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Comorbidities, poverty and social vulnerability as risk factors for mortality in pregnant women with confirmed SARS-CoV-2 infection: analysis of 13 062 positive pregnancies including 176 maternal deaths in Mexico

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Contribution

What are the novel findings of this work?

This is the largest cohort to date on COVID-19 in pregnancy that demonstrates that advanced maternal age, diabetes, hypertension, obesity, very high social vulnerability, and low socioeconomic status are risk factors of COVID-19-related mortality.

What are the clinical implications of this work?

The findings in this article will help identify high-risk women for the prevention of acquiring SARS-CoV-2 through mask-wearing, social distancing, good hand hygiene and preferably vaccination, as well as raising awareness of the possibility of selective vaccination for developing countries where vaccines and resources are scarce.

ABSTRACT

Background. Mortality due to COVID-19 in pregnancy in developing countries is critical. The identification of clinical and socio-demographic risk factors related to mortality in pregnant individuals could guide public policies to prioritize vulnerable individuals for vaccination. We aimed to evaluate the association between comorbidities and social determinants to mortality and severe COVID-19 disease in pregnant individuals.

Methods. This is an ongoing nationwide prospective cohort study, that includes all pregnant women with positive RT-qPCR from the Mexican National Registry of Coronavirus. The primary outcome was death by COVID-19. Secondary outcomes were pneumonia, intubation, and intensive care unit (ICU) admission. The association between comorbidities and sociodemographic characteristics with each adverse outcome was explored by a log-binomial regression model adjusted by possible confounders.

Results. There were 176 (1.35%) maternal deaths among 13,062 consecutive SARS-CoV-2 positive pregnant individuals. Age as a continuous (aRR [adjusted relative risk]: 1.08; 1.05-1.10) or categorical variable was associated with maternal death. Pregnant individuals of 35- 39 years (RR: 3.16; 2.34-4.26) and 40 years and older (RR: 4.07; 2.65-6.25) had higher risk for mortality. Other risk factors associated with maternal mortality were pre-existing diabetes (aRR: 2.66; 1.65-4.27), chronic hypertension (aRR: 1.75; 1.02-3.00), and obesity (aRR: 2.15; 1.46-3.17). Very high social vulnerability had higher risk of mortality (aRR: 1.89; 1.27-2.84), while very low social vulnerability had a lower risk of death (aRR: 0.48; 0.31-0.74). Being poor and extremely poor were also risk factors for maternal mortality (aRR: 1.53; 1.09-2.15, and aRR: 1.83; 1.32-2.53, respectively).

Conclusions. Our study, which is the largest prospective consecutive cohort to date, has confirmed that advanced maternal age, diabetes, hypertension, obesity, very high social vulnerability, and low socioeconomic status are risk factors of COVID-19-related mortality

INTRODUCTION

In Mexico, COVID-19 is the leading cause of maternal death, overtaking obstetric hemorrhage, and preeclampsia. There are several reasons that could explain the higher mortality among pregnant individuals affected by COVID-19. First, current studies have demonstrated that pregnancy is an independent risk factor for adverse outcomes associated with COVID-19. Studies conducted in developing countries, such as Mexico, have demonstrated that pregnant individuals have higher odds of pneumonia (odds ratio [OR] 1.99; 95% confidence interval [CI] 1.81-2.19), intensive care unit (ICU) admission (OR 2.25; 95% CI 1.86-2.71) and death (OR 1.65; 95% CI 1.30-2.09), when compared to non-pregnant individuals of the same age. ² Similar findings have been demonstrated in developed countries, such as the United States of America (USA), where Hispanic/Latina pregnant individuals have experienced an 2.4-times higher risk of death compared to other ethnic groups.³ Second, in the context of any pandemic, there is a strong influence of ethnicity and socio-economic status on health-related outcomes among infectious diseases. 4, 5 The higher mortality among Latin American pregnant individuals raises the questions on why this particular population is more susceptible to developing adverse outcomes associated with COVID-19, and what the clinical and socio-economic risk factors are.⁶ It is then, of major importance, to unveil all possible prognostic factors associated with COVID-19-related mortality, especially those related to socio-economic inequalities, as the identification of these risk factors could help guide the development of heath policies to protect the vulnerable groups, which are not only defined by clinical and demographic criteria, but also by socio-economic indices such as the poverty-vulnerability index.

The objective of this study was to evaluate the association between clinical characteristics and social determinants with COVID-19-related mortality and severe morbidity among pregnant individuals.

METHODS

Study design and participants

This study analyzed data from the Mexican National Registry of Coronavirus⁷, an ongoing prospective cohort based on information from the Mexican government, which is updated weekly with data from 475 monitoring hospitals located across the 32 states of Mexico. Inclusion criteria were all pregnant women with positive RT-qPCR in the Mexican National Registry of Coronavirus between April 1st, 2020 to July 31st, 2021. The study protocol was approved by the General Hospital of Mexico "Dr. Eduardo Liceaga" under the ethics committee number: (CE/23020).

Data collection

Data on patients' medical history were collected and transferred from the Mexican National Registry of Coronavirus. Access to the Mexican National Registry is only available at each hospital by Institutional approval. The following data were collected for each patient: age; pregestational diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, immunosuppression, chronic hypertension, cardiovascular disease, obesity (defined as a body mass index equal or greater than 30), chronic renal disease, or other non-specified morbidities; smoking habit; the presence of pneumonia; ICU admission and maternal death. To avoid bias because of missing data, we retrieved and analyzed data from the last update of the Mexican National Registry of Coronavirus, which contains complete information on the outcomes at each update. Outcomes such as pneumonia and ICU admission have missing data on the outcome, therefore, for the calculation of those outcomes we only used complete data outcome analyses. Social determinants included: ethnicity (including the proportions of individuals who are indigenous), access to private health services, social security for public health services, social lag indices or vulnerability indices and poverty for states. Social determinants were calculated by postal code for every participant, information of postal codes, town, state, and country, is part of the COVID-19 National Database.

Outcomes

The primary outcome was death as a direct result of COVID-19, and COVID-19 was defined as any symptomatic patient with a positive RT-PCR for SARS-CoV-2.

Secondary outcomes were severe pneumonia, ICU admission, and intubation. Severe pneumonia due to COVID-19 was defined according to the American Thoracic Society Criteria, which includes either one major criteria (septic shock with need for vasopressors, or respiratory failure requiring mechanical ventilation) or three or more minor criteria (respiratory rate ≥30 breaths/min; PaO₂/FIO₂ ratio ≤250; multilobar infiltrates; confusion/disorientation; uremia [blood urea nitrogen level ≥20 mg/dl]; leukopenia [white blood cell count <4,000 cells/μl]; thrombocytopenia [platelet count <100,000/ μl]; hypothermia [core temperature <36°C]; hypotension requiring aggressive fluid resuscitation)^{8, 9}; ICU admission was decided according to the Quick Sequential Organ Failure Assessment (qSOFA) score, where a score ≥2 points would require ICU admission¹⁰; viral sepsis was defined according to the Sepsis-3 International Consensus¹¹ associated with SARS-CoV-2 infection¹².

Social vulnerability index

The vulnerability index or social delay index allows ranking of the states of Mexico from the highest to the lowest degree of social delay at a given moment in time. Using the Dalenius-Hodges stratification method, the vulnerability index in Mexico may be divided into five categories: very high vulnerability, high vulnerability, medium vulnerability, low vulnerability, and very low vulnerability. Methods for calculating this index is available at the following: http://www.coneval.org.mx/Medicion/IRS/Paginas/Anex-Metodologico-del-Indice-de-Rezago-Social.aspx. The vulnerability index measures the household living conditions that include four main aspects of social deprivation: education, access to health care services, basic infrastructure, quality and space in housing, and household assets. It provides a summary of four social deficiencies monitored by the National Council for Evaluation of Social Development Policy

(National Council for the Evaluation of Social Development Policy¹⁴): educational lag, access to health services, access to essential services in housing, and quality and space in housing.¹⁴

Poverty in Mexican states

The poverty measurement is based on the CONEVAL methodology¹⁵. It considers the current per capita income, average educational lag in a household, access to health care services, access to social security services, quality and space in housing, access to quality and nutritious food, degree of social cohesion, and degree of accessibility to a paved road. The poverty indices in Mexico are divided into two categories: poverty and extreme poverty. The 2018 poverty report and its methodology were published on July 31st, 2019 (MCS-ENIGH 2018 report) (https://www.coneval.org.mx/InformesPublicaciones/InformesPublicaciones/Documents/Metodol ogia-medicion-multidimensional-3er-edicion.pdf).¹⁶

Statistical methods

Descriptive and inferential statistics were used. Quantitative variables were reported as the mean and standard deviation (SD); categorical variables were summarized as percentages.

A univariate and multivariate log-binomial regression was performed to establish the association between several risk factors and the primary and secondary outcomes. The treatment effect used for this analysis was relative risk (RR) as an univariate analysis and adjusted relative risk (aRR) when statistically significant variables were found in the univariate analysis such as age, diabetes, obesity, hypertension, renal chronic disease-asthma, and ethnicity. A secondary analysis was made to evaluate the association between social vulnerability index and poverty with maternal death as the primary outcome. For this analysis, social vulnerability index was divided into the following categories: very high vulnerability, high vulnerability, medium vulnerability, low vulnerability, and very low vulnerability, while poverty was divided into poverty and extreme poverty according to the previously mentioned methodology.¹⁵

The statistical analysis was performed using Stata v16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). A p-value <0.05 was considered statistically significant.

Role of the funding source

There was no funding for this study.

RESULTS

Description of the cohort and characteristics of the study population

A total of 13,062 consecutive SARS-CoV-2 positive pregnant individuals were included in the analysis. The mean age at diagnosis was 28.3 (SD 6.00) years old. One hundred and seventy-six (1.35%) pregnant individuals died as a direct result of COVID-19, 1,191 (9.12%) were diagnosed with pneumonia, 322 (2.46%) were admitted to ICU, and 185 (1.42%) were intubated. In the univariate analysis (**Table 1**), pregnant individuals who died were older and had more comorbidities, such as pre-existing diabetes, chronic hypertension, obesity, chronic renal disease, and asthma than those who did not die. In addition, death was significantly more common in the very high vulnerability, high vulnerability, poor, and extremely poor groups, but death was less frequent in the very low vulnerability group.

Risk factors for maternal death

Risk factors associated with maternal death are shown in **Table 2**. Age as a continuous (aRR: 1.08; 1.05-1.10) or categorical variable was associated with maternal death. Pregnant individuals of 35-39 years (RR: 3.16; 2.34-4.26) and 40 years and older (RR: 4.07; 2.65-6.25) had higher risk for mortality. Other risk factors associated with maternal mortality were pre-existing diabetes, chronic hypertension, and obesity. Chronic renal disease and asthma were not significant after in the multivariate analysis.

Social determinants for maternal mortality

Pregnant individuals with a very high vulnerability index have an 88% increased risk (aRR: 1.88; 1.26-2.80) of death due to COVID-19, women with high vulnerability also had higher risk of dying (aRR: 1.49; 1.04-2.13), while women with very low vulnerability index had 53% decreased risk of death (aRR: 0.47; 0.30-0.73). Being poor (aRR: 1.53; 1.09-2.15) and extremely poor (aRR: 1.83; 1.32-2.53) were also significant risk factors for death.

Clinical risk factors for pneumonia, intensive care unit admission, and intubation

Risk factors associated with pneumonia were maternal age as either a continuous or categorical variable, pre-existing diabetes, chronic hypertension, immunosuppression, and obesity. Age and immunosuppression were risk factor for ICU admission and intubation.

Social determinants for pneumonia, intensive care unit admission, and intubation

Pregnant individuals with very high, high, and low vulnerability indices had higher risk of pneumonia (aRR: 3.00; 2.43-3.69, and 2.62; 2.17-3.18, respectively) which reflects that overall, the risk of pneumonia does not change across vulnerability groups. Poor and extremely poor pregnant individuals had higher risk for pneumonia (aRR: 1.66; 1.46-1.88, and 1.63; 1.44-1.84). Women with low vulnerability had higher risk of ICU admission and intubation, while high vulnerability also had higher risk of intubation. The relationship between social determinants and comorbidities is found in supplemental table 1.

DISCUSSION

Main findings

This study has demonstrated that (i) increasing maternal age, obesity, pre-existing diabetes, chronic hypertension and obesity are associated with COVID-19-related maternal mortality; (ii) Similar to maternal death, risk factors associated with pneumonia were maternal age as either a continuous categorical variable. pre-existing diabetes. chronic hypertension. immunosuppression, and obesity. Age and immunosuppression were also a risk factor for ICU admission and intubation, while women admitted to the public social security health services had lower risk of being admitted to ICU; and (iii) pregnant individuals with a very high vulnerability index have higher risk of death, while low vulnerability index have reduced risk for maternal death but higher risk for pneumonia pneumonia. Similarly, being poor and extremely poor are significant risk factors for maternal death and pneumonia.

Comparison with existing literature

Recent findings have demonstrated that pregnancy per se constitutes a risk factor of complications in women with SARS-CoV-2 infection during the reproductive period¹⁷. Our findings are in agreement with previous studies involving non-pregnant and pregnant individuals demonstrating that advanced age, diabetes, chronic hypertension, and obesity are risk factors for severe COVID-19 and mortality^{2, 3, 18}. Zambrano et al showed that Latin-American pregnant individuals living in the US, who belong to a vulnerable minority group, are at a higher risk of COVID-19-related mortality³, and therefore in our study we have explored the interplay between comorbidities and social determinants contributing to severe COVID-19 and maternal mortality. Although there is no clear explanation on the possible mechanisms of higher maternal mortality related to COVID-19 in developing countries, some investigators have demonstrated that low socioeconomic status is associated with higher risk of severe maternal morbidity.^{17, 19} Previous studies have shown that minority women disproportionately receive delayed or inadequate prenatal care ²⁰ and a systematic review has identified strong evidence for the impact of race and

ethnicity, insurance and education on maternal mortality and severe morbidity.²¹ Measures of socioeconomic disadvantage as represented by vulnerability and poverty indices are also associated with an increased risk of complications associated with SARS-CoV-2 infection ^{22, 23}. Significant association between higher risk of ICU admission and intubation with low social vulnerability index may be related to that of the socioeconomic status and access to health care, since very high and high vulnerable women may not have access to healthcare and therefore their probability of being admitted to ICU or intubated is lower due to lack of adequate healthcare, on the contrary, women with low vulnerability which in definition have better access to healthcare have higher risk of ICU admission and intubation and at the same time lower risk of death. During the pandemic this is what happened in real life, public hospitals were overcrowded while people who were able to pay a private hospital had almost a secure bed in ICU. Another explanation for the higher risk of intubation and ICU admission in women with low vulnerability could be the higher incidence of chronic hypertension, on the other hand, despite the higher incidence of obesity in the very high vulnerability group, multiple logistic regression analysis showed that very high, high vulnerability as well as obesity are independent predictors of mortality. Our findings that a lower socioeconomic status being associated with higher incidence of SARS-CoV-2 pneumonia and maternal deaths support existing evidence that densely populated communities living in poverty have increased risk of sustained community transmission of various infectious diseases, including SARS-CoV-2.^{24, 25} On the other hand, pregnant individuals with a very low vulnerability index have reduced risk of mortality. Overall, our findings suggest a possible causal relationship between education, access to health services, basic infrastructure, quality and space in housing and household assets with mortality in pregnant individuals with SARS-CoV-2 infection, which could explain why maternal mortality is higher in developing countries and in minority groups with limited access to health services in developed countries.

Regarding maternal mortality, maternal mortality in symptomatic pregnant women with COVID-19 in Mexico is 1.35%. A recent small cohort of 793 patients from Greece, Turkey, United Kingdom, and Austria, showed a similar 1.30% incidence of death which is similar to our cohort²⁶. However, Zambrano et al³, described a 0.14% mortality in symptomatic pregnant women with SARS-CoV-2 infection, which differs greatly from our findings. We speculate that the excess mortality comes from all these factors we are currently exploring which are related to lower socioeconomic status, access to healthcare services, housing, education, and household assets. As shown in our analysis, women with very low vulnerability have a 53% reduction in the risk of mortality and women with very high and high vulnerability have higher risk which makes us think of a possible causal relationship between vulnerability (education, housing, household assets, healthcare services), and mortality. This same situation could happen in the world, in which developed countries have lower risk of mortality compared to developing countries, and inside developing countries, vulnerable groups with higher vulnerability and poverty are at higher risk of death.

Strengths and limitations

This is the first study that has reported results based on one of the largest consecutive cohorts of pregnant individuals with SARS-CoV-2 infection, demonstrating that comorbidities, including diabetes, chronic hypertension, obesity, and social determinants such as poverty and vulnerability indices, are significant risk factors for COVID-19-related mortality and morbidity during pregnancy. The advantage of a population-based cohort is that it minimizes bias by allowing calculation of real-population estimates in an unselected population. Cohort studies with low numbers or overselected population tend to overestimate effect sizes. Our large data including 176 maternal deaths allow us to estimate the effect size of each risk factor with a robust confidence interval thus reducing bias. No other single consecutive cohort has this large number of maternal deaths with sufficient data to calculate robust effect sizes. Another strength is the prospective acquisition of data across the whole country, allowing representative data from a desired population, which is often a limitation from hospital-based cohorts. A limitation of this study is the amount of missing data on pneumonia and ICU admission, which is compensated by the large number of included

participants that has allowed us to calculate robust effect sizes. Another limitation is the population-based origin of the information used for analysis, which does not contain data on other perinatal outcomes such as fetal growth restriction, preeclampsia, preterm birth, stillbirth, or neonatal death. However, data contained in our study have sufficient details to allow us to understand the most important risk factors and social determinants related to the main outcomes related to COVID-19, which are death, pneumonia, intubation, and ICU admission.

Clinical implications

COVID-19 is now the leading cause of maternal mortality in Mexico, and most countries have not characterized which pregnant women are at the highest risk of severe complications of COVID-19. Vaccination against SARS-CoV-2 infection has not been prioritized for pregnant women in most countries, especially in developing countries where the increasing maternal mortality rate related to COVID-19 is alarming. To worsen the situation, there is unequal distribution of the available vaccines, which makes it even more difficult for pregnant individuals to get vaccinated in a timely manner. The results from this study could help guide decision making regarding who should be prioritized for vaccination based on their high-risk status in countries where vaccines are not fully available, especially in developing countries where vaccines and resources are scarce. For example, according to our mortality rate of 1.35% and taking into account a 90% to 100% vaccine efficacy against severe COVID-19 for normal SARS-CoV-2 variants and a 96% efficacy for the Delta variant, we would need to vaccine 77 pregnant individuals to avoid 1 death in a 100% effectiveness scenario, 81 in case of 90% effectiveness, and 78 for a 96% effectiveness against the Delta variant. There is a critical need to identify high risk women for the prevention of acquiring SARS-CoV-2 through mask wearing, social distancing, good hand hygiene and preferably vaccination, as well as raising awareness of the possibility of severe COVID-19 so that for those who are infected with SARS-CoV-2, if they are asymptomatic or with mild disease then they need to be monitored for clinical deterioration; if they are symptomatic then there should be more proactive management to reduce the risk of deterioration.

CONCLUSION

Our study, which is one of the largest prospective consecutive cohorts to date, has confirmed that advanced maternal age, diabetes, hypertension, obesity, very high social vulnerability, and low socioeconomic status are risk factors of COVID-19-related mortality. Pregnant women at risk of serious complications of COVID-19 should be identified and prioritized for vaccination and early healthcare, especially in low resource settings.

AVAILABILITY STATEMENT

Data derived from public domain resources

The authors declare no conflict of interests

This manuscript has been selected for TOP ABSTRACT at the 2021 ISUOG World Congress

- 1. Exceso de Mortalidad en México. http://www.dgis.salud.gob.mx/contenidos/basesdedatos/da exceso mortalidad mexico gobmx. http://www.dgis.salud.gob.mx/contenidos/basesdedatos/da exceso mortalidad mexico gobmx.
- 2. Martinez-Portilla R SA, Chatzakis C, Torres-Torres J, Espino y Sosa S, Sandoval-Mandujano K, Castro-Bernabe D, Medina-Jimenez V, Monarrez-Martin J, Figueras F, Poon L. Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia: propensity score matched analysis of a nationwide prospective cohort (COV19Mx). . *Ultrasound Obstet Gynecol* 2021; **57**: 224-231. DOI http://dx.doi.org/10.1002/uog.23575.
- 3. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, Woodworth KR, Nahabedian JF, 3rd, Azziz-Baumgartner E, Gilboa SM, Meaney-Delman D, Pregnancy CC-R and Infant Linked Outcomes T. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1641-1647. DOI 10.15585/mmwr.mm6944e3.
- 4. Khunti K SA, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? . *BMJ* 2020. DOI http://dx.doi.org/10.1136/bmj.m1548.
- 5. Niedzwiedz CL, O'Donnell CA, Jani BD, Demou E, Ho FK, Celis-Morales C, Nicholl BI, Mair FS, Welsh P, Sattar N, Pell JP and Katikireddi SV. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. *BMC Med* 2020; **18**: 160. DOI 10.1186/s12916-020-01640-8.
- 6. Takemoto M MM, Andreucci C, Nakamura-Pereira M, Amorim M, Katz L, Knobel R. The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. *Int J Gynaecol Obstet* 2020; **151**: 154-156. DOI http://dx.doi.org/10.1002/ijgo.13300.
- 7. . http://www.gob.mx/salud/documentos/datos-abiertos-152127.
- 8. Lean SC, Derricott H, Jones RL and Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. *PLoS One* 2017; **12**: e0186287. DOI 10.1371/journal.pone.0186287.
- 9. Pinheiro RL, Areia AL, Mota Pinto A and Donato H. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. *Acta Med Port* 2019; **32**: 219-226. DOI 10.20344/amp.11057.
- 10. Bianchi DW, Kaeser L and Cernich AN. Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines. *JAMA* 2021; **325**: 1041-1042. DOI 10.1001/jama.2021.1865.
- 11. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Baez AM, Shook LL, Cvrk D, James K, De Guzman RM, Brigida S, Diouf K, Goldfarb I, Bebell LM, Yonker LM, Fasano A, Rabi SA, Elovitz MA, Alter G and Edlow AG. COVID-19 vaccine response in pregnant and lactating women: a cohort study. *medRxiv* 2021. DOI 10.1101/2021.03.07.21253094.
- 12. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T and Group CS. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**: 403-416. DOI 10.1056/NEJMoa2035389.
- 13. Indice de Rezago Social https://www.coneval.org.mx/Medicion/IRS/Paginas/Anexo-Metodologico-del-Indice-de-Rezago-Social.aspx.
- 14. Pobreza en México. https://www.coneval.org.mx/Medicion.
- 15. Social CNdEdlPdD. *Metodología para la medición multidimensional de la pobreza en México* CONEVAL: Ciudad de México, 2019.
- 16. Pobreza en México. https://www.coneval.org.mx/Medicion/MP/Paginas/Pobreza-2018.aspx.

- 17. Friedman AM, Ananth CV, Huang Y, D'Alton ME and Wright JD. Hospital delivery volume, severe obstetrical morbidity, and failure to rescue. *Am J Obstet Gynecol* 2016; **215**: 795 e791-795 e714. DOI 10.1016/j.ajog.2016.07.039.
- 18. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, Sheikh J, Lawson H, Ansari K, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J, Thangaratinam S and for Preg COVLSRC. 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. DOI 10.1136/bmj.m3320.
- 19. Reid LD and Creanga AA. Severe maternal morbidity and related hospital quality measures in Maryland. *J Perinatol* 2018; **38**: 997-1008. DOI 10.1038/s41372-018-0096-9.
- 20. Bryant AS, Worjoloh A, Caughey AB and Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol* 2010; **202**: 335-343. DOI 10.1016/j.ajog.2009.10.864.
- 21. Wang E, Glazer KB, Howell EA and Janevic TM. Social Determinants of Pregnancy-Related Mortality and Morbidity in the United States: A Systematic Review. *Obstet Gynecol* 2020; **135**: 896-915. DOI 10.1097/AOG.0000000000003762.
- 22. Webb Hooper M, Napoles AM and Perez-Stable EJ. COVID-19 and Racial/Ethnic Disparities. *JAMA* 2020; **323**: 2466-2467. DOI 10.1001/jama.2020.8598.
- 23. Gross CP, Essien UR, Pasha S, Gross JR, Wang SY and Nunez-Smith M. Racial and Ethnic Disparities in Population-Level Covid-19 Mortality. *J Gen Intern Med* 2020; **35**: 3097-3099. DOI 10.1007/s11606-020-06081-w.
- 24. Rubin D, Huang J, Fisher BT, Gasparrini A, Tam V, Song L, Wang X, Kaufman J, Fitzpatrick K, Jain A, Griffis H, Crammer K, Morris J and Tasian G. Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of SARS-CoV-2 in Counties Across the United States. *JAMA Netw Open* 2020; **3**: e2016099. DOI 10.1001/jamanetworkopen.2020.16099.
- 25. Bhadra A, Mukherjee A and Sarkar K. Impact of population density on Covid-19 infected and mortality rate in India. *Model Earth Syst Environ* 2020: 1-7. DOI 10.1007/s40808-020-00984-7.
- 26. Kalafat E, Prasad S, Birol P, Tekin AB, Kunt A, Di Fabrizio C, Alatas C, Celik E, Bagci H, Binder J, Le Doare K, Magee LA, Mutlu MA, Yassa M, Tug N, Sahin O, Drokos P, O'Brien P, Dadelszen PV, Palmrich P, Papaioannou G, Ayaz R, Ladhani SN, Kalantaridou S, Mihmanli V and Khalil A. An internally validated prediction model for critical COVID-19 infection and intensive care unit admission in symptomatic pregnant women. *Am J Obstet Gynecol* 2021. DOI 10.1016/j.ajog.2021.09.024.

Table 1. Characteristics of the studied population according to the main outcome

Characteristics	Alive n=12,886	Death n=176	p-value	
Maternal age, mean (SD)	28.3 (6.00)	31.7 (6.63)	<0.001	
<35 years, n (%)	10,699 (83.03)	106 (60.23)		
35-39 years, n (%)	1,745 (13.54)	47 (26.70)	<0.001	
≥40 years, n (%)	442 (3.43)	23 (13.07)		
Pre-existing diabetes, n (%)	391 (3.04)	24 (13.79)	<0.001	
Chronic hypertension, n (%)	345 (2.68)	19 (10.86)	<0.001	
Obesity, n (%)	986 (7.66)	30 (17.14)	<0.001	
Chronic renal disease, n (%)	32 (0.25)	4 (2.30)	<0.001	
Asthma, n (%)	268 (2.08)	8 (4.60)	0.022	
Chronic obstructive pulmonary disease, n (%)	18 (0.14)		0.623	
Immunosuppression, n (%)	93 (0.72)	2 (1.15)	0.511	
Cardiovascular disease, n (%)	50 (0.39)	1 (0.57)	0.696	
Smoking, n (%)	225 (1.75)	3 (1.72)	0.74	
Indigenous, n (%)	330 (2.56)	5 (2.84)	0.815	
Access to private health services, n (%)	295 (2.29)	4 (2.27)	0.988	
Social security, n (%)	5,247 (40.72)	65 (36.93)	0.310	
Vulnerability indices				
Very high, n (%)	1,073 (8.33)	27 (15.34)	0.001	
High, n (%)	2,021 (15.68)	37 (21.02)	0.043	
Medium, n (%)	2,026 (15.72)	20 (11.36)	0.114	
Low, n (%)	4,699 (36.47)	69 (39.20)	0.454	
Very low, n (%)	3,067 (23.80)	23 (13.07)	0.001	
Poor, n (%)	8,455 (65.61)	131 (74.43)	0.014	
Extreme poverty, n (%)	2,229 (17.30)	49 (27.84)	<0.001	

SD: standard deviation; n: number; %: percentage.

Table 2. Risk factors for severe disease among pregnant individuals with COVID-19

	Death (n=176)		Pneumonia (n=1191)		ICU admission (n=322)		Intubation (n=185)	
Risk factor	aRR (95%CI)	p-val	aRR (95%CI)	p-val	aRR (95%CI)	p-val	aRR (95%CI)	p-val
Maternal age	1.08 (1.05-1.10)	<0.001	1.03 (1.02-1.05)	<0.001	1.02 (1.01- 1.04)	0.005	1.06 (1.04- 1.09)	<0.0001
Age 35-39 years	3.16 (2.34-4.26)	<0.001	1.57 (1.39-1.77)	<0.001	1.35 (1.07- 1.69)	0.012	1.98 (1.49- 2.65)	<0.0001
Age ≥40 years	4.07 (2.65-6.25)	<0.001	1.79 (1.44-2.23)	<0.001	1.17 (0.74- 1.84)	0.505	2.26 (1.43- 3.55)	<0.0001
Pre-existing diabetes	2.66 (1.65-4.27)	<0.001	1.35 (1.07-1.69)	0.011	1.08 (0.71- 1.74)	0.707	0.71 (0.37- 1.35)	0.297
Chronic hypertension	1.75 (1.02-3.00)	0.042	1.74 (1.39-2.17)	<0.001	0.99 (0.62- 1.58)	0.973	1.05 (0.58- 1.91)	0.880
Obesity	2.15 (1.46-3.17)	<0.0001	1.35 (1.14-1.59)	<0.001	1.17 (0.85- 1.61)	0.321	1.37 (0.92- 2.04)	0.122
Chronic renal disease	1.59 (0.52-4.79)	0.414	1.86 (0.39-1.85)	0.699	0.57 (0.08- 3.77)	0.556	1.15 (0.17- 7.79)	0.785
Asthma	1.62 (0.74-3.55)	0.228	1.16 (0.82-1.62)	0.400	1.00 (0.52- 1.94)	0.998	1.23 (0.56- 2.71)	0.600
Chronic obstructive pulmonary disease	1		1		1		1	
Immunosuppresi on	1.56 (0.39-6.12)	0.522	1.81 (1.15-2.84)	0.011	2.01 (1.03- 3.94)	0.040	2.57 (1.13- 5.84)	0.024
Cardiovascular disease	1.42 (0.21-9.83)	0.721	0.86 (0.33-2.19)	0.744	1.73 (0.49- 6.13)	0.396	1.62 (0.26- 9.94)	0.599
Smoker	0.93 (0.30-2.89)	0.905	0.94 (0.62-1.44)	0.791	1.08 (0.51- 2.29)	0.842	1.21 (0.47- 3.12)	0.684

Ethnicity Indigenous	0.86 (0.35-2.10)	0.740	1.21 (0.91-1.62)	0.192	0.55 (0.25- 1.22)	0.144	1.25 (0.59- 2.63)	0.559
Using private health services	0.82 (0.30-2.20)	0.695	1.09 (0.78-1.52)	0.608	1.06 (0.62- 1.83)	0.825	0.71 (0.30- 1.69)	0.447
Using public social security health services	0.82 (0.61-1.12)	0.218	1.04 (0.94-1.17)	0.431	0.78 (0.63- 0.96)	0.021	0.91 (0.69- 1.21)	0.525
Social Vulnerabilit	Social Vulnerability Indices							
Very high	1.88 (1.26-2.80)	0.002	3.00 (2.43-3.69)	<0.001	1.29 (0.89- 1.86)	0.165	1.16 (0.70- 1.95)	0.342
High	1.49 (1.04-2.13)	0.028	2.62 (2.17-3.18)	<0.001	0.85 (0.58- 1.26)	0.440	1.11 (0.68- 1.80)	0.041
Medium	0.76 (0.48-1.20)	0.237	1.03 (0.81-1.32)	0.753	0.92 (0.59- 1.42)	0.729	0.98 (0.55- 1.76)	0.188
Low	1.07 (0.79-1.45)	0.653	2.13 (1.79-2.54)	<0.001	1.40 (1.05- 1.86)	0.021	1.40 (0.95- 2.07)	0.003
Very Low	0.47 (0.30-0.73)	0.001	1	1	1	1	1	1
Poverty								
Poor	1.53 (1.09-2.15)	0.014	1.66 (1.46-1.88)	<0.0001	1.17 (0.93- 1.47)	0.185	1.08 (0.79- 1.47)	0.618
Extremely poor	1.83 (1.32-2.53)	<0.0001	1.63 (1.44-1.84)	<0.0001	0.92 (0.71- 1.19)	0.511	1.01 (0.72- 1.42)	0.939

aRR: Log-binomial regression adjusted by the following confounders: age, diabetes, obesity, hypertension, renal chronic disease-asthma, and ethnicity.