Post-COVID-19 condition in pregnant and postpartum women: a long-term follow-up, observational prospective study

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Summary

Background Post-COVID-19 condition has recently been defined as new or persistent common COVID-19 symptoms occurring three months after disease onset. The pathology of the disease is unclear, but immune and vascular factors seem to play a significant role. The incidence, severity, and implications of the disease after COVID-19 infection in pregnancy have not been established. We aimed to study the incidence and main risk factors for post-COVID-19 condition in an obstetric population and their implications for maternal and perinatal morbimortality.

Methods This is a prospective observational cohort study undertaken including women during pregnancy or at admission for labour with acute COVID-19 infection from March 9th, 2020 to June 11th, 2022. The inclusion criteria were confirmed acute COVID-19 infection during the recruitment period, a lack of significant language barrier and consent for follow-up. Patients were clinically followed-up by telephone via semi structured questionnaires. The exclusion criteria were loss to follow-up, spontaneous miscarriage, and legal termination of pregnancy. Patients were classified into groups according to the severity of symptoms at onset. We included patients from the first six first waves of the pandemic according to national epidemiological data in Spain. We studied the incidence of post-COVID-19 condition and their main demographic, clinical and obstetric risk factors.

Findings A total of 409 pregnant women were recruited at acute diagnosis, and 286 were followed-up. The mean time to follow-up was 92 weeks (standard deviation ± 28 weeks; median 100 weeks (Interquartile range: 76; 112)). A total of 140 patients had at least one post-COVID-19 symptom at least three months after acute infection. Neurological (60%) and cutaneous (55%) manifestations were the most frequent findings. The following profiles were identified as presenting a higher risk of post-COVID-19 condition: migrant women born in countries with lower Human Development Index; multiparous women; women with COVID-19 during pregnancy, mainly during the first and third trimesters, and in the first and second waves of the pandemic; women who had a higher number of symptoms; women who had a higher incidence of moderate and severe symptoms; women who required hospitalisation due to COVID-19 complications; and women who were not vaccinated before disease onset. We did not find any significant difference in perinatal results, such as gestational week at delivery, birthweight, the need for neonatal care or 5-min Apgar score, and newborns benefited from a high rate of breastfeeding at

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discharge. Women who were infected during successive waves of the pandemic had a significant and constant decrease in the risk of post-COVID-19 condition comparing to estimated risk in the first wave (OR: 0.70; 95% CI: 0.62, 0.92). Symptoms tended to resolve over time heterogeneously. Symptoms of myalgia and arthralgia took longer to resolve (mean of 60 weeks and 54 weeks, respectively). In a small but significant proportion of patients, neurological and psycho-emotional symptoms tended to become chronic after 90 weeks.

Interpretation At least 34.2% of obstetric patients from our cohort with acute COVID-19 infection presented post-COVID-19 condition symptoms. Demographic and acute disease characteristics as well as specific pregnancy-related risk factors were identified. This is the first study to assess post-COVID-19 condition in pregnant women. Further analysis on the biological pathophysiology of post-COVID-19 is needed to explain the characteristics of the disease.

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Keywords: Post-COVID-19; Long COVID; Pregnancy; Postpartum; Perinatal; COVID-19; Obstetrics

Research in context

Evidence before this study

Post-COVID-19 condition represents a public health concern after the pandemic since the pathology of the disease, possible diagnostic tools, and therapeutic targets are still unclear. In previous meta-analysis, characteristics of acute COVID-19 infection, such as the number of symptoms at onset, severity of the disease and need for hospitalisation, were defined as significant risk factors for the development of post-COVID-19 condition; however, until recently, a lack of consensus on the diagnostic criteria may have led to overestimation of the incidence and strength of the association. We searched Pubmed from database inception to September 30th, 2023 using the terms "obstetrics", "perinatal", "post-COVID-19" and "long COVID". There is scarce data on how post-COVID-19 condition affects pregnant women, and its incidence and implications for obstetric and perinatal morbimortality have not yet been studied. A recent study by Vásconez-González et al. studied long-term COVID-19 symptoms in a cohort of 457 women, of whom 33 were pregnant at the time of the study. Interestingly, the authors found a lower than expected incidence of long-term sequels in the obstetric group.

Added value of this study

To our knowledge, this is the first study to assess post-COVID-19 condition, defined by the WHO diagnostic consensus, and long-term sequelae of COVID-19 in a cohort of women with acute COVID-19 infection during pregnancy or delivery. Our data defined significant socio-demographic, maternal and perinatal risk factors for post-COVID-19 condition. We did not find any significant increase in perinatal morbidity in women affected by post-COVID-19 condition. Nevertheless, neurological and psycho-emotional sequelae tended to become chronic in a small but significant proportion of patients.

Implications of all the available evidence

Social determinants of health seem to play an important role in the risk of post-COVID-19 condition and need further insight. Vulnerable populations such as migrant women should be the focus of rehabilitation and therapeutic programs. However, we found a smaller incidence of post-COVID-19 condition in our cohort when compared to the incidence estimated in previous studies in nonobstetric populations. We propose the inclusion of obstetric populations in further studies to assess the impact of post-COVID-19 and evaluate possible immunological diagnoses and therapeutic targets.

Introduction

From the COVID-19 outbreak, caused by SARS-CoV-2, in January 2020 until June 2022, the WHO reported more than 536 million confirmed cases and more than 6.3 million deaths.[1] In this period, infection prevention measures and public policies were designed and deployed to decrease the incidence and *flatten the curve* with more or less success.[2] Despite these measures, different waves and variants of the COVID-19 pandemic have had a great impact on public health.[3,4]

Compared to the nonobstetric population, pregnant women are considered a population at risk since the incidence of clinical manifestations, severity of symptoms and associated obstetric morbidity seem to be

increased.[5–7] As recent studies have shown, COVID-19 infection could also be a risk factor for pregnancy complications such as preterm birth or hypertensive disorders of pregnancy.[6,7]

The clinical manifestations of acute SARS-CoV-2 infection are well known, although the diverse variants of the virus implicated in different waves of the pandemic[8] could be responsible for the different spectra of symptoms. However, the time-to-recovery and convalescence periods are heterogeneous, and for COVID-19 survivors who may present sequelae, the disease does not end after the acute phase. Post-COVID-19 condition have been recently defined as new or persistent common COVID-19 symptoms occurring three months after the onset of the disease[9] for at least two weeks, without regard to the severity of the acute phase. Suspected risk factors are female sex, obesity, previous psychiatric disorders and the number of symptoms at onset.[10–12] There is scientific consensus about the deeper insight that must be accorded to the study of post-COVID-19 condition.[11]

The objective of this study was to describe the incidence, clinical manifestations and main risk factors of post-COVID-19 condition in pregnant and postpartum women with confirmed COVID-19 infection during pregnancy or at delivery.

Methods

Study design and participants

We designed a prospective observational study of a hospital-based multipurpose obstetric and perinatal cohort including pregnant women enrolled in the COVID-19 and pregnancy programme[13] at a tertiary referral centre in Madrid. All women included were referred to the programme because of a confirmed positive COVID-19 test during pregnancy or at admission for labour, after discharge from the emergency room, after hospitalisation or after the confirmation of COVID-19 infection in obstetric or primary care consultations.[13]

According to WHO recommendations, confirmed SARS-CoV-2 infection was defined as a positive result from a real-time reverse transcriptase-polymerase chain reaction (RT–PCR) assay of a nasopharyngeal swab.[14] We included pregnant women with positive SARS-CoV-2 RT–PCR results from March 9th, 2020, to June 11th, 2022. All patients gave verbal consent to participate in the follow-up study, and they did not present significant language or communication barriers. All patients were asked about their country of origin, and we recorded the Human Development Index for each country.[15]

Patients who were lost to follow-up, experienced spontaneous miscarriage or requested legal termination of pregnancy within the framework of Spanish legislation were studied and compared to our long-term follow-up cohort and were excluded from further analysis.

The Ethics Committee of Gregorio Marañón Hospital (POSTCOV19) approved this study on 9 December 2021. Verbal consent was given by participants and recorded in their clinical history; however, the requirement for written consent was waived because of pandemic-related sanitary limitations.

Procedures

We performed clinical follow-up via telephone during the acute phase[13] and a postacute systematic clinical survey via telephone from November 11th, 2021, to September 15th, 2022 (Appendix). The items included in the systematic questionnaire were based on the Delphi consensus for post-COVID-19 condition.[9] We designed and administered the postacute systematic clinical survey to the patients included in the programme who were willing to participate and gave previous verbal consent. Data were pseudonymized and recorded in our database after the patients were informed about data protection laws and specific rights of access, rectification, cancellation and objection.

Outcomes

Patients were classified into four groups during the acute disease phase according to WHO guidelines: asymptomatic disease, mild disease (when symptoms could be managed in an outpatient regimen), severe disease (when hospitalisation was necessary and symptomatic treatment, noninvasive respiratory therapy or corticosteroids were offered) and critical disease (when patients were transferred to the Intensive Care Unit for invasive respiratory therapy and/or specific treatment).[16] Maternal and perinatal variables and outcome results were evaluated and reported following core outcome sets[17] and recommendations from the CoRe Outcomes in Women's and Newborn health (CROWN) initiative, as shown in Table 1. We defined epidemiological waves in six periods according to data from Spain's Ministry of Health: the first wave (01/03/2020–21/06/2020), second wave (22/06/2020–06/12/2020), third wave (07/12/2020–14/03/2021), fourth wave (15/03/2021–19/06/2021), fifth wave (20/06/2021–13/10/2021), and sixth wave (14/10/2021–27/03/22).[18] Dyspnoea was assessed and stratified using the Medical Research Council (MRC) Dyspnoea scale.[19,20] The evaluation of clinical anxiety and depression was performed using the Whooley questions as a screening tool and by administering the Goldberg Anxiety and Depression Scale (GADS) to patients with an initial positive screening following the National Institute for Health and Care Excellence (NICE) guidelines.[21–23] We used the Primary Care Posttraumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5) for the evaluation of posttraumatic stress symptoms followed by a clinician-guided semi-open questionnaire.[24–26] A pretested Spanish version was used for every scale.[23,27]

Maternal and perinatal variable clusters	Variable and core outcome sets
Maternal characteristics	Age
	Parity
	Body mass index
	ABO blood group
	Human development factor
	Previous medical morbidity
	Previous COVID-19 vaccine
Maternal outcomes	Miscarriage
	Termination of pregnancy
Pregnancy morbidity	Preeclampsia
	Gestational Diabetes
	Obesity in pregnancy
	Intimate partner violence
	Preterm birth
	Very preterm birth
	Multiple pregnancy
	Intrauterine growth restriction
	Stillbirth
	Clinical anxiety
	Clinical depression
	Post-traumatic stress symptoms
	Hospitalisation during pregnancy
Type of delivery	Induction of labour
	Caesarean delivery
	Postpartum haemorrhage
Perinatal morbidity	Neonatal care
	Birthweight
	Umbilical cord pH
	5 min Apgar test

Table 1: **Maternal and perinatal variables and core outcome results (in green core outcome sets registered in the CROWN initiative).**

Statistical analysis

Microsoft Excel and SPSS software (Microsoft Excel, Microsoft 365; IBM SPSS Statistics V28.0.1) were used as statistical software. We calculated the means, medians and standard deviations for quantitative variables. We applied the Wilcoxon rank sum test for the comparison of nonparametric variable medians, Fisher's exact test and Pearson's chi-squared test to evaluate the association of variables and their significance and the Kruskal–Wallis rank test to perform mean comparisons and assess significance when comparing three or more sample groups. Odds ratios and 95% confidence intervals were calculated using univariate logistic regression to analyse the strength of the association between suspected risk and protective factors and post-COVID-19 condition. Statistical significance was assumed when $p < 0.05$. We used Kaplan–Meier curves to illustrate the evolution of symptoms over time.

Role of the funding source

The funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

Results

From March 9, 2020, to June 11, 2022, we assisted in a total of 10,737 deliveries and treated 409 (3.8%) patients with confirmed COVID-19 infection during pregnancy or delivery in our centre. Patients suffering from acute infection during pregnancy or delivery were evaluated and treated within the COVID-19 and pregnancy program[13] and were offered participation in our study through telephone clinical follow-up until delivery and after to evaluate symptomatic recovery. Fig. 1 shows the distribution, demographic characteristics and severity of acute COVID-19 infection in patients included in our study. Overall, 123 patients (30%) were excluded from further assessment: 108 (26.4%) were lost to follow-up, 7 (1.7%) suffered spontaneous miscarriage, 7 (1.7%) underwent legal termination of pregnancy, and 1 (0.2%) patient was excluded because of maternal sudden death. Table 2 shows the demographic characteristics of the cohort with confirmed COVID-19 infection. Patients who were lost to follow-up mainly had asymptomatic and less severe cases and did not present any other significant demographic differences (Table 2). Thus, 286 patients were included in our cohort for long-term follow-up and evaluated for the prolonged clinical convalescence, incidence, and characteristics of post-COVID-19 condition.

The mean follow-up time was 92 weeks (standard deviation ± 28 weeks; median 100 weeks (Interquartile range: 76; 112)) so follow-up was performed for a minimum of one year after the onset of acute symptoms. On December 28, 2020, the first COVID-19 vaccine was administered in Spain, marking the beginning of the immunisation campaign, in our cohort only 18% of the mothers were vaccinated before suffer COVID-19. Table 3 shows the overall acute COVID-19 characteristics and maternal and perinatal results from our cohort with long-term follow-up. For maternal characteristics, patients from six waves of the pandemic were included, and 50% of the cases originated from the first two waves. Acute symptoms were heterogeneous, and only one in three patients presented with fever. Regarding perinatal results, the majority of women delivered at term, with adequate birthweight and favourable neonatal adaptation, and more than three out of four newborns were being breastfed at discharge.

A total of 140 patients out of the 286 patients who were followed-up (49%) presented at least one post-COVID-19 symptom after 3 months, which represented 34.2% of the total cohort of COVID-19-positive patients (n = 409). Fig. 2 shows the incidence of post-COVID-19 represented through the different system-clustered symptoms. Neurological (60%) and cutaneous (55%) manifestations were the most frequent findings.

Fig. 3 shows the distribution of the incidence of post-COVID-19 conditions throughout the different

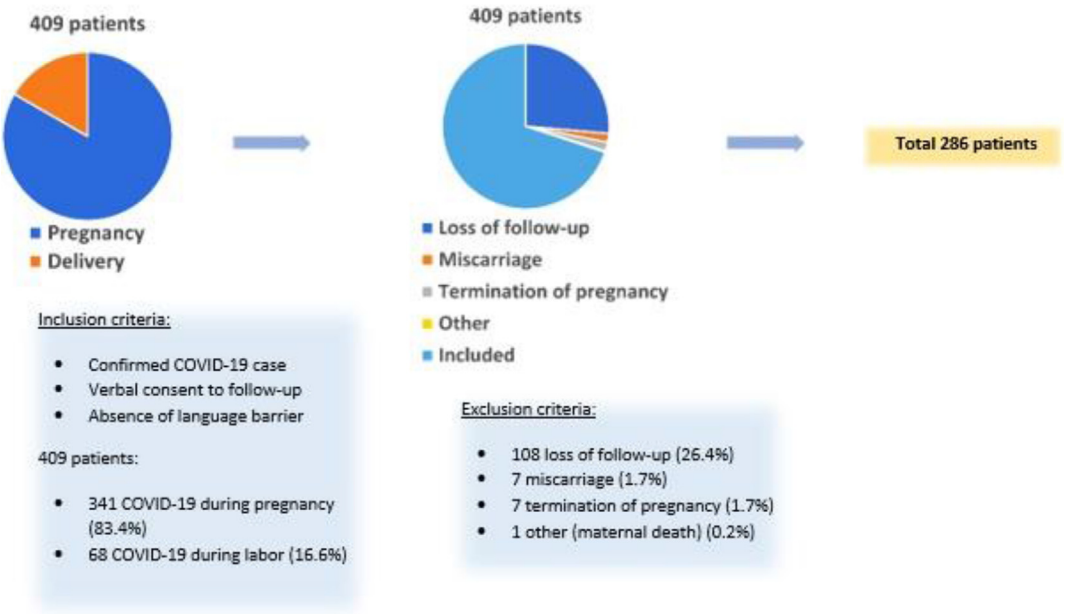


Fig. 1: **Study design: distribution, demographic characteristics and acute COVID-19 severity**.

pandemic waves. As the figure shows, the fifth wave was marked by a significant reduction in confirmed COVID-19 cases and no detection of post-COVID-19. Nevertheless, we found a significant and constant decrease in the incidence of post-COVID-19 condition in each successive wave (OR: 0.70; 95% CI: 0.62, 0.92).

Table 4 presents the association between demographic, clinical, obstetric and perinatal variables in post-COVID-19-affected patients and nonaffected patients. The following patients were more likely to have post-COVID-19 condition: migrant patients born from countries with low Human Development Index; patients who were multiparous; patients who were infected with COVID-19 during pregnancy, mainly in the first and third trimesters and during the first and second waves of the pandemic; patients with a higher number of symptoms; patients with a higher incidence of moderate and severe symptoms; patients with a higher incidence of hospitalisation from COVID-19 complications; and patients who were not vaccinated before disease onset. We did not observe significant differences in obstetric and perinatal variables, such as gestational age at delivery, induction of labour, type of delivery, neonatal weight, umbilical cord pH level and neonatal Apgar score, in women who presented post-COVID-19 condition compared to women who did not experience long-term sequelae.

The total duration of post-COVID-19 and long-term sequelae was also studied: 23 patients (8.04%) showed significant anxiety symptoms, 18 patients (6.3%) showed significant depression symptoms, 22 patients (7.7%) showed attention deficit symptoms, and 68 patients (23.7%) showed at least one posttraumatic stress symptom 6 months after the onset of acute disease.

Fig. 4 shows the evolution of the main persistent clustered-system symptoms over time. Symptoms tended to resolve heterogeneously. Symptoms of myalgia and arthralgia took longer to resolve (mean of 60 weeks and 54 weeks, respectively). A small proportion of neurological and psycho-emotional symptoms tended to become chronic after 90 weeks.

Discussion

As the COVID-19 pandemic has developed throughout the world, the number of cases and survivors has increased, implicating new challenges in public health. Post-COVID-19, defined as new or persistent signs or symptoms 12 weeks after acute COVID-19 infection,[9] is a new and potentially chronic health condition derived from the pandemic. Its incidence and risk factors need to be thoroughly studied to respond to these new post-pandemic challenges. In this scenario, pregnant women constitute an *a priori* vulnerable population, not only because of the pathophysiological, anatomical and immunological specificities of pregnancy but also because of intersectional psychosocial and economic factors.

This study shows the impact of post-COVID-19 in an obstetric population beyond acute disease, and it is, to our knowledge, the first approach to the analysis of incidence and main risk factors of post-COVID-19 condition in women infected during pregnancy and

Characteristic	Followed-up (n: 286)[a]	Not followed-up (n: 123)[a]	Total (n: 409)[a]	p value
Maternal characteristics				
Age	33.0 (30.0–36.8)	32.0 (26.8–36.0)	33.0 (29.0–36.0)	0.055[b]
BMI	25.0 (22.0–29.0)	25.0 (21.4–29.0)	25.0 (21.9–29.0)	0.8[b]
Human development index	0.91 (0.75, 0.91)	0.91 (0.74, 0.91)	0.91 (0.75, 0.91)	0.2[b]
Previous deliveries				0.10[c]
1	72 (25%)	33 (33%)	105 (27%)	
≥2	42 (15%)	19 (19%)	61 (16%)	
Acute COVID-19 characteristics				
Severity of acute COVID-19				**0.002**[c]
Asymptomatic	58 (20%)	43 (35%)	101 (25%)	
Mild	173 (60%)	51 (42%)	224 (55%)	
Moderate	45 (16%)	20 (16%)	65 (16%)	
Severe	10 (3.5%)	8 (6.6%)	18 (4.4%)	
Hospitalisation because of acute COVID-19	52 (18%)	27 (22%)	79 (19%)	0.4[c]
Number of symptoms at onset (mean (SD))	4.01 (2.54)	0.49 (1.55)	2.95 (2.80)	**<0.001**[b]
Epidemiological wave				**0.002**[e]
1	55 (19%)	35 (36%)	90 (23%)	
2	89 (31%)	36 (37%)	125 (33%)	
3	42 (15%)	11 (11%)	53 (14%)	
4	32 (11%)	5 (5.1%)	37 (9.6%)	
5	3 (1.0%)	1 (1.0%)	4 (1.0%)	
6	65 (23%)	10 (10%)	75 (20%)	
Previous vaccine	52 (18%)	6 (6.5%)	58 (15%)	**0.006**[c]
Perinatal characteristics				
Gestational week at delivery				0.069[d]
<37	27 (9.5%)	13 (17%)	40 (11%)	
≥37	256 (90%)	64 (83%)	320 (89%)	
Neonatal weight				0.8[c]
<2500 g	19 (6.9%)	6 (8.0%)	25 (7.2%)	
≥2500 g	255 (93%)	69 (92%)	324 (93%)	
5-min Apgar score				0.6[d]
≤3	1 (0.4%)	1 (1.4%)	2 (0.6%)	
4–6	2 (0.8%)	0 (0%)	2 (0.6%)	
7–10	261 (99%)	72 (99%)	333 (99%)	
Umbilical cord pH				0.6[d]
≤7.10	9 (3.7%)	4 (5.6%)	13 (4.1%)	
7.11–7.25	109 (44%)	28 (39%)	137 (43%)	
>7.25	127 (52%)	40 (56%)	167 (53%)	

[a]n (95% CI; %). [b]Wilcoxon rank sum test. [c]Pearson's chi-squared test. [d]Fisher's exact test. [e]Fisher's exact test for count data with simulated p value (based on 2000 replicates).

Table 2: **Demographic characteristics of the COVID-19 obstetric cohort.**

the postpartum period. At least 34.2% of obstetric patients with COVID-19 infection in our cohort presented post-COVID-19 condition symptoms. For maternal characteristics, the main risk factors were migration from a country with a low Human Development Index, multiparity and COVID-19 infection during pregnancy, mainly during the first and third trimesters. For acute disease characteristics, the main risk factors were COVID-19 infection in the first waves of the pandemic, number of symptoms at onset, moderate and severe symptoms, hospitalisation due to COVID-19 complications and absence of vaccination prior to acute infection. The onset of subsequent waves of the pandemic was shown to be a protective factor against post-COVID-19. We did not find any significant difference in perinatal results between women affected by post-COVID-19 conditions and women who did not experience sequelae. The incidence of most system-clustered symptoms decreased with time. Symptoms of myalgia and arthralgia took longer to resolve. Attention deficit, anxiety, depression and posttraumatic stress symptoms tended to become

Maternal characteristics	N 286 (standard deviation; %)
Epidemic wave	
First wave	55 (19%)
Second wave	89 (31%)
Third wave	42 (15%)
Fourth wave	32 (11%)
Fifth wave	3 (1%)
Sixth wave	65 (23%)
Previous nonobstetric morbidity[a]	94 (33%)
Multiparity	115 (40%)
Previous caesarean section	32 (11%)
High-risk pregnancy	61 (21%)
Acute symptoms	
Fever	154 (38%)
Asthenia	208 (51%)
Myalgia-Arthralgia	180 (44%)
Cough	166 (41%)
Dyspnoea	109 (27%)
Thoracic pain	64 (16%)
Anosmia	130 (32%)
Ageusia-dysgeusia	123 (30%)
Diarrhoea	48 (12%)
Skin alterations	25 (6.1%)
Blood type	
0	136 (48%)
Non-0	145 (51%)
Induction of labour	77 (21%)
Previous COVID-19 vaccination (at least one dose)	52 (18%)
Perinatal results	
Gestational age at delivery (weeks)	39 (±4.4)
Weight at birth (grams)	3220 (±165)
Type of delivery	
Noninstrumental vaginal delivery	192 (68%)
Instrumental vaginal delivery	30 (11%)
Caesarean section	61 (21%)
Umbilical cord pH at birth	7.25 (±0.025)
5-min Apgar test	10 (±0.00)
Breastfeeding at discharge	228 (80%)

[a]Previous nonobstetric morbidities were identified when previous disease of the pregnant women determined a high-risk pregnancy follow-up.

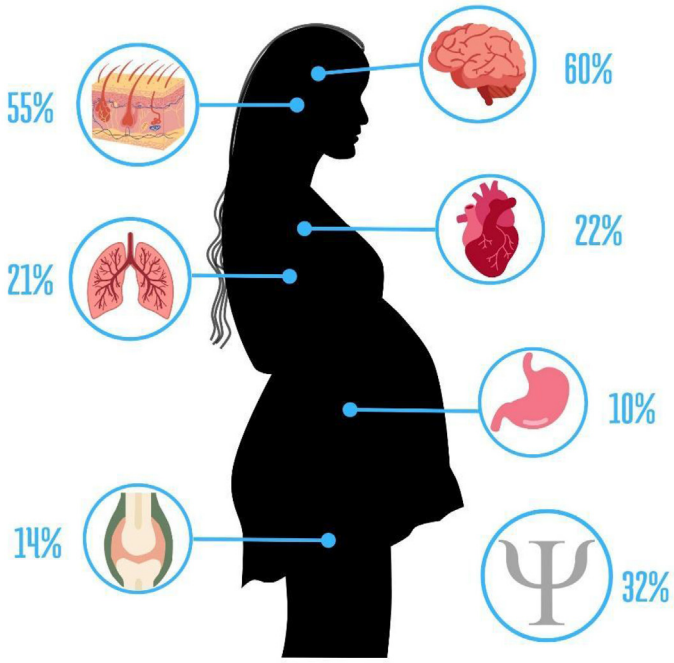
Table 3: **Long-term follow-up: acute COVID-19, maternal characteristics and perinatal results.**

chronic in a small but significant proportion of patients.

One of the main limitations in the present study was the high rate of loss to follow-up. We believe this was facilitated by the long duration of the study and may have been promoted by social factors specific to women in the postpartum period. The rapid incorporation of work for women after delivery and insufficient conciliation policies in Spain may have also played a role in low adherence to follow-up programs, especially in non-severe patients who did not need hospitalisation during the acute phase of the disease. However, we studied the main demographic characteristics of this specific cohort and did not find any other significant difference that may have altered our results. Another important limitation to this study was the lack of a control group, which limited the accuracy and generalization of post-COVID-19 prevalence in general obstetric population. However, since this is a recently defined disease,[9] this study allows to better understand its impact, incidence and main risk factors. The design of the study started from a multipurpose cohort of hospitalised and non-hospitalised women, and follow-up was performed through semistructured telephone questionnaires.[13,28] This may have limited our study since the information extracted from our questionnaires may have presented some bias due to subjectivity, specific language limitations or memory constraints. Women were often contacted while at home with family members, which may have limited or overrate the expression of malaise or the perception and accuracy of the description of their symptoms. This may have introduced bias in our study. Other studies also describe post-COVID-19 conditions based on the subjective perception of symptoms.[19,29–40] The hospital-based study limits the generalization of this data, but sets the base for further studies. The precise role of vaccines in protecting pregnant women needs to be specifically address since one limitation of this study derived from the fact that women were vaccinated with different vaccines (due to availability) with a limited adherence. To our knowledge, this is the first study to assess the incidence of post-COVID-19 condition, defined by diagnostic criteria, in an obstetric population. The sample size was sufficient to show statistically significant differences and to assess risk and protective factors.

There was one case of maternal sudden death during the postpartum period. This case occurred in a young multiparous obese Spanish patient a spontaneous delivery at term. According to the autopsy, she died at home because of a malignant arrhythmia that was probably secondary to the intake of an illegal medication for weight loss that she acquired online (sibutramine).

In a recent study by Wahlgren et al.,[29] the incidence of post-COVID-19 condition and main risk factors were assessed in a cohort of previously hospitalised patients with COVID-19 complications. Of these survivors after hospitalisation, 84% presented with at least one symptom affecting their everyday life 24 months after the onset of acute disease, and cognitive and neurosensorial symptoms were the most frequent findings, which is consistent with our results. Neurocognitive impairment during the pandemic has been described as a consequence of lockdown policies, which may be considered a confounding factor,[29,30] and in Spain, these policies may have indeed taken a toll on the mental and neurological health of these patients. However, to our knowledge,



Neurological (headache, attention deficit, insomnia, anosmia, ageusia-dysgeusia) **84 (60%)**

Cutaneous (skin alterations, persistent hair loss, alopecia) **77 (55%)**

Psycho-emotional (anxiety, depression, PTSD symptoms) **45 (32%)**

Cardiovascular (dyspnoea, dizziness) **31 (22%)**

Respiratory (cough, dyspnoea, thoracic pain) **30 (21%)**

Musculoskeletal (myalgia, arthralgia) **19 (14%)**

Digestive (weight loss, appetite loss, diarrhoea) **14 (10%)**

***Fig. 2:* System-clustered symptoms of post-COVID-19 conditions 3 months after the onset of acute disease (n = 140).** Neurological (headache, attention deficit, insomnia, anosmia, ageusia-dysgeusia) 84 (60%). Cutaneous (skin alterations, persistent hair loss, alopecia) 77 (55%). Psycho-emotional (anxiety, depression, PTSD symptoms) 45 (32%). Cardiovascular (dyspnoea, dizziness) 31 (22%). Respiratory (cough, dyspnoea, thoracic pain) 30 (21%). Musculoskeletal (myalgia, arthralgia) 19 (14%). Digestive (weight loss, appetite loss, diarrhoea) 14 (10%).

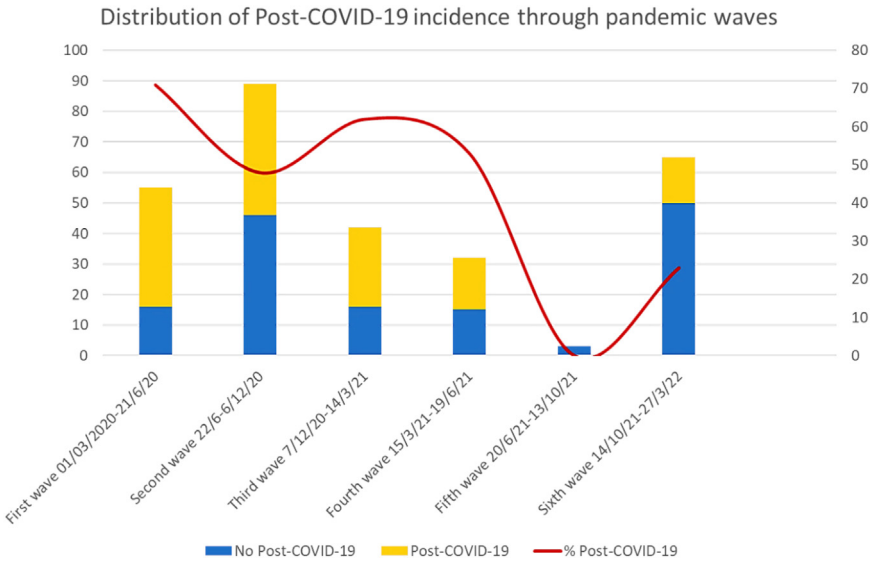


***Fig. 3:* Distribution of the incidence of post-COVID-19 conditions through the different pandemic waves (x: waves of the pandemic following national data; y, right: %; y, left: n).**

Variables	Not suffering post-COVID-19 symptoms[a] (n = 146)	Suffering at least one post-COVID-19 symptom[a] (n = 140)	Total[a] (n = 286)	OR (95% CI)	p value
Demographic					
Maternal Age (years)					0.10[d]
≤35 years	105 (54%)	88 (46%)	193 (67%)		
>35 years	41 (44%)	52 (56%)	93 (33%)		
Body-mass index					0.13[d]
≤25	80 (58%)	59 (42%)	139 (54%)		
26–30	36 (51%)	34 (49%)	70 (27%)		
>30	20 (41%)	29 (59%)	49 (19%)		
Human development index (HDI Spain 0.904)				**0.09 (0.01–1.09)**	**0.039[b]**
Median (IQR)	0.91 (0.76, 0.91)	0.91 (0.74, 0.91)	0.91 (0.75, 0.91)		
Mean (SD)	0.84 (0.09)	0.82 (0.10)	0.83 (0.10)		
Range	[0.51, 0.94]	[0.62, 0.92]	[0.51, 0.94]		
Low HDI (<0.550) (n (%))	2 (1.4%)	0	2 (0.7%)		
Medium HDI (0.550–0.699) (n (%))	11 (7.5%)	23 (16%)	34 (11.9%)		
High HDI (0.70–0.799) (n (%))	32 (22%)	36 (26%)	68 (23.7%)		
Very high HDI (>0.8) (n (%))	101 (69%)	81 (58%)	182 (63.6%)		
Clinical					
Epidemic wave				**0.71 (0.61, 0.81)**	**<0.001[c]**
1	16 (29%)	39 (71%)	55 (19%)		
2	46 (52%)	43 (48%)	89 (31%)		
3	16 (38%)	26 (62%)	42 (15%)		
4	15 (47%)	17 (53%)	32 (11%)		
5	3 (100%)	0 (0%)	3 (1.0%)		
6	50 (77%)	15 (23%)	65 (23%)		
Severity of acute COVID-19					**<0.001[c]**
Asymptomatic	45 (78%)	13 (22%)	58 (20%)	–	
Mild	90 (52%)	83 (48%)	173 (60%)	**3.19 (1.65, 6.55)**	
Moderate	8 (18%)	37 (82%)	45 (16%)	**16.0 (6.27, 45.4)**	
Severe	3 (30%)	7 (70%)	10 (3.5%)	**8.08 (1.96, 41.8)**	
Hospitalisation due to COVID-19 complications	10 (19%)	42 (81%)	52 (18%)	**5.83 (2.89, 12.8)**	**<0.001[d]**
Number of symptoms in the acute phase				**1.48 (1.32, 1.66)**	**<0.001[b]**
Median (IQR)	3.00 (0.00, 5.00)	5.00 (4.00, 7.00)	4.00 (2.00, 6.00)		
Mean (SD)	2.95 (2.30)	5.11 (2.31)	4.01 (2.54)		
Range	[0.00, 8.00]	[0.00, 9.00]	[0.00, 9.00]		
Obstetric					
Previous deliveries (multiparity)				**2.38 (1.21, 4.86)**	**0.003[b]**
Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)		
Mean (SD)	0.44 (0.72)	0.79 (1.06)	0.61 (0.92)		
Range	[0.00, 3.00]	[0.00, 5.00]	[0.00, 5.00]		
Number of previous deliveries: none (n (%))	99 (58%)	72 (42%)	171 (60%)	–	
Number of previous deliveries: 1 (n (%))[e]	33 (46%)	39 (54%)	72 (25%)	1.63 (0.94, 2.84)	0.086
Number of previous deliveries: 2 or more (n (%))	14 (33%)	28 (67%)	42 (15%)	**2.75 (1.37, 5.73)**	**0.005**
Previous medical morbidity	49 (52%)	45 (48%)	94 (33%)		0.84
Obstetric morbidity	48 (53%)	42 (47%)	90 (32%)		0.5[d]
Timing of positive RT–PCR test				**0.42 (0.22, 0.78)**	**0.006[d]**
Positive during pregnancy	110 (47%)	123 (53%)	233 (81%)		
Positive at delivery	36 (68%)	17 (32%)	53 (19%)		
Weeks at diagnosis					**0.007[d]**
0–12	15 (38%)	25 (62%)	40 (14%)		
13–24	31 (55%)	25 (45%)	56 (20%)		
25–32	33 (52%)	30 (48%)	63 (22%)		
33–37	25 (39%)	39 (61%)	64 (22%)		

(Table 4 continues on next page)

Variables	Not suffering post-COVID-19 symptoms[a] (n = 146)	Suffering at least one post-COVID-19 symptom[a] (n = 140)	Total[a] (n = 286)	OR (95% CI)	p value
(Continued from previous page)					
>37	42 (68%)	20 (32%)	62 (22%)	**0.29 (0.12, 0.65)**	**0.03**[d]
Induction of labour	43 (56%)	34 (44%)	77 (29%)		0.3[d]
Type of delivery					0.2[c]
Vaginal-noninstrumental	102 (53%)	90 (47%)	192 (68%)		
Vaginal-instrumental	20 (67%)	10 (33%)	30 (11%)		
Caesarean section	29 (48%)	32 (52%)	61 (22%)		
Neonatal weight at delivery					0.4[b]
Median (IQR)	3160 (2,925, 3490)	3250 (2,935, 3590)	3220 (2,930, 3550)		
Mean (SD)	3179 (491)	3205 (573)	3192 (532)		
Range	[955, 4570]	[910, 4320]	[910, 4570]		
Umbilical cord pH					0.7[b]
Median (IQR)	7.25 (7.20, 7.30)	7.24 (7.19, 7.31)	7.25 (7.20, 7.30)		
Mean (SD)	7.24 (0.08)	7.19 (0.66)	7.22 (0.47)		
Range	[6.98, 7.41]	[0.00, 7.44]	[0.00, 7.44]		
5-min Apgar test					0.6[b]
Median (IQR)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)		
Mean (SD)	9.75 (0.60)	9.68 (1.17)	9.72 (0.92)		
Range	[7.00, 10.00]	[0.00, 10.00]	[0.00, 10.00]		
Previous vaccine	40 (77%)	12 (23%)	52 (18%)	**0.25 (0.12, 0.48)**	**<0.001**[d]

IQR: interquartile range; SD: standard deviation; OR: odds ratio; 95% CI; 95% confidence interval. Non significant OR are not shown. [a]n (%). [b]Wilcoxon rank sum test. [c]Fisher's exact test for count data with simulated p value (based on 2000 replicates). [d]Pearson's chi-squared test. [e]Fisher's exact test.

Table 4: **Association between demographic, clinical, obstetric and perinatal variables and post-COVID-19 condition.**

this is the first study to assess post-COVID-19 symptoms for each successive epidemiological wave, and a significant and novel finding is the progressive and constant decrease in their incidence. After the second wave of the pandemic, public policies for movement restrictions tended to relax, which may have improved the incidence of these symptoms when attributed to lockdown, thus reducing the risk of bias.

A meta-analysis conducted by Han et al. also described system-clustered symptoms[19] and showed that severe cases may be related to a higher rate of post-COVID-19 condition, which is consistent with our findings; however, symptoms were evaluated after one year and did not account for systematic surveys or the WHO post-COVID-19 diagnostic criteria.[9] These authors also noted that female sex was a significant risk factor for post-COVID-19 conditions.[19,31]

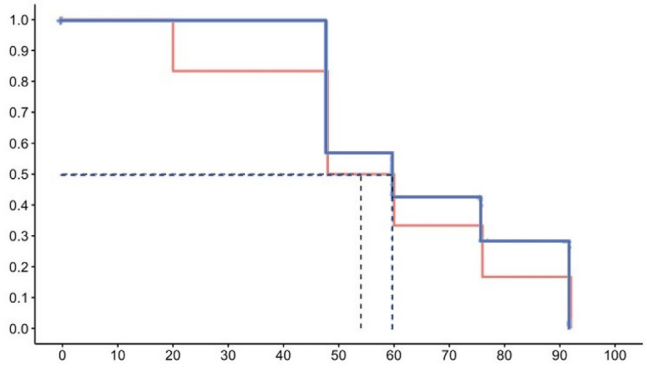
The recent study by Vásconez-González et al.[32] studied long-term sequels of COVID-19 disease in 457 women, of whom 33 were pregnant, using self-reporting closed questionnaires. Despite the fact that no diagnostic criteria of post-COVID-19 condition was used and symptoms were not assessed using objective scales, and despite the small proportion of pregnant women in the cohort, the authors found a lower-than-expected incidence of sequels in the obstetric cohort, which might be attributed to physiological modifications occurring during pregnancy. We also found a lower incidence of post-COVID-19 condition symptoms in our cohort compared to the expected adjusted risk for nonhospitalised female patients, estimated at 53% in the meta-analysis by Chen et al.[33] Prior studies, such as that by Chen et al., assessed the prevalence and main risk factors for COVID-19 sequelae in previously hospitalised patients and used long COVID definitions prior to the WHO consensus,[9] which may overestimate the real incidence of persistent symptoms in general populations. However, during pregnancy, vascular and immunological adaptations may play a role in protecting women against post-COVID-19 conditions. Endothelial dysfunction has already been described as a possible physiopathological factor for COVID-19 sequelae.[34] Pregnancy constitutes a specific scenario in which normal endothelial function is needed for the normal development and delivery of healthy term babies. Immune dysregulation and persistent immune activation[35] have also been proposed as putative physiopathological factors explaining the long-term sequelae of COVID-19.[36] During pregnancy, immune tolerance is key to the placentation process, and previous autoimmune diseases tend to improve during this period. Pregnancy may thus constitute a protective factor against post-COVID-19 condition, and obstetric cohorts may be an important group for further studies.

Individuals in ethnic minority groups have recently been described as a vulnerable cohort for post-COVID-

4.1 Musculoskeletal symptoms

Blue: Myalgia (x: weeks of evolution; y: prevalence proportion; initial number of risk n=7): median 60 weeks

Red: Arthralgia (x: weeks of evolution; y: prevalence proportion; initial number of risk n=6): median 54 weeks



4.2 Respiratory symptoms:

Blue: Dyspnoea: (x: weeks of evolution; y: prevalence proportion; initial number of risk n=7): median 48 weeks

Red: Thoracic pain: (x: weeks of evolution; y: prevalence proportion; initial number of risk n=5): median 48 weeks

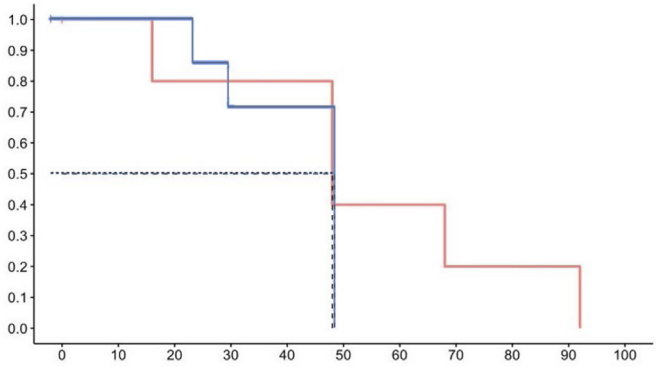
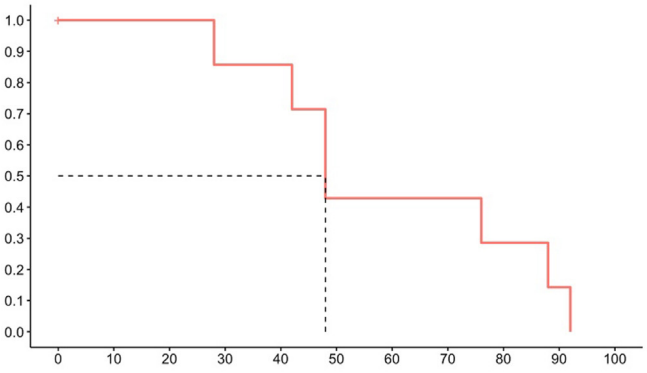


Fig. 4: **Evolution of symptoms over time.** 4.1 Musculoskeletal symptoms: Blue: Myalgia (x: weeks of evolution; y: prevalence proportion; initial number of risk n = 7): median 60 weeksleft481965, Red: Arthralgia (x: weeks of evolution; y: prevalence proportion; initial number of risk n = 6): median 54 weeks. 4.2 Respiratory symptoms: Blue: Dyspnoea: (x: weeks of evolution; y: prevalence proportion; initial number of risk n = 7): median 48 weeks, Red: Thoracic pain: (x: weeks of evolution; y: prevalence proportion; initial number of risk n = 5): median 48 weeks. 4.3 Cutaneous alterations: (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 49): median 48 weeks. 4.4 Neurological symptoms: Blue: Attention deficit: (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 21): median 48 weeks, Grey: Anosmia: (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 19): median 48 weeks, Red: Headache (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 16): median 38 weeksleft20574000. 4.5 Psycho-emotional symptoms: Blue: Posttraumatic stress symptoms: (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 66): median 48 weeks, Red: Psychiatric symptoms (anxiety and depression): (x: weeks of evolution; y: prevalence proportion; initial number at risk n = 28): median 48 weeks.

19 condition[35]; but heterogeneity in the study of socio-economic variables and social determinants of health limit our comprehension of specific risk factors in determining long term sequelae of COVID-19 disease. To our knowledge, this is the first study to acknowledge the specific risk constituted by migration from countries

4.3 Cutaneous alterations: (x: weeks of evolution; y: prevalence proportion; initial number at risk n=49): median 48 weeks



4.4 Neurological symptoms:

Blue: Attention deficit: (x: weeks of evolution; y: prevalence proportion; initial number at risk n=21): median 48 weeks

Grey: Anosmia: (x: weeks of evolution; y: prevalence proportion; initial number at risk n=19): median 48 weeks

Red: Headache (x: weeks of evolution; y: prevalence proportion; initial number at risk n=16): median 38 weeks

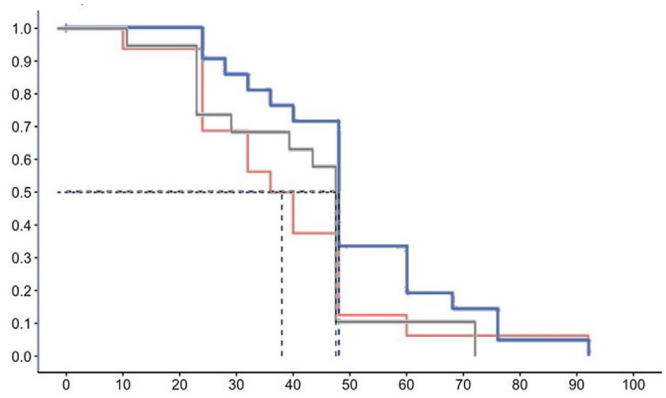


Fig. 4: (continued)

with a low Human Development Index. Future public policies may need to focus on evaluation and rehabilitation in these patients given the specific vulnerabilities they may present.

Vaccination has already been described as a potential preventive factor for post-COVID-19 symptoms,[37] which is consistent with our findings, but further insight is needed to understand the specific role of vaccination in these populations, since the availability and adherence to vaccination in our cohort limited our study.

This is the first study to assess post-COVID-19 condition through semistructured questionnaires in an obstetric population and following WHO diagnostic criteria. We described its incidence, new specific risk factors derived from pregnancy, such as multiparity and COVID-19 infection during the first and third trimesters of pregnancy. Acquiring COVID-19 infection during successive waves of the pandemic and COVID-19 vaccination was shown to be a significant protective factor against developing post-COVID-19 condition. Most symptoms tended to decrease over time, but a small yet significant proportion of symptoms tended to become chronic in some patients. This needs to be specifically addressed in pregnant and postpartum

4.5 Psycho-emotional symptoms

Blue: Posttraumatic stress symptoms: (x: weeks of evolution; y: prevalence proportion; initial number at risk n=66): median 48 weeks

Red: Psychiatric symptoms (anxiety and depression): (x: weeks of evolution; y: prevalence proportion; initial number at risk n=28): median 48 weeks

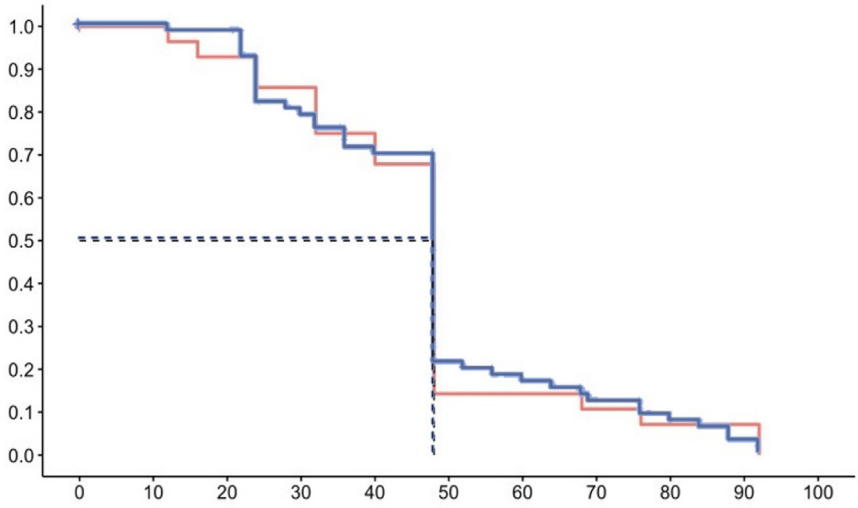


Fig. 4: (continued)

women and will need to be further studied in the general population. More studies are encouraged to explain the biological pathogenesis of post-COVID-19 condition. In our obstetric cohort, we found a lower incidence of post-COVID-19 than expected according to previous meta-analysis studying non-pregnant women, so we propose pregnant patients as an important study cohort because of their specific immunological and vascular adaptations, which may be protective factors against post-COVID-19 condition and may help us design preventive or therapeutic measures.

Contributors

MMChG contributed to conceptualisation, data curation, formal analysis, investigation, methodology and writing. ASP, ADV, MBC, PPM, PPR contributed to data curation, project administration and software. ADV and MVB contributed to formal analysis, methodology. MN contributed to project administration, supervision and validation. PGN contributed to formal analysis, methodology, software and visualization. MAM and MAO were responsible for review and editing of the article, funding acquisition and supervision. JdLL contributed to conceptualisation, formal analysis, methodology, project administration, supervision, validation, reviewing and editing and had final responsibility for the decision to submit for publication. All authors commented on drafts of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Individual participant data collected for the study, after de-identification, ethics comitee documents, study protocol, and written information delivered to patients will be made available through public data repository immediately with publication; no end date. This data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose, and considering european laws concerning protection of data, to achieve aims in the approved proposal. This data will be available online through *Repositorio de Datos UC3M* (https://edatos.consorciomadrono.es/dataverse/UC3M).

Declaration of interests

We report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102398.

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