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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.

Keywords:
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Maternal morbidity

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.
SARS-CoV-2 positive mothers. COVID-19 and obstetric morbidity in a pregnancy cohort of type O blood groups [15–18]. In individuals with type A blood whereas there is a lower risk in such a way that there is a greater risk of infection and severity blood groups and COVID-19 infection, severity and demise exists recently, it has been reported that the association between ABO both in general population [13] and in pregnant women [14]. 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).

This project was supported by public funds obtained in competitive calls: Grant COVID20/00021 (EUR 43,000 from the Instituto de Salud Carlos III—Spanish Ministry of Health and co-financed with Fondo Europeo de Desarrollo Regional (FEDER) funds.

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 prematurity 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–Wilks 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 | SARS-CoV-2 Negative |
|----------------------|---------------------|---------------------|
|                      | n = 1287            | n = 1453            |
|                      | Type A   | Type B   | Type O  | Rh + | Rh – | Type A   | Type B   | Type O  | Rh + | Rh – |
|                      | 54 (42.3) | 154 (12.0) | 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) | Maternal Age Range | Ethnicity |
|----------------------|----------------------------------|--------------------|----------|
|                      | 32.6 (18–49)                     | <0.05a             | White European |
|                      | 31.9 (18–48)                     | <0.05b             | Latino Americans |
|                      | 33 (21–47)                       | 0.312              | Arab |
|                      | 31.8 (18–48)                     | 0.359              | Asian non-Hispanic |
|                      | 32.1 (18–49)                     | 0.186              | Black non-Hispanic |
|                      | 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                            |                    |          |
|                      | 0.186                            |                    |          |

Maternal age (years; mean/range) 32.6 (18–49) vs 31.9 (18–48) p = 0.359.
Maternal Age Range 18–24 vs 25–34 p < 0.05a vs 0.05b.
Ethnicity White European 364/542 (67.2) vs 86/153 (56.2) p = 0.001.

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).
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 +/-).

| Number (%) | Maternal comorbidities | Group A | Group Non-A | p-value | Group O | Group Non-O | p-value | Group A+AB | Group B+O | p-value | Group Rh+ | Group Rh- | p-value |
|------------|------------------------|---------|-------------|---------|---------|-------------|---------|------------|-----------|---------|-----------|-----------|---------|
| 544        | Obesity                | 94      | 133         | 0.842   | 97      | 130         | 0.702   | 100        | 127      | 0.465   | 209       | 17       | 0.054   |
|            | (BMI > 30 kg/m²)       | (17.9)  | (18.3)      | (18.7)  | (17.8)  | (17.3)      | (18.9)  | (18.8)     | (12.1)   |         | (8)       | (8)       |         |
| 23         | Pulmonary comorbidities| 29      | 770         | 0.770   | 18      | 34          | 0.301   | 26         | 26       | 0.602   | 44        | 8        | 0.311   |
|            | (4.2)                  | (3.9)   | (3.4)       | (4.5)   | (4.3)   | (3.8)       | (3.8)   | (3.8)      | (3.6)    |         | (4)       | (6)       |         |
| 21         | Other comorbidities    | 30      | 872         | 0.872   | 19      | 32          | 0.524   | 23         | 28       | 0.842   | 40        | 11       | 0.017   |
|            | (3.9)                  | (4.0)   | (3.6)       | (4.3)   | (3.8)   | (4.1)       | (3.5)   | (7.7)      |           |         |           |           |         |
| Current obstetric history |                       |         |             |         |         |             |         |           |           |         |           |           |         |
| Multiple pregnancy |                      | 9       | 15          | 0.633   | 10      | 14          | 0.992   | 11         | 13       | 0.950   | 17        | 7        | 0.007   |
| In Vitro Fertilization |                    | 33      | 38          | 0.461   | 23      | 48          | 0.110   | 41         | 30       | 0.052   | 18        | 13       | 0.050   |
| Haemoglobin < 10 g/dL |                     | (6.1)   | (5.1)       | (4.3)   | (6.4)   | (6.9)       | (4.4)   | (5.1)      | (9.2)    |         |           |           |         |
| Platelets < 100,000/μL |                   | (24)    | 38          | 0.830   | 25      | 37          | 0.650   | 27         | 35       | 0.936   | 60        | 3        | 0.093   |
| Pregnancy-induced Hypertension |              | (4.4)   | (5.1)       | (4.7)   | (4.9)   | (4.5)       | (5.1)   | (5.2)      | (2.1)    |         |           |           |         |
| Gestational diabetes |                      | (24)    | 24          | 0.347   | 17      | 30          | 0.445   | 25         | 22       | 0.347   | 44        | 3        | 0.307   |
| SARS-CoV-2 Clinical presentation |               | (36)    | 57          | 0.485   | 38      | 55          | 0.869   | 40         | 53       | 0.499   | 85        | 8        | 0.443   |
| Asymptomatic (N = 654) |                 | (6.8)   | (7.9)       | (7.3)   | (7.5)   | (6.9)       | (7.9)   | (7.6)      | (5.8)    |         |           |           |         |
| Symptomatic (N = 633) |                  | (282)   | 374         | 0.594   | 248     | 408         | 0.005   | 313        | 343      | 0.359   | 567       | 88       | 0.006   |
| Mild symptoms |                    | (51.8)  | (50.3)      | (46.4)  | (54.3)  | (52.3)      | (49.8)  | (49.6)     | (62.0)   |         | (57)      | (54)     |         |
| Severe symptoms |                    | (262)   | 369         | 0.344   | 287     | 45.7        | 0.757   | 285        | 346      | 0.775   |           |           |         |
| Mild-moderate pneumonia |                 | (48.2)  | (49.7)      | (53.6)  | (45.7)  | (47.7)      | (50.2)  | (50.4)     | (38.0)   |         |           |           |         |
| Severe pneumonia/Shock |                  | (73.3)  | (68.6)      | (67.9)  | (72.7)  | (74.0)      | (67.6)  | (70.4)     | (72.2)   |         |           |           |         |

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 blood types; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

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 2.60, 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...
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 with PROM, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of obstetric complications, blood group A was associated with PPROM, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of neonatal outcomes, blood group A was associated with NEC, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of medical complications, blood group A was associated with TE events, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of obstetrical complications, blood group A was associated with hemorrhagic events, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity. In terms of neonatal morbidity, blood group A was associated with postpartum hemorrhage, and the Rh− status was associated with a lower risk of symptomatic COVID-19 after adjusting for maternal age and ethnicity.

**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 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. |
|---------------------------------------------------------------|
| Odds Ratio (OR) adjusted for maternal age and ethnicity. |
| Group | OR (95% CI) | aOR* (95% CI) |
|-------|-------------|---------------|
| SARS-CoV-2 Positive | 1.19 (1.02–1.40) | 1.48 (1.20–2.37) |
| Non-O | 1.16 (0.99–1.37) | 1.48 (1.20–2.37) |
| A | 1.19 (1.02–1.40) | 1.48 (1.20–2.37) |
| AB | 1.16 (0.99–1.37) | 1.48 (1.20–2.37) |

Clinical presentation of SARS-CoV-2 infection

- Asymptomatic (N = 654)
  - 408 (54.3%)
  - 484 (45.7%)

Perinatal outcomes

- PPROM
  - 248 (1.17) (95% CI: 1.10–1.71)
  - 577 (1.17) (95% CI: 1.10–1.71)

Obstetrical complications

- Hemorrhagic events
  - 69 (1.05–65.76)
  - 59 (1.03–65.57)

Postpartum hemorrhage

- 1 (1.03–55.76)

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.

§ 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.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2021.07.008.

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