HYPERTENSION IN PREGNANCY

Hypertension in Pregnancy

ISSN: (Print) (Online) Journal homepage: www.informahealthcare.com/journals/ihip20

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To cite this article: Niraj N. Mahajan, Shweta Kesarwani, Padmaja Kumbhar, Periyasamy Kuppusamy, Madhura Pophalkar, Pratiksha Thamke, Ruchi Asawa, Saumya Sharan, Smita D Mahale & Rahul K Gajbhiye (2023) Increased risk of early-onset preeclampsia in pregnant women with COVID-19, Hypertension in Pregnancy, 42:1, 2187630, DOI: 10.1080/10641955.2023.2187630

To link to this article: https://doi.org/10.1080/10641955.2023.2187630

Published online: 09 Mar 2023.

HYPERTENSION IN PREGNANCY
2023, VOL. 42, NO. 1, 2187630
https://doi.org/10.1080/10641955.2023.2187630

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Increased risk of early-onset preeclampsia in pregnant women with COVID-19

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ABSTRACT

Objective: To estimate incidence, risk of early and late-onset preeclampsia (PE) and understand their relationship with severity of COVID-19.

Methods: Pregnant women with COVID-19 (n = 1929) were enrolled from 1 April 2020 to 24 February 2022. Primary outcome measure was incidence and risk of early onset PE in women with COVID-19.

Results: The incidence of early and late-onset PE was 11.4% and 5.6%. Moderate to severe COVID-19 was associated with eight times higher risk of early onset PE [aOR = 8.13 (1.56–42.46), $p = 0.0129$] compared to asymptomatic group.

Conclusions: Risk of early onset PE was higher in pregnant women with symptomatic COVID-19 as compared to asymptomatic women.

ARTICLE HISTORY
Received 23 June 2022
Accepted 1 March 2023

KEYWORDS
COVID-19; early onset preeclampsia; first wave, late-onset preeclampsia; SARS-CoV-2 infection, second wave, third wave

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 536 million people and has caused more than 6.3 million deaths globally (1). India is one of the worst affected countries due to COVID-19 contributing to a total burden of 43 million infected cases and 0.53 million deaths (2). Although COVID-19 is known to cause respiratory disease, evidence is emerging on extra-pulmonary manifestations including cardiovascular, renal, hematologic, endocrine, etc. suggesting multi-system disorder (3). Pre-eclampsia (PE), complicates about 3–5% of all pregnancies and is estimated to cause 76,000 maternal deaths and 500,000 fetal and new-born deaths annually (4). Low-income and middle-income countries (LMIC) have the major burden of complications related to PE mainly due to limited resources and poor access to adequate obstetric care compared to high-income countries.

During the early phase of the COVID-19 pandemic, "*PE like syndrome*" was reported in pregnant women with severe COVID-19 (5). The causal relationship between severity of COVID-19 disease and risk of PE was reported in the U.K. population (6). A large scale, multi-county study demonstrated strong association of COVID-19 during pregnancy with PE, especially in nulliparous women. They further reported that this association was independent of any risk factors and preexisting conditions. The association between COVID-19 and PE was not affected by severity of COVID-19 (7). Additionally, there is no information on the incidence and risk of early onset and late-onset PE in women with COVID-19. The primary aim of this study was to estimate the incidence, risk of early and late-onset PE; and to understand their relationship with severity of COVID-19. The aim was also to compare the incidence of early and late-onset PE during the first, second and third waves of COVID-19 pandemic.

Methods

The retrospective data analysis included 1929 pregnant women with confirmed SARS-CoV-2 infection admitted at BYL Nair Charitable Hospital (NH), a dedicated COVID-19 hospital and one of the participating centers of the PregCovid registry in Mumbai, India (8). Women aged≥18 years with a confirmed diagnosis of COVID-19 and completed 20 weeks of gestation admitted from 4 April 2020, and 24 February 2022 were included for the data analysis. All the cases of hypertension in pregnancy in the study were diagnosed concomitantly or after the diagnosis of

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COVID-19. PE was categorized as early onset PE before 34 weeks of gestation and late-onset PE after 34 weeks of gestation. The information on symptoms of COVID-19, and signs and symptoms of preeclampsia was collected at the time of admission, and subsequently during the period of hospitalization till the discharge. COVID-19 pandemic period was divided in three waves; first wave from 1st April 2020 to 31st January 2021 and second wave was from 1st February 2021 to 10th December 2021 and third wave was from 18th December to 24th February 2022. The hospital admission policy (8) was uniform during all three waves of the COVID-19 pandemic period. The asymptomatic cases were identified by universal testing (9) of those women who were admitted at NH needing obstetrics intervention, as per the admission policy of NH (8). An asymptomatic case was defined as laboratory-confirmed case of COVID-19 who have never developed symptoms before or during the hospital stay. The gestational age was reported at the time of admission due to SARS-CoV-2 infection.

Clinical characteristics of study population

The existing national testing guidelines for confirmation of COVID-19 testing were adopted (9) and the disease was categorized into asymptomatic, mild, moderate, and severe COVID-19 (10). As per admission policy of NH (8), pregnant women who were near-term or those required obstetric interventions or high-risk pregnancies or pregnant women with moderate or severe disease were admitted during all the waves of COVID-19. Intrauterine fetal death (IUFD) was defined as *in-utero* or intrapartum death of a fetus delivered after completed 20 weeks' gestation. The post-partum hemorrhage was defined as any amount of blood loss intrapartum or post-partum (within 24 hours) accompanied by signs and symptoms of hypovolemia within 24 hours of birth process regardless of route of delivery (11). Gestational age (GA) at COVID-19 diagnosis was calculated based on last menstrual period and obstetric ultrasound.

Definition of gestational hypertension and preeclampsia

Gestational hypertension was defined as hypertension arising de novo after 20 weeks' gestation in the absence of proteinuria and without biochemical or hematological abnormalities (12). Preeclampsia was defined as presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury (AKI), liver dysfunction, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction (12). To measure the impact of PE, all rates were calculated from the pregnancy outcomes which included all deliveries, spontaneous abortions beyond 20 weeks.

Statistical analyses

Incidence of early and late-onset PE was calculated. The chi-square/Fisher exact test was used to assess the difference between women with and without PE. Multivariate logistic regression was performed to assess an association between severity of COVID-19 (asymptomatic group was a reference) and risk of early and late-onset PE, adjusted with prior risk factors like maternal age>35 years, chronic hypertension, bronchial asthma, gestational diabetes mellitus (GDM), multiple gestation, nulliparous, IVF conception, previous history of abortion and still birth. A two-tailed $p < 0.05$ was considered significant. Analysis was carried out using SPSS software, version 26 (SPSS South Asia Pvt Ltd., Bengaluru).

Ethical approval

This study protocol was reviewed and approved by Ethics Committees of TNMC (No. ECARP/2020/63 dated 27.05.2020) and ICMR-NIRRCH (IEC no. D/ICEC/Sci-53/55/2020 dated 04.06.2020) approved the study. A waiver of consent was granted as the data was collected from the medical case records.

Results

Of the 1929 pregnant women with COVID-19, 247 (12.8%) were diagnosed to have *de novo* hypertension in pregnancy [gestational hypertension ($n = 122$, 6.3%) and PE/E ($n = 125$, 6.5%)]. The median age was higher amongst pregnant women with moderate-severe COVID-19 [31 (27–33.25)] compared to asymptomatic patients [27 (24–30)] ($p < 0.001$). The maternal characteristics, clinical factors and pregnancy complications are presented as per the severity of COVID-19 in Table 1. The median gestational age (GA) at COVID-19 diagnosis was significantly higher in women who were asymptomatic [39 (37–39)] than symptomatic for COVID-19 [mild 37 (34–39), moderate-severe 32 (28–36)] ($p < 0.001$). Higher proportion of women with GA <34 weeks were symptomatic for COVID-19 ($p < 0.001$). Gestational diabetes mellitus (GDM) was significantly associated with moderate to severe COVID-19 disease

Table 1. Stratification of pregnant women with SARS-CoV-2 infection.

Maternal characteristics & clinical factors ($N = 1929$)	Severity of COVID-19			P value #	P value ≠
	Asymptomatic ($n = 1450$)	Mild ($n = 371$)	Moderate–severe ($n = 108$)		
Maternal age (years) [median (IQR)]	27 (24–30)	27 (24–30.5)	31 (27–33.25)	0.4549	<0.001
Gestational age (weeks) at the time of admission [median [IQR)]	39 (37–39)	37 (34–39)	32 (28–36)	<0.001	<0.001
≤28 weeks	24 (1.7)	45 (12.1)	28 (25.9)	<0.001[a]	<0.001†
28–34 weeks	71 (4.9)	67 (18.1)	46 (42.6)	<0.001†	<0.001†
>34 weeks	1355 (93.4)	259 (69.8)	34 (31.5)	Reference	Reference
Nulliparous	681 (47.0)	190 (51.2)	50 (46.3)	0.1439	0.8930
Multiple gestation	33 (2.3)	9 (2.4)	3 (2.8)	0.8636	0.7346
In vitro fertilization	29 (2.0)	7 (1.9)	3 (2.8)	0.8888	0.4826
Diabetes mellitus	9 (0.6)	1 (0.3)	4 (3.7)	0.6973	0.0096
Gestational diabetes mellitus	41 (2.8)	12 (3.2)	8 (7.4)	0.6774	0.0169
Chronic hypertension	11 (0.8)	6 (1.6)	3 (2.8)	0.1329	0.0673
Bronchial asthma	12 (0.8)	1 (0.3)	2 (1.9)	0.4865	0.2526
Severe anemia (Hb <7 gm %)	13/1366 (1.0)	3/359 (0.8)	4/108 (3.7)	>0.999	0.0308
Cardiac disease	11 (0.8)	4 (1.1)	3 (2.8)	0.5232	0.0673
de novo hypertension in pregnancy	185 (12.8)	49 (13.2)	13 (12.0)	0.8176	0.8280
Gestational hypertension	96 (6.6)	20 (5.4)	6 (5.6)	0.3867	0.6659
Preeclampsia/Eclampsia	89 (6.1)	29 (7.8)	7 (6.5)	0.2411	0.8861
Preterm birth[a]	125/1170 (10.7)	35/222 (15.8)	14/71 (19.7)	0.0295	0.0191
Intrauterine fetal death[a]	17/1170 (1.5)	9/222 (4.1)	4/71 (5.6)	0.0148	0.0281
Maternal death[a]	0	1/222 (0.5)	43/71 (60.6)	-	-
Comparison between three waves of COVID-19					
First wave	950 (65.5)	128 (34.5)	25 (23.1)	Reference	Reference
Second wave	331 (22.8)	123 (33.2)	81 (75.0)	<0.001	<0.001
Third wave	169 (11.7)	120 (32.3)	2 (1.9)	<0.001	0.4112

[a]Total pregnancy outcome includes all deliveries, abortions beyond 20 weeks and maternal mortality ($n = 1463$).
#Comparison was made between mild versus asymptomatic.
≠Comparison was made between moderate-severe versus asymptomatic.
†Gestational weeks>34 was considered as a reference category for<28 weeks and 28–34 weeks.
Mild COVID-19 was defined as patients with uncomplicated upper respiratory tract infection with mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache without shortness of breath or Hypoxia [10].
Moderate COVID-19 was defined as pneumonia with no signs of severe disease. It included patients with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 90 to≤93% on room air, respiratory rate more or equal to 24 per minute [10].
Severe COVID-19 was defined as patients with severe pneumonia, acute respiratory distress syndrome, sepsis or septic shock. It included women with clinical signs of pneumonia plus one of the following; respiratory rate>30 breaths/min, severe respiratory distress, SpO2 < 90% on room air[10].

compared to the asymptomatic group ($p = 0.01$) [Table 1].

Association between COVID-19 and early onset preeclampsia

The risk of early and late-onset PE in pregnant women with COVID-19 is presented in Table 2. The incidence of early and late-onset PE was 11.4% and 5.6%, respectively. There was significant difference in incidence of early onset PE than late-onset PE in women with COVID-19 [uOR = 2.15 (1.41–3.28), $p = 0.0003$]. Risk of early onset PE was higher in symptomatic women with COVID-19 [uOR = 2.51 (1.08–5.85)]. Early onset PE was 6 times higher as compared to late-onset PE in women with previous history of still birth [uOR = 6.5 (1.13–37.38, $p = 0.0370$]. Women with GDM reported 2 times higher risk of early onset PE as compared to late-onset PE [uOR = 2 (0.32–12.55, $p = 0.6016$].Early onset PE was reported higher (40.6%) during the first wave compared to second wave (25%) and third wave (34.4%) of COVID-19 pandemic. Early onset PE was 3 times higher than late-onset PE during third wave of COVID-19.

Risk of early onset PE with severity of COVID-19

Table 3 presents the correlation of severity of COVID-19 and risk of early and late-onset PE compared to the asymptomatic group. Moderate to severe COVID-19 was associated with eight times higher risk of early onset PE [aOR = 8.13 (1.56–42.46), $p = 0.0129$] as compared to the asymptomatic group. Similarly, there was also 2 times higher risk of early onset PE for patients with mild COVID-19 compared to asymptomatic group [aOR = 1.99 (0.72–5.45)].

Impact of COVID-19 and PE on the outcomes

Higher proportion of cesarean birth was reported in women with late-onset PE (53.4%) as compared to early onset PE (40%). Pregnancy complications such as abruptio placentae, IUFD were higher in women with early onset PE. Postpartum hemorrhage was higher in

Table 2. Association of maternal and clinical characteristics of women with COVID-19 who developed early and late-onset preeclampsia.

Maternal characteristic & clinical factors	Early onset preeclampsia	Late-onset preeclampsia	Early onset[a] preeclampsia	Late-onset preeclampsia	
n = 1929	**n = 32%)**	**n = 93%)**	**uOR (95% CI)**	**uOR (95% CI)**	**P value**
Incidence rate per 100	11.4[†]	5.6[††]	2.15 (1.41–3.28)	0.47 (0.31–0.71)	0.0003
Maternal age (years) >35	5 (15.6)	10 (10.8)	1.54 (0.48–4.89)	0.65 (0.20–2.07)	0.530
Severity of COVID-19 disease					
Asymptomatic	18 (56.3)	71 (76.3)	Reference	Reference	
Symptomatic	14 (43.8)	22 (23.7)	2.51 (1.08–5.85)	0.40 (0.17–0.93)	0.0304
Pregnancy characteristics					
Nulliparous	19 (59.4)	52 (55.9)	1.15 (0.51–2.61)	0.87 (0.38–1.96)	0.7332
Multiple gestation	2 (6.3)	3 (3.2)	2.00 (0.32–12.55)	0.50 (0.08–3.14)	0.6016
IVF conception	3 (9.4)	4 (4.3)	2.30 (0.49–10.89)	0.43 (0.09–2.06)	0.3708
Previous spontaneous abortion	6 (18.8)	13 (14.0)	1.42 (0.49–4.11)	0.70 (0.24–2.04)	0.5707
Previous still birth	4 (12.5)	2 (2.2)	6.50 (1.13–37.38)	0.15 (0.03–0.89)	0.0370
Gestational diabetes mellitus	2 (6.3)	3 (3.2)	2.00 (0.32–12.55)	0.50 (0.08–3.14)	0.6016
Comorbidities/Co-infections					
Chronic hypertension	0	8 (8.6)	-	-	-
Bronchial asthma	0	1 (1.1)	-	-	-
Hypothyroidism	2 (6.3)	12 (12.9)	0.45 (0.10–2.13)	2.22 (0.47–10.52)	0.5160
Tuberculosis	3 (9.4)	1 (1.1)	9.52 (0.95–95.1)	0.11 (0.01–1.05)	0.0513
Malaria/Dengue	1 (3.1)	1 (1.1)	2.97 (0.18–48.9)	0.34 (0.02–5.55)	0.448
Anemia (Hb <11 gm %)	19/32 (59.4)	42/91 (46.2)	1.71 (0.75–3.86)	0.59 (0.26–1.33)	0.1982
Comparison between three waves					
First wave	13 (40.6)	51 (54.8)	Reference	Reference	
Second wave	8 (25.0)	28 (30.1)	1.12 (0.41–3.03)	0.89 (0.33–2.41)	0.8219
Third wave	11 (34.4)	14 (15.1)	3.08 (1.14–8.36)	0.32 (0.12–0.88)	0.0236
Pregnancy complications & Adverse outcomes (*n* = 1463) [a]	n = 30	n = 88			
Cesarean birth	12 (40.0)	47 (53.4)	0.58 (0.25–1.35)	1.72 (0.74–3.99)	0.2046
Abruption placentae	1 (3.3)	2 (2.3)	1.48 (0.13–16.9)	0.67 (0.6–7.72)	>0.999
Intrauterine fetal death	5 (16.7)	4 (4.5)	4.20 (1.05–16.84)	0.24 (0.06–0.96)	0.0454
Postpartum hemorrhage	1 (3.3)	5 (5.7)	0.57 (0.06–5.11)	1.75 (0.20–15.6)	>0.999
Maternal mortality	3 (10.0)	1 (1.1)	9.67 (0.97–96.8)	0.10 (0.01–1.04)	0.0501

[a]Total pregnancy outcome includes all deliveries, abortions beyond 20 weeks and maternal mortality.
[b]Early onset PE rate per 100 was calculated from pregnant women who had gestational weeks of < 34 (*n* = 281) and [††]Late-onset PE rate per 100 from pregnant women who had gestational weeks≥34 (*n* = 1648).
[c]The post-partum hemorrhage was defined as intrapartum or post-partum (within 24 hours) accompanied by signs and symptoms of hypovolemia within 24 hours of birth process regardless of route of delivery.

Table 3. Association of severity of COVID-19 disease and preeclampsia (early onset and late-onset PE).

Total pregnant women	PE	Without PE	Women with PE				Early onset PE	Late-onset PE	Early onset PE			
(*N* = 1929)	**(*n* = 125)**	**(*n* = 1804)**	**uOR (95% CI)**	**P value**	**aOR * (95% CI)**	**P value**	**(*n* = 32)**	**(*n* = 93)**	**uOR (95% CI)**	**P value**	**aOR # (95% CI)**	**P value**
Asymptomatic	89 (71.2)	1361 (75.4)	Reference		Reference		18 (56.3)	71 (76.3)	Reference		Reference	
Mild	29 (23.2)	342 (19.0)	1.30 (0.84–2.00)	0.2423	1.20 (0.77–1.88)	0.4242	10 (31.3)	19 (20.4)	2.08 (0.82–5.23)	0.1213	1.99 (0.72–5.45)	0.1834
Moderate to severe	7 (5.6)	101 (5.6)	1.06 (0.48–2.35)	0.8861	0.83 (0.36–1.91)	0.6544	4 (12.5)	3 (3.2)	5.26 (1.08–25.63)	0.0399	8.13 (1.56–42.46)	0.0129

*Adjusted with maternal age>35 years, chronic hypertension, bronchial asthma, GDM, multiple gestation, nulliparous, IVF conception, previous history of abortion and still birth.
#Adjusted with maternal age>35 years,GDM, multiple gestation, nulliparous, IVF conception, previous history of abortion and still birth.
PE- Preeclampsia; uOR- unadjusted odds ratio; aOR- adjusted odds ratio.

late-onset PE as compared to early onset PE. Maternal mortality was higher in women with early onset PE as compared to late-onset PE ($p = 0.0501$) [Table 2]. However, these differences could not reach statistical significance.

Discussion

Our study demonstrated association of COVID-19 as a risk factor of PE and further showed eight times higher risk of early onset PE in women with moderate-severe COVID-19 as compared to asymptomatic women with COVID-19. This observation is extremely important for the management of early onset PE in women with COVID-19 especially in low resource settings as there is an overlap of symptoms such as dyspnea, headache and cough amongst moderate-severe COVID-19 and PE. PE like syndrome associated with SARS-CoV-2 infection (5) poses challenges for distinguishing this syndrome from "true" PE as both these conditions share similar characteristics of the severe endothelial dysfunction. Several mechanisms could explain role of COVID-19 in pathogenesis of PE. COVID-19 is reported to alter the ACE-2 receptors and dysregulation of Renin – angiotensin system (RAS) (13). RAS act as a regulator of placental function as it is involved in control of trophoblast proliferation, angiogenesis and blood flow which may contribute to the development of PE (14).

Although, our study is a single center study, it is representative of the large population living in Mumbai Metropolitan Region as NH is a dedicated COVID-19 hospital since the beginning of the COVID-19 pandemic in Mumbai, India (8). The study population is inclusive of both the urban and rural areas. Majority of pregnant women were asymptomatic (75.2%) for COVID-19 and only 24.8% of women were symptomatic in our cohort. We observed an increased rate of early onset PE suggesting that COVID-19 may alter physiology in pregnancy and thereby increase the risk of PE. The overall incidence of PE in our study is 6.5% which is lower than INTERCOVID study (8.1%) (7) but higher than U.K study (4.2%) (6). The overall incidence of PE in Maharashtra was reported as 2.2% (Urban 2.1%, Rural 2.3%) based on the third National Family Health Survey (NFHS-3) data of 2005–2006 (15). The incidence of PE reported in women with COVID-19 in the present study is nearly three times higher than a study based on NFHS-3 survey in the same geographical region suggesting the possible impact of COVID-19 for development of PE. We observed an increased incidence of cesarean birth in late onset PE compared to early onset PE. This could be due to the fact that there were higher IUFDs and higher maternal mortality in early onset PE compared to late onset PE.

In our study cohort, higher incidence of GDM was reported with moderate-severe COVID-19 group compared to the asymptomatic group in our study. We further observed a higher risk of early onset PE in women with GDM. Role of glycan-protein and glycan-glycan interactions are reported in the SARS-CoV-2 viral spike protein-ACE2 human receptor complex (16) suggesting hyperglycemia as a cofactor in virulence of SARS-CoV-2. Additionally, pre-infection increased blood glucose levels is reported as a risk factor for severe COVID-19 even in non-diabetics (17). A study based on NFHS-4 data, reported 1.0% of pregnant women in Maharashtra had a basal glycaemia≥200 mg/dL for non-fasting (18). Further studies are required to understand the severity of COVID-19 and maternal and neonatal outcomes in women with GDM and PE.

The results of our study suggest an urgent need of point of care tests which can differentiate between PE and PE-like syndrome induced by severe COVID-19. Investigations such as uterine artery pulsatility index (UtAPI), angiogenic factors (sFlt-1/PlGF) and Lactate dehydrogenase (LDH) have limitations. UtAPI and

sFlt-1/PlGF ratio have a high negative predictive value to predict the short-term absence of PE, they are not diagnostic criteria of PE. Therefore, it is difficult to categorically state that the case with PE features and elevated UtAPI and sFlt-1/PlGF was an actual PE and not a PE-like syndrome (5). Therefore, differentiating PE from the PE-like syndrome still remains a challenge and misdiagnosis can occur in some of these cases because of overlapping clinical features and high negative predictive value of these tests. There is also non-availability of Doppler test and obstetricians have to rely on the clinical findings in low resource settings. However, we suggest that health care providers should be aware of available tests and monitor pregnancies with suspected PE with caution as PE-like syndrome might not be an indication for earlier delivery.

During all the three waves of COVID-19 pandemic, challenges were faced especially in low resource settings like ours for the diagnosis and management of the cases of PE with moderate/severe COVID-19: (1) Rely only on bedside investigations like dipstick test, blood pressure; and chest X-ray to differentiate between pulmonary edema due to severe PE and COVID pneumonia; (2) non-availability of reliable point of care tests which can differentiate PE from severe COVID-19.

This study has important clinical implications as we show that severity of COVID-19 is associated with risk of early onset PE. This knowledge could be useful for strict monitoring of severe COVID-19 cases for development of early onset PE. Increased ICU admissions and high mortality was reported in pregnant women with COVID-19 especially during the second wave of COVID-19 (11,19). Our data supports the earlier observation of combined effect of COVID-19 and PE during pregnancy suggesting women having COVID-19 should also be considered at a higher risk for early onset PE (7).

To the best of our knowledge, this is the first study to describe the incidence and risk of early onset PE in women with COVID-19. We have documented association of SARS-CoV-2 and increased risk of early onset PE in a large cohort of pregnant women in an Indian population during 18 months of COVID-19 pandemic.

Limitations of our study include; single-center study, no comparison in pregnancies without COVID-19 or appropriately controlled pregnancies with negative SARSCoV-2 testing, and lack of genome sequencing data on SARS-CoV-2 strains. Our study was retrospective study and therefore, the clinical management of pregnancy complications associated with COVID-19 and PE was based on our hospital practices and was not standardized. The small number of early-onset preeclampsia in moderate to severe COVID-19 women is a limitation of the study.

Conclusion

Our study reports association of early onset PE with COVID-19 during pregnancy. More the severity of COVID-19, greater the risk of early onset PE suggesting the dose response relationship. Obstetricians involved in care of women with COVID-19 should be aware on additional risks of pregnancy complications and adverse pregnancy outcomes like IUFD associated with PE with COVID-19 so that adequate care can be ensured to these high-risk women. Reliable point of care tests should be made available to differentiate PE from the PE-like syndrome associated with severe COVID-19.

Acknowledgments

The authors thank Network of National Registry of Pregnant women with COVID-19 in India (CTRI/2020/05/025423). Faculties, Resident doctors, and Interns in the Department of Obstetrics and Gynecology at TNMC, Mumbai, are sincerely acknowledged.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Intramural grant of ICMR-NIRRCH (No. ICMR-NIRRCH/RA/1130/09-2021). Rahul K. Gajbhiye is an awardee of the DBT Wellcome Trust India Alliance Clinical and Public Health Intermediate Fellowship (Grant no. IA/CPHI/18/1/503933).

Author contributions

Niraj N Mahajan and Rahul Gajbhiye contributed to the study conception and design. Material preparation was done by Rahul Gajbhiye and Niraj N. Mahajan. Data collection was done by all authors. Analysis was performed by Periyasamy Kuppusamy, Rahul Gajbhiye and Niraj N. Mahajan. The first draft of the manuscript was written by Niraj N. Mahajan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate and publish

A waiver of consent was granted as the data was collected from the medical case records.

Ethics Approval

Ethics Committees of TNMC (No. ECARP/2020/63 dated 27.05.2020) and ICMR-NIRRCH (IEC no. D/ICEC/Sci-53/55/2020 dated 04.06.2020) approved the study.

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