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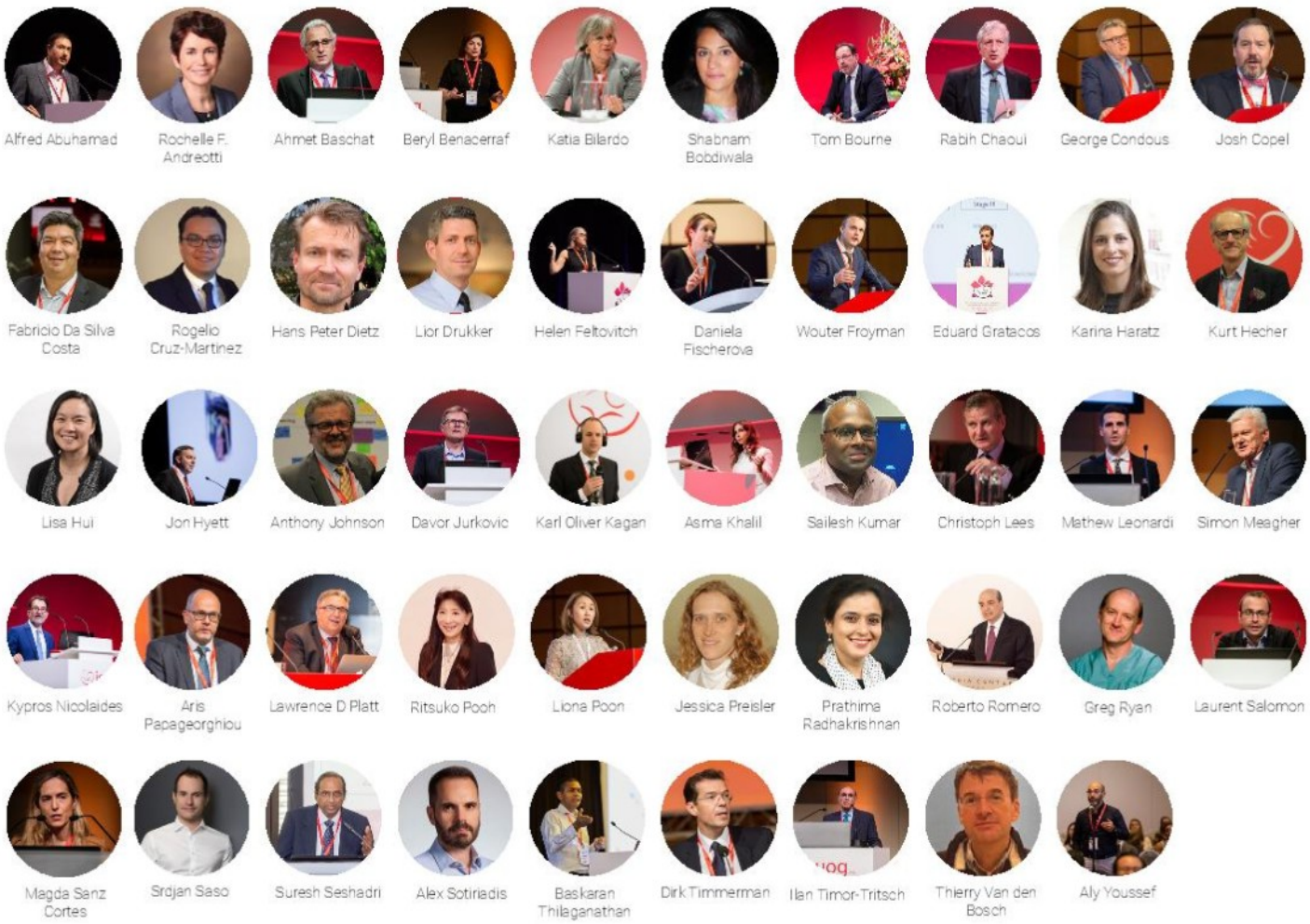

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Pregnant women with SARS-CoV-2 infection are at higher risk of death and severe pneumonia: propensity score-matched analysis of a nationwide prospective cohort study (COV19Mx)

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Contribution

What are the novel findings of this work?

This study provides estimates of COVID-19-related pregnancy complications after Propensity Score Matching. Pregnancy emerges as a risk factor for death (odds ratio [OR] 1·84, 95% CI 1·26–2.69), pneumonia (OR 1·86, 95% CI 1·60–2·16) and ICU admission (OR 1·86, 95% CI 1·41–2·45).

What are the clinical implications of this work?

Our data reveal that pregnancy per se is a risk factor for several COVID-19-related complications when compared to non-pregnant women. Economic, social, health, and political interventions that aim to tackle SARS-CoV-2 infection in pregnant women, are likely to reduce adverse outcomes, such as death, ICU admission and pneumonia.

Abstract

Background

Limited, unmatched data reported low complication rates in pregnant women with COVID-19. This study compared COVID-19-related outcomes in pregnant women versus non-pregnant women after adjusting for potential risk factors for severe outcomes.

Methods

Data were obtained from the COVID-19 National Data Registry of Mexico, which is an ongoing prospective cohort of people of any age with clinically suspected SARS-CoV-2 infection and admitted to 475 monitoring hospitals. This study included pregnant and non-pregnant women of reproductive age (15–49 y) with COVID-19 confirmed by reverse transcription polymerase chain reaction. To adjust for underlying risk factors, propensity score matching was conducted for chronic obstructive pulmonary disease, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes, and age. The primary outcome was death. Secondary outcomes were pneumonia, intubation, and intensive care unit (ICU) admission.

Results

The initial sample comprised of 5183 pregnant and 175,908 non-pregnant COVID-19 patients. The crude (unmatched) rates of death, pneumonia, intubation, and ICU admission in pregnant and non-pregnant women were 1.5% vs. 1.5%, 9.9% vs. 6.5%, 8.1% vs. 9.9%, 13.0% vs. 6.9%, respectively. After propensity score matching (5183 pregnant- and 5183 non-pregnant matched women), pregnant women had higher

odds of death (odds ratio [OR] 1·65, 95% CI 1·30–2.09), pneumonia (OR 1·99, 95% CI 1·81–2·19) and ICU admission (OR 2.25, 95% CI 1·86–2·71) than non-pregnant women, but similar odds of intubation (OR 0·93, 95% CI 0·70–1·25).

Conclusions

After adjusting for background demographic and medical factors, pregnancy is a risk factor for death, intubation and ICU admission in SARS-CoV-2–infected women of reproductive age.

Introduction

Since the first reported case of pneumonia, 2019 novel coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) infection and its clinical disease (coronavirus disease-19 [COVID-19]) have spread rapidly throughout the world, being declared a pandemic by the World Health Organization on March 11, 2020. As of October 14, 2020, more than 38 million infections and 1 million deaths were reported globally by John Hopkins University[1]. With 825,340 infections and more than 84,420 deaths, Mexico had the ninth highest number of confirmed cases and the fourth highest fatality rate (10.23%) among all countries[1].

A major risk factor for adverse outcomes in patients affected by COVID-19 is the presence of comorbidities, including diabetes, hypertension, and obesity [2]. In addition, age and severity of SARS-CoV-2 infection are strongly associated[3], which may be at least partly mediated by a higher prevalence of non-communicable comorbidities with advancing age.

Epidemiologic data from high-prevalence countries reveal that women are 50% less likely to die or require admission to an intensive care unit (ICU), compared with men[4]. Indeed, women of reproductive age between 15 and 49 years of age have a 60% lower likelihood of ICU admission than their age-matched male counterparts[4]. This suggests that pregnant women may not be more susceptible to SARS-CoV-2 infection or its serious complications. However, it is unknown whether higher maternal age or comorbidities confer a higher risk of adverse outcomes in pregnant women with COVID-19[5,6].

In this case-control study based on data from the Mexican National Registry of Coronavirus, we aim to compare COVID-19 outcomes in pregnant women with outcomes in matched non-pregnant women of reproductive age (15–44 years).

Methods

Study design and approval

This study analysed data from the Mexican National Protocol for Suspected COVID-19 (COV19Mx), which is an ongoing prospective cohort based on information from the Mexican National Registry of Coronavirus from February 1st, to October 28th, 2020. The Mexican National Registry of Coronavirus is the government's database for coronavirus, which is updated weekly with data from 475 monitoring hospitals dedicated to COVID-19 and located in all 32 states of Mexico. An approved study protocol was required to obtain information from the COV19Mx registry. The protocol for the current study was approved by the ethics committee of the General Hospital of Mexico "Dr. Eduardo Liceaga", approval number CE/23020. The protocol itself, as well as the non-conflict of interest letter and Ethics' committee aproval, can be found at http://doi.org/10.17605/OSF.IO/QM3FA. The study is reported in accordance with the STROBE Statement[7].

Setting

The 475 COVID-19–dedicated monitoring hospitals are components of the Mexican Public Health Network (MPHN). Hospitals within MPHN are part of the National Mexican Institute of Social Security, Institute of Security and Social Services for State Workers, Secretary of National Defense, Secretary of the Navy of the Mexican Republic, and National Health Department. These monitoring hospitals are the only institutions approved to perform reverse transcription-polymerase chain reaction (rt-PCR) analysis for SARS-CoV-2 in Mexico and are, therefore, the reference centres for all patients with suspected COVID-19. Data for the Cov19Mx cohort (last accessed

October 28, 2020) are fully available at http://datosabiertos.salud.gob.mx/gobmx/salud/datos_abiertos/datos_abiertos_covid19.zip.

Participants

Criteria for inclusion in the Mexican National Registry of Coronavirus were any age and admitted with suspected SARS-CoV-2 infection to any of the 475 monitoring hospitals in Mexico. The decision regarding whether to perform rt-PCR testing was made by the attending clinicians based on the definition of suspected SARS-CoV-2 infection. The definition required the presence of two main symptoms—cough, fever, headache—plus at least one of the following: dyspnoea, arthralgia, myalgia, odynophagia, conjunctivitis, or chest pain[8–10]. All tested patients were entered into the registry before testing, regardless of rt-PCR results, but the analysis was restricted to rt-PCR-positive patients. Clinical information and history were acquired from each patient. The Mexican National Institute of Health does not require informed consent to register patient information.

Outcomes

The primary outcome was death among women of reproductive age (15–45 years) with COVID-19. COVID-19 was defined as any symptomatic patient with a positive rt-PCR for SARS-CoV-2. Secondary outcomes included pneumonia (defined as symptoms and signs of lower respiratory tract infection with no other apparent cause, plus a pulmonary infiltrate on chest radiograph), intubation, or admission to the ICU.

Data sources and measurements

Data on the demographics and medical history of the patients were collected and transferred to the Mexican National Registry of Coronavirus, which is a web-based platform developed by the Mexican National Government and National Institute of Health. Access to this database is only available to each hospital's epidemiologist, who is responsible for uploading the data. The following data were collected for each patient: state and location of enrolment; sex; state and country of birth; spoken language(s); health insurance; date of symptom onset; date and age at hospital admission; pregnancy status at enrolment; history of diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, immunosuppression, chronic hypertension, cardiovascular disease, obesity, chronic kidney disease, or other non-specified morbidities; smoking habits; SARS-CoV-2 rt-PCR results; the presence of pneumonia; and need for intubation or admission to the ICU.

To avoid bias because of missing data, we acquired and analysed data from the last update of the Mexican National Registry of Coronavirus, which contains full information on the main outcomes at each update. Because of the nature of this study and the large quantity of missing data, we opted to describe data as originally uploaded, without imputing missing data. The strength of this approach is that it avoids assumptions regarding missing information. However, imputation is a strategy for avoiding difficulties during data analysis arising from listwise removal of cases with missing outcome values.

Statistical methods

Normally distributed continuous variables were described as mean and standard deviation values, while non-normally distributed values were expressed as median

and interquartile range. Categorical variables were summarised as percentages. T-test or Mann-Whitney U test was used to compare continuous variables between the non-pregnant and pregnant women groups. Chi-square or Fisher's exact test was used for pairwise comparisons of proportions, and odds ratios (ORs) plus their corresponding 95% confidence intervals (CIs) were calculated. For all tests, a p-value <0·05 was considered significant.

We performed propensity score matching to address potential differences between baseline characteristics of pregnant and non-pregnant women and therefore, the possibility of bias because of confounding variables[11]. The propensity score expresses the probability of assignment based on observed baseline covariates[12]. In a set of patients with the same propensity score, the distribution of the baseline covariates will be the same between groups[13]. Thus, by conditioning on the propensity score, the distribution of observed baseline confounding variables should be similar between pregnant and non-pregnant women.

Propensity scoring was conducted using age, language, nationality, health insurance agency, COPD, asthma, smoking, hypertension, cardiovascular disease, diabetes mellitus, obesity, chronic renal disease and immunosuppression as covariates. We performed propensity score-matching using the MatchIt package with nearest-neighbour in R 2·15·1 (The R Foundation for Statistical Computing)[14]. Improved balance of covariates between groups after propensity score-matching was determined by evaluating the reduction in standardised mean differences between unmatched and propensity score-matched samples. Standardised mean differences >0·1 were considered indicative of a substantial imbalance between groups. [12]

Regression models were used on the whole sample to test for independent risk factors for death, pneumonia, intubation, or ICU admission in women with COVID-19. Overlaps of outcomes in the two groups were presented using Euler diagrams (Figure 2). In order to assess for two-way interactions among covariates, we calculated the Variable Inflation Factor (VIF) for each covariate. The estimated VIF of the covariates ranged from 1.005 to 1,115, showing no two-way interactions between covariates.

Public and patient involvement

There was no public and patient involvement at any stage of this study because of the urgent need to obtain national data regarding pregnancy during the ongoing COVID-19 pandemic.

Role of the funding source

No non-departmental funding was received

Results

Participants

A total of 289,331 women of reproductive age were included in the initial cohort. Of these, 7705 (2·7%) were pregnant and 281,626 (97·3%) were non-pregnant. Complete data regarding the outcomes of death and pneumonia were available for all women. After removal of cases with missing data, the total number of women with data regarding intubation and ICU admission was 21,374, of which 1549 were pregnant, and 19,825 were non-pregnant (***Figure 1***).

Descriptive data

Among 7705 symptomatic pregnant women who underwent SARS-CoV-2 rt-PCR testing, 5183 (67·3%) tested positive. The corresponding number for non-pregnant women was 175,908 (62.5%). All further analyses were based on these SARS-CoV-2–positive women. The descriptive data of the two groups are shown in ***Table 1***.

Outcome data in unmatched patients

The crude death rates (in unmatched samples) were 1·5% (77/5183) in pregnant women and 1·5% (2589/175,905) in non-pregnant women with COVID-19 (p=0·935; OR 1·01 95% CI 0·80–1·26). The crude rates of pneumonia were 9·9% (513/5183) in pregnant women and 6·5% (11490/175,905) in non-pregnant women (p<0·001; OR 1·57, 95% CI 1·43–1·72). The crude rates of intubation were 8·1% (96/1182) in pregnant women and 9.9% (1364/13728) in non-pregnant women (p=0·044; OR 0·80, 95% CI 0·64–0·99). The crude rates of ICU admission were 13·0% (154/1182) in pregnant women and 6·9% (941/13728) in non-pregnant women (p<0.001; OR 2·03,

95% CI 1·69–2·44). Overlaps of outcomes for both pregnant and non-pregnant women are shown in ***Figure 2***.

Logistic regression

Potential predictors included age, nationality, indigenous language, health insurance agency, COPD, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes mellitus, and pregnancy status. The ORs for significant predictors are shown in ***Table 2***. Pregnancy, maternal age, diabetes mellitus, indigenous language, obesity, hypertension, immunosuppression, renal chronic disease, smoking, low level health insurance and high-level health insurance were significant independent predictors for death (Nagelkerke R^2=0·150; area under the curve [AUC] 0·810, 95% CI 0·801–0·818) and pneumonia (Nagelkerke R^2=0·069; AUC 0·677, 95% CI 0·672–0·682). In addition, asthma was a significant independent predictor for death. Diabetes mellitus, obesity, hypertension, immunosuppression, low level health insurance and medium level health insurance were significant independent predictors for intubation (Nagelkerke R^2=0·018; AUC 0·591, 95% CI 0·576–0·607), whilst pregnancy, diabetes mellitus, cardiovascular disease , obesity, low level health insurance and high level health insurance were independent significant predictors for ICU admission (Nagelkerke R^2=0·046; AUC 0·652, 95% CI 0·636–0·659).

Outcome data in the propensity score-matched patients

After matching by propensity scoring for background demographic and medical factors, the patient characteristics were balanced between pregnant and non-pregnant women, with absolute standardised mean differences <0·1 (Figures S1 and S2). The matched patients' analysis included data from 5183 pregnant and 5183 non-pregnant women with COVID-19. The mortality rates were 1·5% in pregnant women and 0·8% in non-pregnant women with COVID-19 (OR 1·84, 95% CI 1·30–2·609; p=0·001). Pneumonia rates were 9.9% in pregnant women and 5·6% in non-pregnant women (OR 1·99, 95% CI 1·81–2·19; p<0·001). Intubation rates were 8·1% in pregnant women and 8·6% in non-pregnant women (OR 0·93, 95% CI 0·70–1·25; p=0·65). ICU admission rates were 13·0% in pregnant women and 7·4% in non-pregnant women (OR 2·25, 95% CI 1·86–2·71; p<0·001).

Discussion

Analysing data from the open, prospective COV19Mx cohort, we found that, although the death rates from COVID-19 were similar in unmatched pregnant and non-pregnant patients, after matching for background demographic and medical characteristics, pregnant women had increased odds for death (OR 1.65), pneumonia (OR 1·99) and ICU admission (OR 2.25) compared to non-pregnant women.

Strengths and limitations

The main strengths of this study were (i) its large sample size, (ii) the accessibility of the COV19Mx cohort, which ensures the transparency of the results, and (iii) the adjustments for relevant background demographic and medical factors which may affect COVID-19 severity. Prior to our study, evidence regarding COVID-19 outcomes in pregnant women originated exclusively from small case series[15], and only one study compared ICU admission rates in pregnant and non-pregnant women[16]. In the majority of observational studies regarding COVID-19, covariates were not balanced between groups, leading to biased results[17]. In this large-scale nationwide cohort we accounted for differences in baseline risk factors that could affect the likelihood of a severe COVID-19 course and thereby confound the results. Furthermore, our analysis involved the use of data from an open, public database, which increases its credibility and transparency.

The main limitations of the study were that testing was only performed in symptomatic women and, although data on the primary outcome of death and secondary outcome of pneumonia were available for all 289,331 women in the cohort, data were available for the secondary outcomes of ICU admission and intubation in

only a proportion of patients (n=21,374). However, background data on confounders for COVID-19 severity were available for all 289,331 women and complete data outcome analysis was used for those outcomes.

Interpretation

There has been intense interest in the prognosis of pregnant women affected by COVID-19, as immunomodulation during pregnancy may affect the clinical course of viral infections. As SARS-CoV-2 is a new virus, innate immunity is the first line of defence and may significantly determine the time and viral load that reaches the lungs[18]. SARS-CoV-1 is the human virus with the closest genetic resemblance to SARS-CoV-2. The case fatality rate in the 2003 SARS-CoV-1 outbreak was high in pregnant women[2,19]—higher than that of their non-pregnant counterparts[19]. Although data on COVID-19 are continuously accumulating, the vast majority are derived from small series, and reported rates of serious symptoms and death vary widely. In a high-quality systematic review[15], the rate of maternal mortality was 7/304 (2·3%), with all seven deaths reported in a single case series[20]. Rates of ICU admission, severe pneumonia, and mechanical ventilation in the review were 5·1%, 4·7%, and 1·8%, respectively[15]. Another systematic review and living meta-analysis reported that pregnant women with pre-existing comorbidities such as high maternal age and high body mass index are more likely to experience severe COVID-19, and pregnancy itself was reported as a risk factor for the need of intensive care treatment[21].

Theoretically, pregnant women may be more susceptible to pneumonia because of physiological respiratory changes resulting in potentially increased interstitial fluid within the lungs, coupled with decreased interstitial space secondary to reduced lung

volumes. Limited, unmatched data, indicated that pneumonia tends to be non-severe in approximately 80% of pregnant women with COVID-19[22], and that maternal death is uncommon[15,22,232425]. However, initial commentaries about pregnancy being a protective factor for mortality were very premature without adequate data[26]. The current study is one of the largest-scale investigations showing that, when matched for medical and demographic characteristics, pregnant women with COVID-19 have a higher risk of pneumonia and death than their non-pregnant counterparts. There is no simple explanation for these observations; although, similar phenomena observed with varicella and SARS-Cov-1 were attributed to physiological mechanical and immunological adaptations of pregnancy as predisposing factors. The only previous study comparing ICU admission rates in pregnant and non-pregnant women of reproductive age with COVID-19, reported that these rates were generally unrelated to age in non-pregnant women, but increased with age in pregnant women, from 0% in women aged 25–29 years to 33% in those aged 40–49 years [16]. More recently, another large-scale cohort of 23,434 symptomatic pregnant woman showed that pregnancy indeed has a higher risk for death (adjusted risk ratio [aRR]: 1.7; CI: 1.2-2.4), ICU admission (aRR: 3.0; CI: 2.6-3.4), and invasive ventilation (aRR: 2.4; CI: 1.5-4.0)[24]. A major difference with our cohort is the propensity score-matching analysis, that enabled us to compare pregnant and non-pregnant on similar baseline characteristics to ensure that estimates are adjusted and fairly compared. The information on this manuscript strengthens the message that pregnant women are indeed at higher risk of severe adverse outcomes.

Another multicentre study of 201 patients conducted in France and Belgium conducted a similar analysis using propensity score matching to account for baseline

differences between pregnant and non-pregnant women, showing that pregnant women diagnosed with COVID-19 at 20 weeks or later, have more severe outcomes[27].

Although, female sex has been associated with a better clinical course of COVID-19 [28], and this "protective" effect has been extrapolated to pregnant women, especially in the context of unmatched data[15,22,2325], pregnancy is an independent risk factor for mortality and severe illness in COVID-19.

Generalizability

The main concerns for generalizability arise from the particular conditions and limitations of the Mexican Health System, from which our data are derived. For example, some women may have been intubated in the emergency department or operating room, without being admitted to the ICU, and some may have died in the emergency department or operating room or at home before reaching the hospital. The availability of resources explains some counterintuitive findings, such as the non-overlap of intubations with ICU admissions, as shown in our Euler diagrams. This type of variation is not unique to our situation, as it can be observed in any overwhelmed health system and may even vary locally depending on the temporal balance between demand and availability of resources; it would almost exclusively affect the secondary outcomes of intubation and ICU admission. In favour of our data, we have to acknowledge that the message goes in line with the CDC report from the US data[24] and the multicentre study in France and Belgium[27], all three stating the same observation, that pregnant women are at higher risk of severe complications including death.

Future research

There are still several questions that need to be answered about pregnancy in this pandemic, including vertical transmission[29,30], placental damage and receptors[31], diagnostic tests for severe disease[32,33], risk factors for maternal mortality, neonatal-maternal long-term effects, and, especially, vaccination in pregnancy.. Modifications of clinical practice to ensure the best outcome for healthcare workers and patients[34–37] are also constantly updating, also shaping the wider context of pregnancy care.

Conclusions

After accounting for differences in baseline characteristics for severe COVID-19 between pregnant and non-pregnant women, pregnancy itself emerged as a risk factor for death and pneumonia in SARS-CoV-2–infected women of reproductive age.

Funding

There was no funding for this study

Data sharing

Data is available on reasonable request to the corresponding author

Transparency declaration

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Legends for Figures

Figure 1. Flow diagram of the study population

Figure 2. Euler diagrams illustrating overlap of outcomes in pregnant (A) and non-pregnant (B) women with COVID-19

Figure S1. Histograms before and after propensity score matching.

Figure S2. Jitter plot of the propensity score matching where each circle represents a case's propensity score.

Table 1. Characteristics of women COVID-19 in the two groups

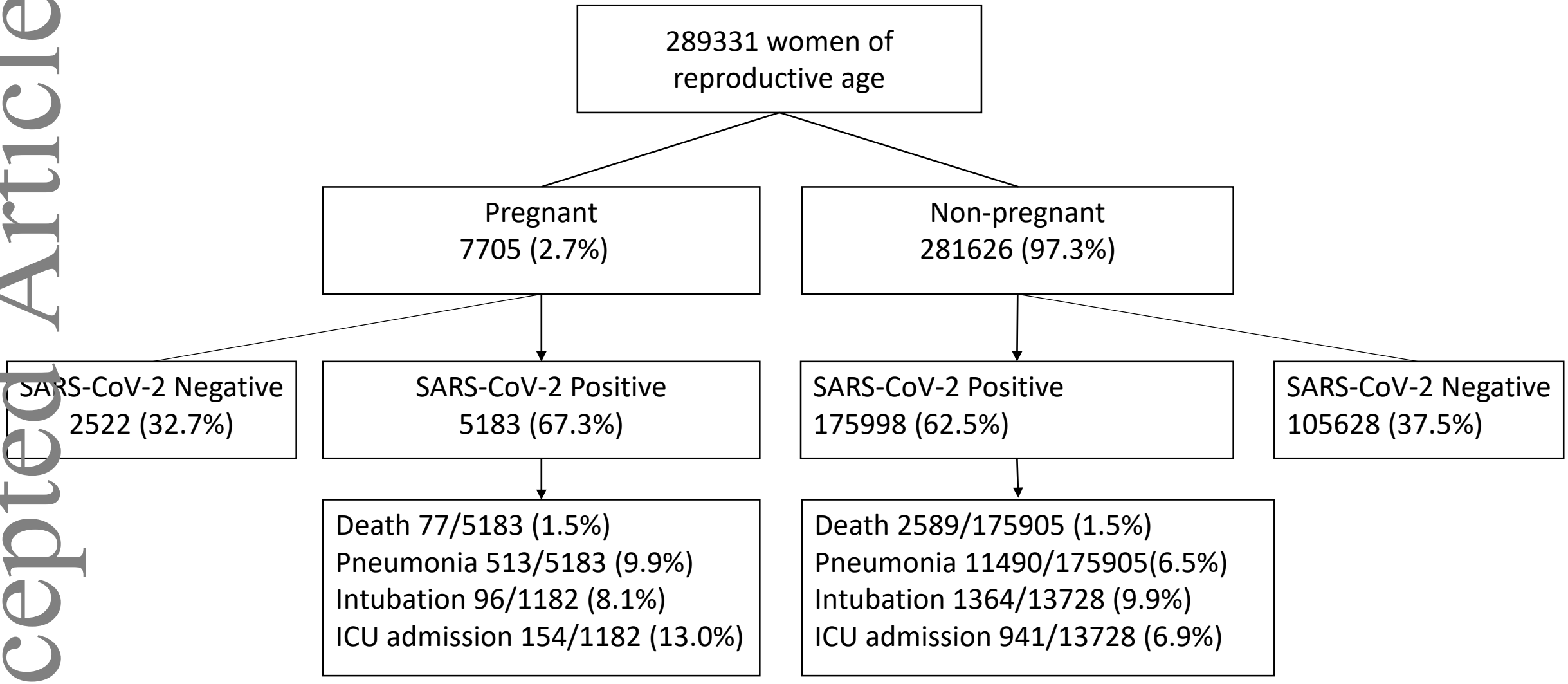
Variable	Pregnant women n=5183	Non pregnant women n=175908	P value
Chronic Obstructive Pulmonary Disease n (%)	10 (0.2)	487 (0.3)	0.255
Asthma n (%)	112 (2.2)	6048 (3.4)	<0.001
Cigarette Smoking, n (%)	91 (1.8)	9644 (5.5)	<0.001
Hypertension, n (%)	150 (2.9)	10518 (6.0)	<0.001
Cardiovascular disease, n (%)	24 (0.5)	1166 (0.7)	0.079
Obesity, n (%)	477 (9.2)	28791 (16.4)	<0.001
Diabetes, n (%)	174 (3.4)	8669 (4.9)	<0.001
Immunosuppression, n (%)	52 (1.0)	1210 (0.7)	0.007
Age, mean (SD)	28.5 (5.9)	33.1 (7.5)	<0.001
Indigenous language, n (%)	100 (2.0)	1138 (0.7)	<0.001
Nationality, n (%)	5155 (99.5)	175281 (99.6)	0.03
Very low-level health insurance	118 (2.3)	1410 (0.8)	<0.001
Low level health insurance	2925 (56.5)	108679(61.8)	<0.001
Medium level health insurance	2002 (38.6)	61523 (35.0)	<0.001
High level health insurance	137 (2.6)	4293 (2.4)	0.352

Quantitative variables are presented in mean and standard deviation. Comparisons between the groups were carried out using student's t- test. Qualitative data are presented in percentages. Chi-square test.

Table 2. Regression coefficients for the primary and secondary outcomes

	Death, adjusted R^2=0.15 (95% CI)	Pneumonia, adjusted R^2=0.07 (95% CI)	Intubation, adjusted R^2=0.01 (95% CI)	ICU admission adjusted R^2=0.04 (95% CI)
Predictors				
Pregnancy	1.654 (1.304 – 2.097)	1.997 (1.814 – 2.199)	NS	2.252 (1.868 – 2.716)
Age	1.068 (1.062 – 1.075)	1.036 (1.034 – 1.039)	NS	NS
Diabetes mellitus	3.501 (3.163 – 3.875)	2.766 (2.603 – 2.939)	1.385 (1.206 – 1.590)	1.205 (1.026 – 1.416)
Indigenous language	1.860 (1.285 – 2.692)	1.646 (1.363 – 1.987)	NS	NS
Cardiovascular disease	NS	NS	NS	1.639 (1.065 – 2.522)
Obesity	1.899 (1.740 – 2.073)	1.538 (1.470 – 1.610)	1.443 (1.282 – 1.624)	1.494 (1.303 – 1.713)
Hypertension	1.951 (1.755 – 2.169)	1.416 (1.328 – 1.510)	1.353 (1.172 – 1.561)	NS
Immunosuppression	2.068 (1.773 – 2.412)	2.068 (1.773 – 2.412)	1.388 (1.025 – 1.879)	NS

Asthma	2.435 (1.927 – 3.096)	NS	NS	NS
Renal chronic disease	7.626 (6.473 – 8.994)	3.870 (3.415 – 4.386)	NS	NS
Smoking	0.591 (0.479 – 0.729)	0.749 (0.683 – 0.822)	NS	NS
Low level health insurance	0.482 (0.4444 – 0.523)	0.696 (0.669 – 0.724)	1.436 (1.008 – 2.045)	6.573 (2.086 – 20.715)
Medium level health insurance	NS	NS	1.679 (1.182 – 2.385)	NS
High level health insurance	0.255 (0.163 – 0.398)	1.560 (1.410 – 1.726)	NS	10.022 (3.077 – 32.642)
NS: Not statistically significant				



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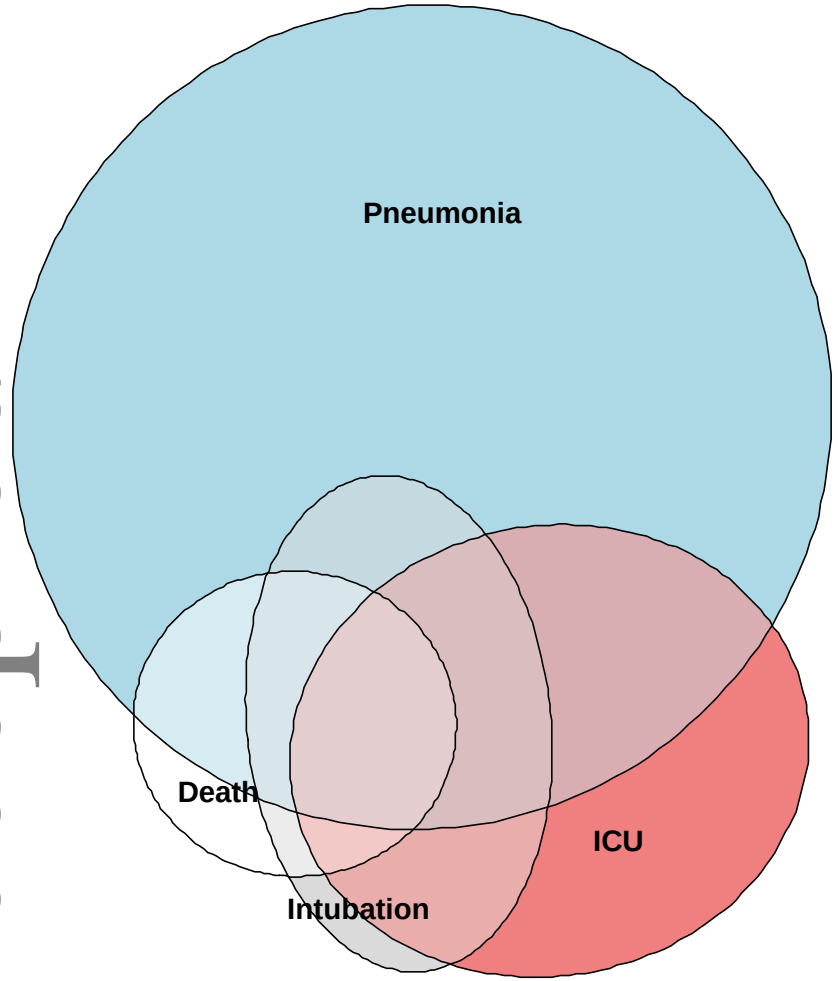

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