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Full length article

Association of ABO and Rh blood groups with obstetric outcomes in SARS-CoV-2 infected pregnancies: A prospective study with a multivariate analysis

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Tweetable Abstract: Among pregnant women with SARS-CoV-2, blood group A and Rh+ are associated with medical and obstetric morbidity.

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ABSTRACT

Objective: To evaluate the influence of ABO and Rh blood groups on morbidity among SARS-CoV-2 infected pregnancies.
Design: Prospective observational study.
Setting: 78 centers of the Spanish Obstetric Emergency Group.
Population: Pregnant women with SARS-CoV-2 tested with polymerase-chain-reaction between 26-February and 5-November 2020. A cohort of 1278 SARS-CoV-2(+) pregnant women was analyzed and a concurrent comparison group of 1453 SARS-COV-2(−) patients was established.
Methods: Data were collected from medical charts. SARS-COV-2(+) was compared with SARS-COV-2(−) for differences in distribution of blood groups. We performed multivariate analysis, controlling for maternal age and ethnicity, to evaluate association of ABO and Rh blood groups with maternal and perinatal outcomes in SARS-CoV-2(+) patients with adjusted odds ratios (aOR) and 95% confidence intervals (CI).
Main outcomes measures: Medical morbidity: Symptomatic COVID-19 and medical complications. Obstetric outcomes: caesarean delivery, preterm deliveries, preterm premature rupture of membranes (PPROM), hemorrhagic events, pre-eclampsia, maternal and neonatal mortality, stillbirth.
Results: Differences were noted between blood types and Rh for age and ethnicity comparing SARS-CoV-2 (+) and SARS-CoV-2(−) groups ($p < 0.05$). Among the SARS-CoV-2(+) cohort, the odds of symptomatic COVID-19 and obstetric hemorrhagic event were higher in Rh+ vs Rh− mothers (aOR 1.48, 95% CI 1.02–2.14, p = 0.037, and aOR 8.72, 95% CI 1.20–63.57, p = 0.033, respectively), and PPROM were higher among blood type A vs non-A mothers (aOR 2.06, 95% CI 1.01–4.18, p = 0.046).

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[1] A list of the Spanish Obstetric Emergency Group collaborators appears in the Acknowledgements section.

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Conclusions: In SARS-CoV-2(+) pregnant women, Rh− status was associated with a lower risk of symptomatic COVID-19, while Rh+ and blood group A were associated with obstetric hemorrhage and PPROM, respectively.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified in December 2019, causes the symptomatic COVID-19 illness [1]. With more than 109 206 497 confirmed cases and at least 2 407 469 deaths by February 8, 2021, Spain remains one of the European countries most severely affected by the ongoing pandemic [2,3]. At the start of the pandemic, it was widely reported that pregnant women were not at increased risk of COVID-19 susceptibility, infectivity, and severity compared to the general population or non-pregnant women [4–8]. Recently, Zambrano et al. [9] reported, evaluating over 23,000 pregnant women affected by symptomatic COVID-19, the existence of an increased risk of admission in the intensive care unit (ICU), need of invasive ventilation and receive extracorporeal membrane oxygenation (ECMO) among pregnant COVID-19 patients compared to non-pregnant women of similar age, race and ethnicity. The Spanish Obstetric Emergency group (SOEG), has observed that pregnant women with COVID-19 have a higher rate of obstetric emergencies and caesarean sections [10], as well as a higher rate of obstetric complications with the presence of an increase in prematurity, premature rupture of membranes at term and neonatal intensive care unit admissions [11].

Several risk factors for COVID-19 infection, morbidity, and mortality are now known, including age, sex, and a number of chronic conditions (hypertension, diabetes, cardiovascular and respiratory diseases) and laboratory findings [12,13]. Additionally, the presence of severe symptoms is associated with a higher risk of complications and mortality from COVID-19 compared to mild symptoms, both in general population [13] and in pregnant women [14]. Recently, it has been reported that the association between ABO blood groups and COVID-19 infection, severity and demise exists in such a way that there is a greater risk of infection and severity in individuals with type A blood whereas there is a lower risk in type O blood groups [15–18].

We evaluated the influence of the ABO and Rh blood group on COVID-19 and obstetric morbidity in a pregnancy cohort of SARS-CoV-2 positive mothers.

Methods

Study design and population

This was a multicenter prospective study of consecutive cases of SARS-CoV-2 infection in a pregnancy cohort registered by the Spanish Obstetric Emergency Group in 78 hospitals between February 26th and November 5th, 2020. The registry's objective updates were approved by the coordinating hospital's Medical Ethics Committee on March 23rd, 2020 (reference number: PI 55/20); each collaborating center subsequently obtained protocol approval locally. The registry protocol is available in ClinicalTrials.gov, identifier: NCT04558996. A complete list of the centers contributing to the study is provided in Table S1. Upon recruitment, mothers consented by signing a document. We developed an analysis plan using the recommended contemporaneous methods and followed existing STROBE guidelines (Table S2).

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SARS-CoV2 infected [SARS-CoV-2(+)] group

We included infected obstetric patients detected by screening for SARS-CoV-2 infection at admission on delivery ward during the study period. SARS-CoV-2 infection was diagnosed by positive double-sampling polymerase-chain-reaction (PCR) from nasopharyngeal swabs. All identified cases were included in the study, irrespective of clinical signs and symptoms or the result of another serological test. The cases with a clinical presentation of SARS-CoV-2 infection were classified following the WHO classification for adults: mild symptoms, mild-moderate pneumonia, severe pneumonia and septic shock [19]. The patients, regardless of the time of diagnosis or symptoms, were prescribed thromboprophylaxis with Low Molecular Weight Heparin (LMWH) for at least 10 days [20,21].

SARS-CoV2 non-infected [SARS-CoV-2(−)] concurrent comparison group for blood type distribution

Non-infected patients were those defined by a negative PCR at admission on delivery ward. Each center identified 1–2 PCR negative pregnancies delivered immediately before and/or after delivery of each SARS-CoV-2 infected mother, regardless of the outcome. This method of identifying mothers not exposed to SARS-CoV-2 infection was deployed to adjust for center conditions at the time of delivery and decreased the risk of bias.

Data collection

Hospitals collected the encoded information in two separate phases: during the enrolment period that occurred at the time of the SARS-CoV-2 test during pregnancy and within 6 weeks after birth. Information regarding the demographic characteristics of each pregnant woman, comorbidities and current obstetric history was extracted from the clinical history and from the interview with the patient; subsequently, age and race were categorized following the classification used by the CDC [22]. ABO blood type of patients was determined by standard RBC typing performed for clinical purposes. Medical outcomes (symptomatic COVID-19, thromboembolic events, pulmonary embolism, deep venous thrombosis, invasive ventilation, admitted in ICU) and obstetric and perinatal outcomes [caesarean delivery, preterm deliveries, preterm premature rupture of membranes (PPROM), hemorrhagic events, gestational hypertensive disorders, maternal and neonatal mortality, stillbirth] were recorded. Definitions of obstetric conditions followed international criteria [23–25]. Patients were followed until six weeks postpartum. Neonatal events were recorded until 14 days postpartum.

Statistical analysis

Quantitative variables, such as maternal age (years) and gestational age at delivery (weeks + days), were tested for normal distribution using Kolmogorov–Smirnov or Shapiro–Wilk tests. Descriptive data were presented as mean (range), or percentage

Table 1
Demographic characteristics of mothers according to SARS-CoV-2 positivity and blood group.

	SARS-CoV-2 Positive n = 1287						SARS-CoV-2 Negative n = 1453						p1	p2
	Type A	Type B	Type AB	Type O	Rh +	Rh −	Type A	Type B	Type AB	Type O	Rh +	Rh −	0.312	0.186
	544 (42.3)	154 (12.0)	54 (4.2)	535 (41.6)	1144/1286 (−89.0)	142/1286 (−11.0)	619 (42.6)	158 (10.9)	45 (3.1)	631 (43.4)	1267/1451 (−87.3)	184/1451 (−12.7)		
Maternal age (years; mean/ range)	32.6 (18–49)	31.9 (18–48)	33 (21–47)	31.8 (18–48)	32.1 (18–49)	32.7 (18–44)	32.2 (18–49)	31.6 (18–44)	31.9 (21–45)	31.9 (18–46)	32 (18–49)	32 (18–42)	0.359	0.288
Maternal Age Range													<0.05[a]	<0.05[b]
18–24	59 (11.0)	17 (11.0)	6 (11.1)	91 (17.1)	159 (14.0)	14 (9.9)	74 (12.2)	21 (13.5)	2 (4.8)	61 (9.7)	135 (10.8)	22 (12.2)		
25–34	258 (48.0)	89 (57.8)	25 (46.3)	237 (44.6)	540 (47.6)	68 (48.2)	312 (51.3)	85 (54.8)	27 (64.3)	355 (56.6)	689 (55.1)	89 (49.4)		
35–49	221 (41.1)	48 (31.2)	23 (42.6)	203 (38.2)	436 (38.4)	59 (41.8)	222 (36.5)	49 (31.6)	13 (31.0)	211 (33.7)	426 (34.1)	69 (38.3)		
Ethnicity													<0.05[c]	<0.001
White European	364/542 (67.2)	86/153 (56.2)	40 (74.1)	268 (50.1)	647/1142 (56.7)	111/141 (–78.7)	509/616 (82.6)	115/157 (73.2)	31/44 (70.5)	458/629 (72.8)	943/1260 (74.8)	169 (91.8)		
Latino Americans	118/542 (21.8)	29/153 (19.0)	7 (13.0)	203 (37.9)	336/1142 (29.4)	20/141 (14.2)	41/616 (6.7)	10/157 (6.4)	1/44 (2.3)	93/629 (14.8)	143/1260 (11.3)	2 (1.1)		
Arab	39/542 (7.2)	19/153 (12.4)	5 (9.3)	37 (6.9)	93/1142 (8.1)	7/141 (5.0)	51/616 (8.3)	16/157 (10.2)	8/44 (18.2)	56/629 (8.9)	121/1260 (9.6)	10 (5.4)		
Asian non-Hispanic	10/542 (1.8)	14/153 (9.2)	1 (1.9)	12 (2.2)	36/1142 (3.2)	1/141 (0.7)	13/616 (2.1)	8/157 (5.1)	4/44 (9.1)	14/629 (2.2)	36/1260 (2.9)	2 (1.1)		
Black non-Hispanic	11/542 (2.0)	5/153 (3.3)	1 (1.9)	15 (2.8)	30/1142 (2.6)	2/141 (1.4)	2/616 (0.3)	8/157 (5.1)	0/44 (0.0)	8/629 (1.3)	17/1260 (1.3)	1 (0.5)		

Data are shown as n (% of total), except for maternal age.
p1: comparison by blood group distribution (A, B, AB and O) between SARS-CoV-2 (+) and SARS-CoV-2 (−) patients.
p2: comparison by Rh type (+/-) between SARS-CoV-2 (+) and SARS-CoV-2 (−) patients.
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.
[a] due to differences between O SARS-CoV-2 (+) and O SARS-CoV-2 (−) ($p < 0.001$).
[b] due to differences between Rh+ SARS-CoV-2 (+) and Rh+ SARS-CoV-2 (−) ($p < 0.001$).
[c] with the exception of AB SARS-CoV-2 (+) vs AB SARS-CoV-2 (−) ($p = 0.085$).

Table 2
Maternal comorbidities, current obstetric history and clinical presentation of SARS-CoV-2 infection, stratified by blood group (A vs non-A, O vs non-O, A+AB vs B+O and Rh +/−).

	Group A	Group Non-A [a]	p-value	Group O	Group Non-O [b]	p-value	Group A+AB	Group B+O	p-value	Group Rh +	Group Rh −	p-value
Number (%)	544 (42.3)	743 (57.7)	–	535 (41.6)	752 (58.4)	–	598 (46.5)	689 (53.5)	–	1144 (89.0)	142 (11.0)	–
Maternal comorbidities												
Obesity (BMI > 30 kg/m^2)	94 (17.9)	133 (18.3)	0.842	97 (18.7)	130 (17.8)	0.702	100 (17.3)	127 (18.9)	0.465	209 (18.8)	17 (12.1)	0.054
Pulmonary comorbidities	23 (4.2)	29 (3.9)	0.770	18 (3.4)	34 (4.5)	0.301	26 (4.3)	26 (3.8)	0.602	44 (3.8)	8 (5.6)	0.311
Other comorbidities	21 (3.9)	30 (4.0)	0.872	19 (3.6)	32 (4.3)	0.524	23 (3.8)	28 (4.1)	0.842	40 (3.5)	11 (7.7)	0.017
Current obstetric history												
Multiple pregnancy	9 (1.7)	15 (2.0)	0.633	10 (1.9)	14 (1.9)	0.992	11 (1.8)	13 (1.9)	0.950	17 (1.5)	7 (4.9)	0.007
In Vitro Fertilization	33 (6.1)	38 (5.1)	0.461	23 (4.3)	48 (6.4)	0.110	41 (6.9)	30 (4.4)	0.052	58 (5.1)	13 (9.2)	0.050
Haemoglobin < 10 g/dL Platelets < 100,000/μL	24 (4.4)	38 (5.1)	0.830	25 (4.7)	37 (4.9)	0.650	27 (4.5)	35 (5.1)	0.936	60 (5.2)	3 (2.1)	0.093
Pregnancy-induced Hypertension	23 (4.2)	24 (3.2)	0.347	17 (3.2)	30 (4.0)	0.445	25 (4.2)	22 (3.2)	0.347	44 (3.8)	3 (2.1)	0.307
Gestational diabetes	36 (6.8)	57 (7.9)	0.485	38 (7.3)	55 (7.5)	0.869	40 (6.9)	53 (7.9)	0.499	85 (7.6)	8 (5.8)	0.443
SARS-CoV-2 Clinical presentation												
Asymptomatic (N = 654)	282 (51.8)	374 (50.3)	0.594	**248 (46.4)**	**408 (54.3)**	**0.005**	313 (52.3)	343 (49.8)	0.359	**567 (49.6)**	**88 (62.0)**	**0.006**
Symptomatic (N = 633)	262 (48.2)	369 (49.7)		**287 (53.6)**	**344 (45.7)**		285 (47.7)	346 (50.2)		**577 (50.4)**	**54 (38.0)**	
Mild symptoms	192 (73.3)	253 (68.6)	0.200	195 (67.9)	250 (72.7)	0.195	211 (74.0)	234 (67.6)	0.079	406 (70.4)	39 (72.2)	0.775
Severe symptoms	70 (26.7)	116 (31.4)		92 (32.1)	94 (27.3)		74 (26.0)	112 (32.4)		171 (29.6)	15 (27.8)	
Mild-moderate pneumonia	57 (81.4)	103 (88.8)	0.164	82 (89.1)	78 (83.0)	0.229	60 (81.1)	100 (89.3)	0.118	146 (85.4)	14 (93.3)	0.408
Severe pneumonia/Shock	13 (18.6) (0.4)	13 (11.2) (0.3)		10 (10.9) (0.2)	16 (17.0) (0.4)		14 (18.9) (0.5)	12 (10.7) (0.1)		25 (14.6) (0.3)	1 (6.7) (0.7)	

Data are shown as n (% of total). In bold: statistical significant differences between blood groups in the univariate analysis.
[a] Group non-A: AB+B+O blood types.
[b] Group non-O: A+AB+B blood types; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

(number). The possible association of ABO and Rh blood group with maternal and perinatal outcomes was analyzed using the Pearson's Chi-square test or Fisher's exact test and the Mann–Whitney *U* test (after checking the absence of normality of the data using the Kolmogorov-Smirnov test). Statistical tests were two-sided and were performed with SPSS V.20 (IBM Inc., Chicago, Il, USA); statistically significant associations were considered to exist when the p value was less than 0.05.

For computing measures of association of ABO and Rh blood group with maternal and perinatal outcomes, variables statistically significant in the univariable analysis were controlled for maternal age and ethnicity in multivariable logistic regression modelling (and Poisson regression modelling) to derive adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). Modeling was performed after excluding pregnancies with missing data. Regression analyses were carried out using lme4 package in R, version 3.4 (RCoreTeam, 2017) [26].

Results

A cohort of 1278 SARS-CoV-2(+) pregnant women was analyzed Figure Supplementary figure 1. The comparison group of SARS-COV-2(−) patients was composed of 1453 mothers. Blood type distribution according to SARS-CoV-2 positivity and demographic characteristics of mothers is shown in Table 1. Differences were noted between blood types and Rh for age and ethnicity and there was a higher proportion of Latin American women in the SARS-CoV-2(+) group compared to the SARS-CoV-2(−) group (p < 0.05).

Maternal comorbidities, current obstetric history and clinical presentation of SARS-CoV-2 infection among positive pregnancies are shown in Table 2, whereas medical, obstetric and neonatal morbidity are compiled in Table 3, both tables stratified by blood group (A vs non-A, O vs non-O, A+AB vs B+O and Rh+/−); p-values correspond to the univariate analysis. Among SARS-CoV-2 infected pregnancies, no associations of blood groups with maternal comorbidities or the current obstetric history were observed (Table 2) nor with neonatal morbidity or maternal medical complications at delivery or (Table 3) except for PPROM that was more prevalent in patients of blood group A (p = 0.0023). After adjusting for maternal age and ethnicity (Table 4), the odds of symptomatic COVID-19 and hemorrhagic event were higher in Rh+ (vs Rh-) mothers (aOR 1.48, 95% CI 1.02–2.14, p = 0.037, and aOR 8.72, 95% CI 1.20–63.57, p = 0.033, respectively), and those of preterm premature rupture of membranes (PPROM) were higher among blood type A (vs non-A) mothers (aOR 2.06, 95% CI 1.01–4.18, p = 0.046).

Discussion

Main findings

This is the first prospective study with multivariable analysis to evaluate the association of ABO and Rh blood group with medical

Table 3
Medical, obstetric and neonatal morbidity, stratified by blood group (A vs non-A, O vs non-O, A+AB vs B+O and Rh +/−).

	Group A	Group Non-A [a]	p-value	Group O	Group Non-O [b]	p-value	Group A+AB	Group B+O	p-value	Group Rh +	Group Rh −	p-value
Number (%)	544 (42.3)	743 (57.7)	–	535 (41.6)	752 (58.4)	–	598 (46.5)	689 (53.5)	–	1144 (89.0)	142 (11.0)	–
Perinatal outcome												
Gestational age at delivery (weeks + days; mean/range)	38 + 4 (25–42)	38 + 6 (23–42)	0.711	38 + 5 (24–42)	38 + 5 (23–42)	0.482	38 + 4 (23–42)	38 + 5 (24–42)	0.488	38 + 6 (23–42)	38 + 6 (26–41)	0.830
Cesarean delivery	163 (30.0)	190 (25.7)	0.089	132 (24.8)	221 (29.4)	0.065	175 (29.3)	178 (25.9)	0.173	310 (27.1)	43 (30.5)	0.401
Preterm deliveries (<37 weeks of gest age)	67 (12.3)	74 (10.0)	0.181	48 (9.0)	93 (12.4)	0.056	75 (12.5)	66 (9.6)	0.091	124 (10.8)	17 (12.0)	0.684
PROM	84 (15.4)	112 (15.1)	0.856	81 (15.1)	115 (15.3)	0.940	93 (15.6)	103 (14.9)	0.764	174 (15.2)	22 (15.5)	0.929
PPROM	**21 (3.9)**	**13 (1.7)**	**0.023**	11 (2.1)	23 (3.1)	0.272	21 (3.5)	13 (1.9)	0.074	29 (2.5)	5 (3.5)	0.491
Medical complications												
TE events/Pulmonary embolism	5 (0.9)	6 (0.8)	0.830	4 (0.7)	7 (0.9)	0.725	6 (1.0)	5 (0.7)	0.591	11 (1.0)	0 (0.0)	0.973
Deep venous thrombosis	3 (0.6)	3 (0.4)	0.702	2 (0.4)	4 (0.5)	0.683	4 (0.7)	2 (0.3)	0.333	6 (0.5)	0 (0.0)	0.971
Pulmonary embolism	4 (0.7)	4 (0.5)	0.658	3 (0.6)	5 (0.7)	0.815	4 (0.7)	4 (0.6)	0.841	8 (0.7)	0 (0.0)	0.965
Pneumonia with ICU admission	13 (2.4)	11 (1.5)	0.164	8 (1.5)	16 (2.1)	0.229	14 (2.3)	10 (1.5)	0.118	23 (2.0)	1 (0.7)	0.408
Admitted in ICU	19 (3.5)	16 (2.2)	0.148	12 (2.2)	23 (3.1)	0.377	20 (3.3)	15 (2.2)	0.202	33 (2.9)	2 (1.4)	0.318
Invasive ventilation	9 (1.7)	8 (1.1)	0.248	5 (0.9)	12 (1.6)	0.312	10 (1.7)	7 (1.0)	0.309	16 (1.4)	1 (0.7)	0.503
Obstetrical complications												
Hemorrhagic events	30 (5.5)	40 (5.4)	0.918	35 (6.5)	35 (4.7)	0.143	31 (5.2)	39 (5.7)	0.707	**69 (6.0)**	**1 (0.7)**	**0.029**
Abruptio placentae	7 (1.3)	4 (0.5)	0.165	4 (0.7)	7 (0.9)	0.726	7 (1.2)	4 (0.6)	0.261	11 (1.0)	0 (0.0)	0.974
Postpartum hemorrhage	23 (4.2)	37 (5.0)	0.528	32 (6.0)	28 (3.7)	0.061	24 (4.0)	36 (5.2)	0.301	**59 (5.2)**	**1 (0.7)**	**0.044**
Gestational hypertensive disorders	30 (5.5)	36 (4.8)	0.669	23 (4.3)	43 (5.9)	0.219	35 (5.9)	32 (4.6)	0.331	60 (5.3)	6 (4.2)	0.577
Maternal mortality	2 (0.4)	0 (0.0)	0.958	0 (0.0)	2 (0.3)	0.948	2 (0.3)	0 (0.0)	0.940	2 (0.2)	0 (0.0)	0.974
Stillbirth	2 (0.4)	8 (1.1)	0.172	4 (0.7)	6 (0.8)	0.919	2 (0.3)	8 (1.2)	0.114	9 (0.8)	1 (0.7)	0.916
Neonatal data												
Umbilical artery pH < 7.10	16 (3.7)	20 (3.3)	0.722	10 (2.3)	26 (4.4)	0.086	17 (3.6)	19 (3.4)	0.868	31 (3.4)	5 (4.2)	0.677
Admitted in NICU number	52 (9.6)	74 (10.0)	0.811	52 (9.7)	74 (9.8)	0.942	57 (9.5)	69 (10.0)	0.771	112 (9.8)	14 (9.9)	0.979
Neonatal mortality	2 (0.4)	2 (0.3)	0.754	1 (0.2)	3 (0.4)	0.511	3 (0.5)	1 (0.1)	0.282	3 (0.3)	1 (0.7)	0.391

Data are shown as n (% of total). In bold: statistical significant differences between blood groups in the univariate analysis.
[a] Group non-A: AB+B+O blood types.
[b] Group non-O: A+AB+B blood types; PROM: Premature rupture of membranes; PPROM: Preterm Premature Rupture of Membranes; TE events: Thromboembolic events; ICU: Intensive Care Unit.

and obstetric morbidity in SARS-CoV-2 infected mothers. We found that the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of perinatal outcomes, blood group A was associated to PPROM, and regarding obstetric complications Rh+ patients developed more hemorrhagic events, in particular, more postpartum hemorrhage.

Strengths and limitations

The main strength of our work is the large cohort of SARS-CoV-2 positive deliveries (1287) from 78 centers across Spain, adding to the reliability and generalizability of its findings. Our blood type comparison group was representative since was is not a historical cohort but a group of pregnant patients recruited from the same hospitals and at the same time as the SARS-CoV-2 positive group. The main known risk factors for morbidity associated with SARS-CoV-2 infection were included in the analysis, such as age, presence of medical comorbidities and clinical severity. Additionally, we carried out a detailed analysis of medical, obstetric and neonatal complications as well as to have evaluated the relationship between ABO blood groups both simply and associatively (Type A vs Type No A, Type O vs Type No O and Type A+AB vs Type B+O). The main limitations of our study were the following: symptomatic patients are over-represented in our study population since not all participating hospitals had a universal antenatal screening program for SARS-CoV-2 infection (so only identified symptomatic cases by passive surveillance) or implemented the program later; and that early and universal prescription of LMWH thromboembolism prophylaxis in SARS-CoV-2+ pregnant patients could have influenced our results.

Interpretation

It has been suggested that ABO blood group system is related to many bacterial and viral infections, such as helicobacter pylori,

Table 4
Odds Ratio and adjusted Odds Ratio for outcomes associated with blood group in SARS-CoV-2 infected pregnancies.

SARS-CoV-2 Positive (N = 1287) Number (%)	Group A 544 (42.2%)	Group Non-A [a] 743 (57.8%)	OR (95%CI)	aOR* (95%CI)	Group O 535 (41.5%)	Group Non-O [b] 752 (58.5%)	OR (95%CI)	aOR* (95%CI)	Group Rh+ 1144 (88.8%)	Group Rh− 142 (11.2%)	OR (95%CI)	aOR* (95%CI)
Clinical presentation of SARS-CoV-2 infection												
Asymptomatic (N = 654)					**248 (46.4)**	**408 (54.3)**	**1.37 (1.10–1.71)**	1.19 (0.94–1.51)	**567 (49.6)**	**88 (62.0)**	**1.66 (1.16–2.37)**	**1.48 (1.02–2.14)**
Symptomatic (N = 633)					**287 (53.6)**	**344 (45.7)**			**577 (50.4)**	**54 (38.0)**		
Perinatal outcomes												
PPROM	**21 (3.9)**	**13 (1.7)**	**2.25 (1.12–4.54)**	**2.06 (1.01–4.18)**								
Obstetrical complications												
Hemorrhagic events									**69 (6.0)**	**1 (0.7)**	**9.05 (1.25–65.66)**	**8.72 (1.20–63.57)** [§]
Postpartum hemorrhage									**59 (5.2)**	**1 (0.7)**	**7.67 (1.05–55.76)**	**7.55 (1.03–55.22)** [§]

Data are shown as n (% of total). In bold: statistical significant differences between blood groups.
PROM: Premature rupture of membranes; PPROM: Preterm Premature Rupture of Membranes; TE events: Thromboembolic events; ICU: Intensive Care Unit.
* Odds Ratio adjusted for maternal age and ethnicity.
§ Poisson regression modelling, adjusting for maternal age and ethnicity, was also applied: Hemorrhagic events aIRR = 8.21 (1.14–59.31), p-value = 0.037; Postpartum hemorrhage aIRR = 7.15 (0.99–51.77), p-value = 0.052.
[a] Group non-A: AB + B + O blood types.
[b] Group non-O: A + AB + B blood types.

norovirus, HBV, SARS-CoV and MERS-CoV [27–30]. Recently, several studies about COVID-19 in China and America discovered relationships between ABO blood group and COVID–19 infection, severity and demise in general population [15–18]. About the association between ABO blood groups and infectivity due to SARS-CoV-2, initial studies assessed a greater risk of infectivity in the A blood group [15–18] and that O blood group protects from infection [15,16,18,31]. However, Dzilk et al. [32] performed a re-evaluation of the data from those studies and did not observe an association between the ABO blood groups and the risk of infection by SARS-CoV-2. There is even greater controversy between the association of the ABO blood group and COVID-19 severity and mortality. According to Wu et al. [15], AB blood group is associated with greater severity and mortality, while Zhao et al. [17] affirmed that A blood group is the one with the greatest association with severity of the disease. Nevertheless, different authors agreed that the O blood group is the one associated to milder symptoms [15–18,31]. These associations are not causal, and need further investigation [33].

In our study, we found the presence of Rh− status protective in terms of development of COVID-19 after adjusting for maternal age and ethnicity, in line with Ray et al findings [31]. In terms of obstetric outcomes, blood group A was associated to PPROM. No other adverse obstetric outcomes associations were detected. The early and universal prescription of LMWH thromboembolism prophylaxis in those pregnant patients could have influenced our results. On the other hand, Rh+ patients developed more postpartum haemorrhagic events; we still do not have any explanation for this association, but SARS-CoV-2 infection induces an inflammatory state that could potentially explain this condition.

The reason why the ABO blood group could modify the infection and severity by COVID-19 is not yet fully known. Several mechanisms are suggested: firstly, ABO blood group is a specific antigen in the erythrocyte membrane, but it is also expressed in airway epithelial cells, alveolar epithelial cells and even in body fluids [34,35], thus, by means of receptor-mediated affinity binding, the difference in susceptibility to infection could be justified as occurs in other infections [36]. Blood group antigens have already been shown to be receptors used by some infectious microorganisms [37] and it seems that the adhesion of cells expressing the SARS-CoV S protein, could be specifically inhibited by anti-A antibodies [35]. In addition, SARS-CoV and SARS-CoV-2 have a similar nucleic acid sequence and a similar receptor combination with angiotensin converting enzyme 2 (ACE2) [38,39]. Therefore, anti-A antibodies could play a similar role in COVID-19. On the other hand, Koike et al. [39] suggest that anti-A and / or anti-B antibodies can neutralize the virus when polymorphic blood group antigens expressed on the surface of red blood cells and epithelia are used as receptors, as occurs in HIV infection [40]. Other authors [15] suggest that type O blood can prevent possible SARS-CoV-2 infections through rosette reduction mechanisms, like what occurs in severe plasmodium falciparum malaria. In addition, the existence of high levels of factor VIII and von Willebrand factor is known in non-O blood group [41], especially A blood group [41], and this situation favors the presence of arterial and venous thrombosis [42]. Finally, there seems to be an association between the presence of no O blood group (particularly the A1A1 / A1B / BB groups) and the risk of venous thrombosis [41].

Conclusion

According to our study the presence of Rh− status was protective in terms of development of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of perinatal and obstetric outcomes, blood group A was associated to PPROM

and Rh+ patients developed more hemorrhagic events, in particular, more postpartum hemorrhage.

Contribution to authorship

Concept and design: JAS, OM-P and MdlCC; Data acquisition: JASB, LCG, AA-S, MVRG, RLP, AMFA, RAS, MMO, AC-SO, OM-P and SOEG; Statistical analysis: MdlCC, JASB, AC-SO and OMP; Drafting of manuscript: JASB, MdlCC and OMP; Review of manuscript: JASB, LCG, AA-S, MVRG, RLP, AMFA, MdlCC, RAS, MMO, AC-SO, OM-P and SOEG.

Details of ethics approval

All procedures were approved by Puerta de Hierro University Hospital (Madrid, Spain) ethics committees on 23rd March 2020 (registration number, 55/20).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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