The role of shared risk factors for COVID-19 and preeclampsia: An observational study

Berta Serrano[1], Manel Mendoza[1], Paula Garcia-Aguilar[1], Erika Bonacina[1], Itziar Garcia-Ruiz[2], Pablo Garcia-Manau[1], Judit Gil[3], Mireia Armengol[1], Nuria Fernández-Hidalgo[2], Elena Sulleiro[4], Rosa Maria Lopez-Martinez[1], Marta Ricart[5], Lourdes Martin[6], Eva Lopez-Quesada[7], Angels Vives[8], Anna Maroto[9], Nerea Maiz[3], Anna Suy[2], and Elena Carreras[2]

[1]Vall d'Hebron Hospital
[2]Vall d'Hebron University Hospital
[3]Hospital Universitari Vall d'Hebron
[4]Vall d'Hebron Hospital Universitari
[5]University Hospital Germans Trias i Pujol
[6]Joan XXIII University Hospital in Tarragona
[7]Grup Mutua Terrassa
[8]Consorci Sanitari de Terrassa
[9]Doctor Josep Trueta University Hospital of Girona

January 27, 2022

Abstract

Objective: To examine baseline risk factors measured in the first-trimester screening for preeclampsia (PE) in pregnant women with COVID-19 versus the general population. To compare risk factors among patients with mild and severe COVID-19. Design: Observational retrospective study. Setting: Six maternities in Catalonia. Population: Study patients were 231 pregnant women undergoing first-trimester screening for PE and positive for SARS-CoV-2. Reference cohort were 13,033 pregnant women with first-trimester screening for PE from 6 maternities. Methods: Recording of maternal history, mean arterial blood pressure (MAP), mean uterine artery pulsatility index (UtAPI), placental growth factor (PlGF) and pregnancy-associated plasma protein-A at first trimester. Confirmation of SARS-CoV-2 infection. Based on the need for hospitalization, patients were classified into mild and severe COVID-19. Main outcome measures: Comparison of proportion of cases at a high risk for PE and of risk factors for PE among groups. Results: High risk for PE was significantly higher amongst COVID-19 patients compared to the general population, showing higher rates of obesity, chronic hypertension, higher UtAPI, and lower rates of smokers. PlGF did not differ significantly. In women with severe COVID-19, compared with mild COVID-19, BMI and MAP were significantly higher, whereas PlGF and UtAPI did not differ significantly. Conclusions: In patients with COVID-19 there was a higher proportion of women at a high risk for PE than in the general population, mainly due to maternal risk factors, rather than placental signs of a deficient trophoblastic invasion. Likewise, according to COVID-19 severity, differences were due to maternal risk factors only.

INTRODUCTION

The relationship of SARS-CoV-2 and pregnancy has been under study since the outset of the coronavirus pandemic. Evidence shows that pregnant women with COVID-19 are at an increased risk of severe pregnancy complications, including preeclampsia (PE), admission at the intensive care unit, preterm birth or maternal

mortality[1].

One of the first studies about COVID-19 and pregnancy, published in February 2020, suggested an increased PE incidence amongst pregnant women with COVID-19[2]. This was confirmed in a systematic review published online in March 2020, where a PE incidence of 14.6% was observed in pregnant women with COVID-19[3], as compared with 2-8% in the general population[4]. INTERCOVID, a prospective comparative study matching pregnant women with and without COVID-19, showed that the risk of developing PE/eclampsia was almost 4 times greater in women with COVID-19[1]. Subsequent analysis of the same population examining PE incidence showed a risk ratio of 1.95 (95%CI: 1.38-2.75)[5]. Recently, a large meta-analysis that included 28 studies showed an increased PE incidence risk, with an odds ratio of 1.62 (95%CI: 1.45-1.82)[6].

Different theories have been suggested regarding the association between PE and COVID-19[5–9]. One of them hypothesises that PE and COVID-19 are associated due to sharing risk factors for endothelial damage, such as obesity, hypertension, diabetes and maternal age. In that case, PE in the preclinical stage could be an additional risk factor for endothelial damage, thereby increasing the risk of developing COVID-19, mostly in its severe forms. The question is whether preexisting endothelial damage due to abnormal trophoblastic invasion increases the risk of developing COVID-19 and its severity, or whether the association between both conditions is driven by the fact that COVID-19 and PE share risk factors increasing the risk of both conditions. If preexisting endothelial damage due to abnormal trophoblastic invasion[10] makes patients more vulnerable to COVID-19 (or more likely to develop a severe form of COVID-19), women with COVID-19 would have lower placental growth factor (PlGF) levels and increased mean uterine artery pulsatility index (UtAPI) as compared to the reference population.

The primary aim of this study was to examine baseline risk factors, as well as biochemical and biophysical markers measured in the first-trimester combined screening for PE in pregnant women with COVID-19 versus the general population. The secondary aim was to compare these baseline characteristics and markers between women with mild and severe COVID-19.

METHODS

This was an observational retrospective study conducted at Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. This study was approved by the Vall d'Hebron Barcelona Hospital Campus Ethics Committee (PR[AMI]556/2021) on 5th November 2021. For the study group, inclusion criteria were women (a) attending our site with confirmed SARS-CoV-2 infection at any point during pregnancy and (b) undergoing the first-trimester combined screening for PE. The recruitment period for the SARS-CoV-2 group was from February 2020 to September 2021. Our centre was a referral hospital for severe COVID-19 pneumonia, especially during pregnancy; therefore, cases were both patients from our area and patients referred from all across Catalonia. For the population group, data was obtained from general population attending first-trimester screening for PE in 6 centres across Catalonia (Vall d'Hebron Barcelona Hospital Campus, Hospital Universitari Germans Trias i Pujol, Hospital Universitari de Tarragona Joan XXIII, Hospital Universitari Mútua Terrassa, Consorci Sanitari de Terrassa, Hospital Universitari de Girona Doctor Josep Trueta) between May 2019 and June 2021. A previous study assessing the screening performance of the first-trimester screening for PE was approved (PR(AMI)147/2021), and, therefore, data from general population was prospectively recorded.

SARS-CoV-2 infection was confirmed either by real-time polymerase chain reaction (RT-PCR) or an antigen test. Several changes in screening protocols have occurred during the study period, while scientific evidence or assistance care needs were changing. Therefore, our study population included both patients systematically screened at hospital admission and patients screened because of symptomatology or close contact. In the study group, severity of the symptoms was the criteria used for classification: mild forms of COVID-19, including asymptomatic and symptomatic women not requiring hospitalization, and severe forms of COVID-19, including patients requiring hospitalization due to severe pneumonia.

In Catalonia, the first-trimester screening for PE is routinely performed during the first-trimester scan between 11+0 and 13+6 weeks of gestation. Gestational age is confirmed by fetal crown-rump length measu-

rement during this scan[11]. Demographic characteristics, obstetric history, maternal history and biophysical and biochemical markers are documented in the clinical records. Biophysical markers, including transabdominal mean uterine artery pulsatility index (UtAPI) and mean arterial blood pressure (MAP), are assessed during the first-trimester scan. Biochemical markers, including serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), are measured at the routine first-trimester blood test (from 8+0 to 13+6 weeks of gestation). Maternal serum PAPP-A and PlGF levels were determined by the fully automated Elecsys assays for PAPP-A and PlGF on an immunoassay platform (cobas e analysers; Roche® Diagnostics, Rotkreuz, Switzerland). First-trimester risk for PE was then calculated[4]. High risk for PE was defined as a risk for early-onset PE [?] 1/170. This cut-off value provides a 90.9% detection rate for early-onset PE at a 12.7% false-positive rate[12].

All examiners were certified by the Fetal Medicine Foundation for PE risk assessment and Doppler ultrasound assessment.

Statistical Analysis

Categorical data were reported as frequency and percentage, and comparisons between groups were estimated by chi-square or Fisher tests, as appropriate. Continuous variables were reported as the median and interquartile range, and Mann-Whitney U test was used to assess differences between groups. The statistical significance level was set at $p<0.05$.

The statistical software package R (version 4.0.3) was used for data analysis (R Foundation for Statistical Computing, Vienna, Austria)[13].

RESULTS

For the study group (or COVID-19 group), 231 women fulfilled the inclusion criteria. In the population group (or reference group), 13,033 women underwent the routine first-trimester screening for PE.

Comparison of the COVID-19 and reference groups

In the COVID-19 group, 44 out of 231 (19.0%) cases were identified to be at a high risk for PE at the first-trimester screening, and this incidence was significantly higher than the 1,719 out of 13,033 (13.2%) found in the general population ($p=0.012$). When PE risk factors were examined individually, we found that women with COVID-19 had higher UtAPI and body mass index (BMI), higher incidence of chronic hypertension, and fewer were smokers. No significant differences were found in MAP, PlGF, maternal age, black race, or history of PE or diabetes mellitus between the COVID-19 group and the general population (Table 1).

Comparison between mild and severe forms of COVID-19

In the COVID-19 group, 160 (69.3%) women developed mild COVID-19 and 71 (30.7%) women developed severe COVID-19. Of the 160 women with mild COVID-19, 25 (15.6%) were at a high risk for PE in the first-trimester screening. Likewise, of the 71 women with severe COVID-19, 19 (26.8%) were also at a high risk for PE in the first-trimester screening. Nevertheless, this difference was not statistically significant ($p=0.071$). In women with severe COVID-19 MAP in the first trimester was higher, as well as BMI. No other significant differences were found in other markers or risk factors for PE between the groups with mild and severe forms of COVID-19 (Table 2).

DISCUSSION

Main findings

This study shows a higher prevalence of risk factors for PE during the first trimester in women with COVID-19 as compared with the reference population. In the COVID-19 group the proportion of high BMI and chronic hypertension was higher, whereas the proportion of smokers was lower, which are also risk factors for developing PE. Regarding biochemical and biophysical markers, no differences were found in PlGF levels.

However, in the COVID-19 group there was a slight increase, although statistically significant, in UtAPI (1.08 MoM versus 1.00 MoM).

When we examined the COVID-19 group according to severity (mild or severe), no differences were observed in PlGF and UtAPI. However, women with severe COVID-19 had significantly higher BMI and MAP at the first-trimester screening.

The findings of this study support the hypothesis that women with COVID-19 are at a higher risk for PE than the general population; however, it seems that this was due mainly to shared maternal risk factors (obesity and hypertension), as there was no significant difference in PlGF levels, and the small difference in UtAPI is probably not correlated with abnormal trophoblastic invasion, as first-trimester multiple of the median (MoM) UtAPI values in our population ranges from 1.12 to 1.67 in women that subsequently develop PE, whereas MoM UtAPI values are 1.03 in women without PE[14].

Strengths and limitations

The present study provides novel evidence that women with COVID-19 are at a higher risk for PE at the first trimester mainly due to maternal risk factors, which are shared by both conditions. In addition, there does not seem to be an association between COVID-19 and risk factors for placental insufficiency. One of the main strengths of this study is the large number of subjects. Additionally, the first-trimester screening for PE was routinely performed; therefore, despite this being a retrospective study, maternal risk factors, PlGF and UtAPI were prospectively recorded for all patients at the time of the routine first-trimester scan.

One of the main limitations of this study is its retrospective nature. Additionally, this study may have a selection bias. On the one hand, cases in the study group with severe disease might be over-represented, as our site was a referral hospital for severe COVID-19 with pneumonia in Catalonia. On the other hand, asymptomatic cases in the study cohort might also be over-represented, since a RT-PCR was incorporated during the pandemic as a routine test for all admitted patients.

Another limitation of the study is that the general population used as the reference group cannot be considered purely a control group due to the lack of specific information about SARS-CoV-2 infection. For this reason, some asymptomatic and mild COVID-19 cases might be found in the reference group. Nevertheless, this might have reduced the chances of finding differences between groups making our findings even more meaningful.

Interpretation

The association between PE and COVID-19 has been studied since the beginning of the coronavirus pandemic. Some studies have hypothesized that the association between PE and COVID-19 may be explained by the fact that both conditions share common systemic risk factors, such as obesity, advanced maternal age, diabetes, or hypertension, among others[5,9]. However, the potential association between PE and COVID-19 due to specific placental risk factors has never been examined.

Giorgione and Thilaganathan suggested that subclinical cardiovascular dysfunction in general population may induce placental malperfusion and ischemia, thus increasing PE risk. Therefore, subclinical cardiovascular dysfunction due to COVID-19 may lead to acquired utero-placental malperfusion, potentially causing PE. Although we agree that maternal systemic risk factors may explain the association between COVID-19 and PE, we believe that the association between both conditions is unlikely to be due to an abnormal trophoblastic invasion[9]. Therefore, our results might partly support the findings of the INTERCOVID study, which showed that the association between COVID-19 and PE did not not decrease with aspirin treatment[5].

Other studies have demonstrated a clear association between diabetes, increased BMI and the risk of developing COVID-19[15]. Additionally, these studies showed that severe COVID-19 was associated with higher maternal age, higher BMI, hypertension and diabetes[16]. Our results support these findings.

Determining whether the association of PE and COVID-19 is due to shared risk factors or whether it is driven by placental predisposition is crucial to provide appropriate treatment and surveillance. Our data provide

evidence that PE and COVID-19 share systemic risk factors that may account for the association between these two conditions. However, our data suggest that placental insufficiency is unlikely to be involved in the development of COVID-19 or its severity. Given that aspirin's mechanism of action for PE prevention primarily involves the improvement of trophoblastic invasion[10], aspirin treatment is unlikely to be effective for reducing COVID-19 risk in pregnancies at a high risk for PE in the first trimester; nevertheless, more research is needed to ascertain the role of aspirin in pregnant women with COVID-19.

CONCLUSION

In patients with COVID-19, there was a higher proportion of women at a high risk for PE at the first-trimester screening than in the general population, mainly due to maternal risk factors, rather than placental signs of a deficient trophoblastic invasion.

Likewise, when comparing according to COVID-19 severity, the proportion of women with a high risk for PE tended to be greater amongst those with severe forms of COVID-19 and it was due to maternal risk factors only.

ACKNOWLEDGMENTS

We thank Maria del Mar Jimenez Quesada for English language corrections of the manuscript and all the physicians who provided healthcare to pregnant women with COVID-19 during these uncertain times and under unusual circumstances.

One of the authors is a member of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516].

DISCLOSURE OF INTEREST

Manel Mendoza, Lourdes Martin and Itziar Garcia-Ruiz received lecture fees from Roche Diagnostics. The other authors declare that they have no conflicts of interest.

CONTRIBUTION TO AUTHORSHIP

BS, MM and EC had full access to all of the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis. BS, MM and EC conceived and designed the study. BS, MM, PGA, EB, IGR, PGM, NFH, ES, NM and AS contributed to literature research. BS, MM, JG, MA, RMLM, MR, LM, ELQ, AV and AM contributed to data collection and confirmation. BS and MM contributed to data analysis and data interpretation. BS and MM were in charge of writing the manuscript draft. EC made substantial revisions to the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection. *JAMA Pediatr* . 2021;**175** (8):1-10.

2. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* . 2020; **395** (10226):809-815.

3. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* . 2020; **2** (2):100107.

4. Serra B, Mendoza M, Scazzocchio E, Meler E, Nolla M, Sabria E, et al. A new model for screening for early-onset preeclampsia. *Am J Obstet Gynecol* . 2020; **222** (6):608.e1-608.e18.

5. Papageorghiou AT, Deruelle P, Gunier RB, Rauch S, Garcia-May PK, Mhatre M, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. *Am J Obstet Gynecol* . 2021;**225** (3):289.e1-289.e17.

6. Conde-Agudelo A, Romero R. SARS-COV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol* . Published online July 21, 2021.

7. Conde-Agudelo A, Romero R. Mechanisms that may underlie a causal association between SARS-COV-2 infection and preeclampsia. *Am J Obstet Gynecol* . Published online September 14, 2021:S0002-9378(21)01004-8.

8. Khalil A, Samara A, Chowdhury T, O'Brien P. Does COVID-19 cause pre-eclampsia? *Ultrasound Obstet Gynecol* . Published online November 11, 2021.

9. Giorgione V, Thilaganathan B. SARS-COV-2 related myocardial injury might explain the predisposition to preeclampsia with maternal SARS-COV-2 infection. *Am J Obstet Gynecol* . Published online October 5, 2021.

10. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *Am J Obstet Gynecol* . Published online August 21, 2020:S0002-9378(20)30873-5.

11. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* . 1975;**82** (9):702-710.

12. Mendoza M, Tur H, Garcia-Manau P, Hurtado I, Serrano B, Lopez-Martinez RM, Castellote L, et al. Cut-off values for Gaussian first-trimester screening for early-onset preeclampsia with maternal history, biochemical markers and uterine artery Doppler. *J Gynecol Obstet Hum Reprod* . Published online June 5, 2020:101827.

13. R: The R Project for Statistical Computing. Accessed November 9, 2021. https://www.r-project.org/

14. Mendoza M, Garcia-Manau P, Arevalo S, Aviles M, Serrano B, Sanchez-Duran MA, Garcia-Ruiz I, Bonacina E, Carreras E. Diagnostic accuracy of first-trimester combined screening for early-onset and preterm preeclampsia at 8-10 weeks compared to 11-13 weeks gestation. *Ultrasound in Obstetrics & Gynecology* . n/a(n/a).

15. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, Solomon SD. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. *JAMA Internal Medicine* . 2021; **181** (5):714-717.

16. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* . 2020;**370** :m3320.

Table 1. Comparison of preeclampsia risk factors between the COVID-19 group and the general population

	COVID-19 N=231	**General population N=13,033**	**p**
High risk of preeclampsia	44 (19.0%)	11,719 (13.2%)	0.012
Mean arterial pressure (MoM)	1.09 (1.01-1.18)	1.09 (1.01-1.17)	0.906
Uterine artery PI (MoM)	1.08 (0.88-1.31)	1.00 (0.82-1.20)	<0.001
PLGF (MoM)	0.96 (0.77-1.89)	0.97 (0.77-1.20)	0.760
BMI (kg/m^2)	25.2 (22.2-29.4)	24.5 (21.8-28.3)	0.041

	COVID-19 N=231	**General population N=13,033**	**p**
Maternal age (y)	31.8 (26.8-36.2)	32.6 (28.2-36.4)	0.065
Black race	7/230 (3.0%)	402 (3.1%)	1
Chronic hypertension	6/218 (2.8%)	104/11698 (0.9%)	0.015
History of preeclampsia	9/218 (4.1%)	261/11917 (2.2%)	0.100
Smoking	13/229 (5.7%)	1494/12847 (11.6%)	0.007
Nulliparous	66/219 (30.1%)	4249/11664 (36.4%)	0.065
Assisted reproduction technique	8/231 (3.5%)	303/13033 (2.3%)	0.361
Diabetes mellitus	2/228 (0.9%)	158/12552 (1.3%)	1.0

Continuous variables are shown as the median and interquartile range (1st and 3rd quartiles). Categorical data are shown as absolute frequency and percentage.

PLGF = Placental growth factor; MoM = multiples of the median; PI = pulsatility index; BMI = body mass index

Table 2. Comparison of preeclampsia risk factors between mild and severe forms of COVID-19

	Mild N=160	**Severe N=71**	**p**
High risk of preeclampsia	25 (15.6%)	19 (26.8%)	0.071
Mean arterial pressure (MoM)	1.08 (1.00-1.16)	1.12 (1.05-1.22)	0.008
Uterine artery PI (MoM)	1.07 (0.85-1.33)	1.09 (0.94-1.26)	0.756
PLGF (MoM)	0.97 (0.77-1.22)	0.96 (0.77-1.11)	0.862
BMI (kg/m^2)	23.7 (21.7-27.6)	28.2 (24.6-30.8)	<0.001
Maternal age (y)	31.3 (26.3-36.0)	34.1 (28.0-37.9)	0.069
Black race	5 (3.1%)	2 (2.9%)	1.0
Chronic hypertension	3 (2.0%)	3 (4.6%)	0.366
History of preeclampsia	7 (4.6%)	2 (3.1%)	1.0
Smoking	12 (7.6%)	1 (1.4%)	0.069
Nulliparous	49 (31.8%)	17 (26.2%)	0.426
Assisted reproduction technique	5 (3.1%)	3 (4.2%)	0.704
Diabetes mellitus	1 (0.6%)	1 (1.4%)	0.521

Continuous variables are shown as median and interquartile range (1st and 3rd quartiles). Categorical data are shown as absolute frequency and percentage.

PLGF = Placental growth factor; MoM = multiples of the median; PI = pulsatility index; BMI = body mass index