Hypertension	20(33.89)	39(66.1)	59	
	Bronchial Asthma	1(16.6)	5(83.3)	6	
	Hypothyroidism	8(44.4)	10(55.5)	18	
	Cardiac diseases	0(0)	6(100)	6	
	Others	2(33.3)	4(66.6)	6	
Symptoms	Asymptomatic	85	588	673	<0.001
	Symptomatic	47	136	183	

Association of age with the severity of infection is given in Table 2e.

So, looking at Tables 2a, 2c, 2d and 2e, the association of different factors with severity of infection, it was seen that diabetes and age are significantly associated with severity.

On doing Univariate logistic regression analysis:

Diabetic status: Crude OR = 4.949, 95% Confidence interval (2.534–9.663), $p < 0.001$.

Age: Crude OR = 3.773, 95% Confidence interval (1.650–8.629), $p = 0.002$.

On doing Multivariate logistic regression analysis:

Diabetic status: Adjusted OR = 4.492, 95% Confidence interval (2.277–8.865), $p < 0.001$.

Age: Adjusted OR = 2.977, 95% Confidence interval (1.262–7.023), $p = 0.013$.

So, as the odds of severe infection in people with diabetes are 4.492 times the odds of severe infection in non-diabetics, the presence of diabetes increases the severity of COVID infection.

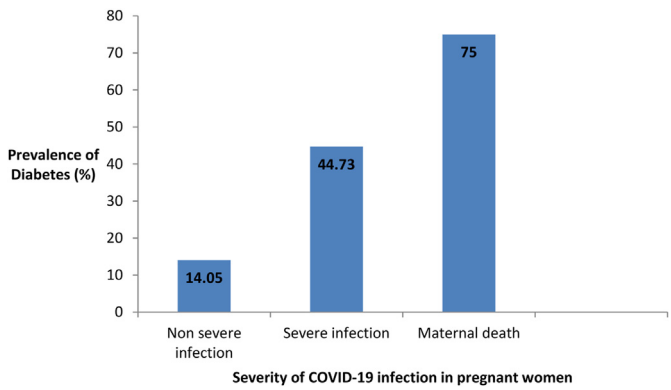

Fig. 2. Prevalence of Diabetes in COVID-19 infection of varying severity in pregnant women.

3.4. Maternal outcome

Table 3 describes the maternal outcome of pregnant COVID-19 infected women.

Cesarean delivery: The Cesarean rate among pregnant women with diabetes was 78.3%(n = 83/106), and those without diabetes was 64.41%(n = 353/548). The most common indication for Cesarean was previous Cesarean(34.71%), followed by fetal distress (18.8%). Among the 5 cases of Cesarean done for maternal distress, four belonged to the diabetic group. Thus a higher rate of Cesarean section was seen in patients with severe COVID-19 infection.

Eight patients with severe COVID-19 infection died. All were having COVID pneumonia, and one had a pulmonary embolism. Six of the deceased were diabetic, and three among them had pre-gestational diabetes.

3.5. Neonatal outcome

The neonatal outcome is shown in Table 4.

New-borns born to mothers in the diabetic group were more frequently admitted to Neonatal ICU (14.81%) than the non-diabetic group (9.76%). The most frequent reasons for Neonatal ICU admissions were transient tachypnea of newborn followed by respiratory distress syndrome and neonatal jaundice requiring phototherapy. The rate of perinatal transmission was similar between newborns born to mothers in the diabetic and non -diabetic groups.

4. Discussion

856 lab-confirmed COVID-19 positive pregnant women were included in the study. To the best of our knowledge, we presented the largest single-centre cohort worldwide for COVID-19 infected pregnant women to identify the association of diabetes with adverse outcomes.

Pregnancy itself is a risk factor for severe COVID-19 infection. 38 patients (4.43%) had a severe disease in our study. Other risk factors for severe infection include maternal age>35 years, pre-gestational and gestational diabetes, hypertensive disorders, pre-existing pulmonary, cardiovascular, renal, oncologic disease, obesity and immunosuppression.

However, there is marked variation in the prevalence of risk factors for severity of COVID-19 infection with age, gender and ethnicity. Risk factors in the present obstetric study population differed from that of the general population due to young age,

Table 2
Association of risk factors with severity of COVID-19 infection.

Table 2a: Diabetes and severity of COVID-19 infection					
	Diabetic		Non diabetic		P
	N	%	N	%	
Severe infection	17	12.9	21	2.9	<0.001
Non severe infection	115	87.1	703	97	
Total	132	100	724	100	
Table 2b: Type of Diabetes and severity of COVID-19 infection					
	Gestational Diabetes		Pre gestational diabetes		P
	N	%	N	%	
Severe infection in diabetics	12	10	5	41.7	<0.009
Non severe infection in diabetics	108	90	7	58.3	
Total	120	100	12	100	
Table 2c: Hypertension and severity of COVID-19 infection					
	Hypertensive		Non-hypertensive		P
	N	%	N	%	
Severe infection	4	6.89	34	4.26	<0.552
Non severe infection	54	93.10	764	95.73	
Total	58	100	798	100	
Table 2d: Bronchial Asthma and severity of COVID-19 infection					
	Bronchial Asthma		Non −asthmatics		P
	N	%	N	%	
Severe infection	0	0	38	4.47	0.999
Non-severe infection	6	100	812	95.53	
Total	6	100	850	100	
Table 2e: Age & severity of COVID-19 infection					
	Maternal Age >35 years		Maternal Age ≤35 years		P
	n	%	N	%	
Severe infection	8	12.9	30	3.8	<0.004
Non severe infection	54	87.1	764	96.2	
Total	62	100	794	100	

Table 3
Maternal outcome of pregnant COVID-19 infected women.

	Diabetic N = 132		Nondiabetic N = 724		P
	N	%	N	%	
Mode of delivery					
Vaginal delivery	23	17.4	195	26.9	<0.04
Cesarean	83	62.8	353	48.75	
Abortion	4	3	38	5.24	
On going pregnancy	22	16.6	138	19.06	
Maternal complications					
Preclampsia	6	4.5	12	1.6	
Preterm Labour	16	12.1	86	11.87	
Postpartum haemorrhage	1	0.75	1	0.13	
Severe COVID-19 infection	17	12.87	21	2.9	
Pulmonary embolism	1	0.75	0	0	
Invasive ventilation	6	4.5	3	0.41	
Maternal deaths	6	4.5	2	0.27	

Table 4
Neonatal outcome of pregnant COVID-19 infected women.

	Diabetic (n = 108)		Nondiabetic (n = 543)		
	N	%	N	%	P
Birth weight					0.3
<2.5 Kg	21	19.4	105	19.3	
2.5–3.5 Kg	78	72.2	414	76.24	
>3.5 Kg	9	8.33	24	4.41	
Sex					
Male	52	48.14	267	49.17	
Female	56	51.85	276	50.83	
Apgar < 7					
I minute	5	4.62	23	4.23	0.999
5 min	2	1.8	4	0.74	0.247
Intrauterine death	1	0.9	13	2.3	
NICU admission	16	14.81	53	9.76	0.223
Neonatal COVID infection	8	7.4	54	9.9	
Neonatal death	1	0.9	2	0.3	

female gender and behavioral differences like the absence of addictions like smoking and alcohol. There was no pregnant woman in the study group with coronary artery disease, chronic kidney disease, chronic liver diseases or chronic respiratory disease other than bronchial asthma.

There were no vaccinated females in the study group, as the COVID-19 vaccination drive for pregnant women was approved in our state only from July 2021 due to maternal and fetal safety concerns.

Prevalence of comorbidities other than diabetes, like hypertension, bronchial asthma, hypothyroidism, cardiovascular diseases, were low in the study group and showed no association with severity of infection statistically. This finding is consistent with studies from India that COVID-19 severity and mortality were significantly associated with the status of diabetes, and its risk may not be modified by the presence of hypertension [7].

The prevalence of diabetes in pregnancy in the present study was 15.43% (n = 132/856). The prevalence of Gestational diabetes mellitus in different parts of India was about 3.8%–17.9% [8], which is high compared to about 2–5% in the western population [9].

Our data show that the prevalence of diabetes increases with an increase in severity of COVID-19 infection in pregnant women. The prevalence of diabetes in non-severe infection, severe infection and maternal death was 14%, 44% and 75%, respectively. Our finding is consistent with the study by Guan WJ et al. [10], which showed that in COVID-19 patients, diabetes was significantly more prevalent among those with severe form than in patients with a non-severe form of the disease (34.6% vs 14.3%).

A meta-analysis by Guo et al. [1] showed that COVID-19 patients with diabetes had a higher risk (risk ratio: 2.96; 95% CI: 2.31–3.79). ShiQ et al. [11] also showed that patients with diabetes had a higher risk of severe disease or death and a higher rate of ICU admissions.

The age-adjusted Odds Ratio for Diabetes for severe infection in our study was 4.492 (95% Confidence interval 2.277–8.865, $p < 0.001$). A study by Manon Vouga et al. estimated the diabetic risk for severe disease requiring advanced oxygen support among COVID-19 positive pregnant women (Odds Ratio of 2.2, adjusted for specific COVID-19 risk factors for severe adverse maternal outcomes) [12].

The strong association of diabetes with COVID-19 is supported by evidence from the literature that the expression of ACE2, the entry receptor of SARS-CoV-2, is increased in type 2 diabetes mellitus patients in the lungs and other tissues [13]. This upregulation is associated with chronic inflammation, endothelial cell activation and insulin resistance which aggravates the inflammatory response and leads to dysfunction of the alveolar-capillary barrier [14,15].

Even when diabetic patients without other comorbidities were analyzed, the results remained the same—inflammatory and procoagulant factors were significantly higher in diabetic patients [1].

Pre gestational diabetes was more associated with severe COVID-19 infection in pregnancy than gestational diabetes in our study. This finding is consistent with other studies that show that Type 2 diabetes mellitus is more associated with a worse prognosis since hyperglycemia, in addition to the association with the formation of advanced glycation end products, results in oxidative stress and inflammatory process that can also favor viral replication [16].

Therefore, patients with diabetes in pregnancy deserve more intensive attention and should be closely monitored due to the risk of rapid deterioration.

There was a higher Cesarean section rate in the diabetic group, reflecting the higher rate of pregnancy complications in this group. Preeclampsia was also higher in the diabetic group. Studies from South India have shown that cesarean section and preeclampsia rates were significantly higher among women with gestational diabetes [17].

At the time of exposure, Gestational age was more than 37 weeks in most women in our study because detection was more in these patients as they had undergone COVID-19 screening near term or when admitted to the labor ward.

Most of the women admitted with SARS-CoV-2 infection in pregnancy were in the third trimester, as reported in other studies, which replicates the pattern seen for other respiratory viruses, with women in later pregnancy being more severely affected [18]. This finding supports the guidance for strict social distancing measures among pregnant women, particularly in their third trimester.

Clinical characteristics of the study group showed that symptomatic patients were more in the diabetic group, which also suggest that diabetes increase the severity of COVID-19 infection.

There were eight maternal deaths during the study period, with a case fatality rate of 0.9% (n = 8/856). This rate is similar to other studies by Marian Knight et al. (1%, n = 5/427) [17] and Manon Vouga et al. (0.6%, n = 6/926) [11].

Six of the deceased (75%, n = 6/8) were diabetic. The case fatality rate among diabetic pregnant women was 4.54%(n = 6/132).

One death occurred in the first half of the study period and seven deaths in the second half. More deaths in the second half was due to the second wave of the pandemic in India, caused by the Delta variant of the virus, which was more severe than the first wave.

More newborns in the diabetic group were admitted to the

Neonatal ICU, suggesting that complications were more in this group.

One risk factor for morbidity and mortality in COVID-19 infection during the study period was the resource crunch at the peak of the second pandemic wave in many parts of India. But such overwhelming of health care system was less marked in Kerala state, which showed the lowest COVID-19 seroprevalence rate among the Indian states in National seroprevalence survey on May 2021 [19].

Vaccination drive in pregnant women for COVID-19 got approval in India by July 2021 only, near the end of the study period. Hence none of the cases in the study group was vaccinated. Reports from Indian states as of October 2021 shows that there is gender disparity with fewer women being vaccinated for COVID-19 [20]. Vaccination among pregnant women could be lower due to vaccination hesitancy due to fetal safety concerns. However, public health authorities should focus on the vulnerable group like diabetic pregnant women with awareness programmes and prioritize them in public health intervention strategies like vaccination.

Gestational diabetes is strongly linked with lifestyle. Promoting a healthy lifestyle with a balanced diet and adequate exercise can decrease the prevalence of gestational diabetes, which can be an effective long term strategy against further COVID-19 pandemic waves.

The study's strength includes its large sample size as the study center catered to a large geographic area. The study had a mono centre design with samples from similar ethnicity and socio-demographic background, uniform admission criteria and the same treatment guideline, thus minimizing the heterogeneity seen with multicentre design and makes the comparison valid.

4.1. Limitations of study

The level of glycemic control in patients with diabetes may influence the severity of disease in pregnant women [21] but was not analyzed in the study. Obesity, a risk factor for severe COVID-19 infection, was not analyzed in the study due to logistic reasons.

5. Conclusion

Diabetes in pregnant women is strongly associated with the severity of COVID-19 infection. The prevalence of diabetes increases as the severity of COVID-19 infection increases. Diabetes is associated with more adverse maternal and neonatal outcomes. Pregnant women with diabetes were more symptomatic and also had a higher rate of Cesarean section.

A healthy lifestyle with a balanced diet and exercise will decrease the risk of gestational diabetes and is a good long term strategy against future pandemic waves. Awareness of the strong association of diabetes with adverse outcomes will help the public health system focus on pregnant women with diabetes and prioritize health intervention strategies like vaccination.

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