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ORIGINAL ARTICLE

SARS-CoV-2 in pregnancy: characteristics and outcomes of hospitalized and non-hospitalized women due to COVID-19

Patricia Barbero[a], Laura Mugüerza[a], Ignacio Herraiz[b], Antonio García Burguillo[a], Rafael San Juan[c], Laura Forcén[a], Inmaculada Mejía[a], Emma Batllori[a], María Dolores Montañez[a], Paloma Vallejo[a], Olga Villar[a], Diana García Alcazar[a] and Alberto Galindo[b]

[a]Perinatal Medicine Unit, Department of Obstetrics and Gynecology, Hospital Universitario "12 de Octubre", Madrid, Spain; [b]Fetal Medicine Unit-SAMID, Department of Obstetrics and Gynecology, Hospital Universitario 12 de Octubre. Instituto de Investigación Hospital 12 de Octubre (imas12), Universidad Complutense de Madrid, Madrid, Spain; [c]Infectious Diseases Unit, Hospital Universitario "12 de Octubre", Madrid, Spain

ABSTRACT

Background: There is little evidence about how novel coronavirus (SARS-CoV-2) affects pregnant women and their newborns. Comparisons with other members of the coronavirus family responsible for severe acute respiratory syndrome (SARS) have been done to predict maternal and neonatal outcomes; however, more information is required to establish clinical patterns, disease evolution and pregnancy prognosis in this group of patients.

Methods: This paper is reporting a series of 91 women diagnosed with SARS-CoV-2 infection during pregnancy and puerperium. The analysis showed that 40 patients developed pneumonia, bilateral in most cases, with a 46.2% rate of hospitalization and 4 patients requiring intensive care unit (ICU) admission. In confront with previous publications, we have found a higher rate of coronavirus disease (COVID-19) severe forms, even when compared to non-pregnant women with the same baseline characteristics. We have analyzed the demographic characteristics, pregnancy-related conditions and presenting symptoms to identify features that could determine which patients will need hospitalization because of COVID-19 (Group 1-G1) and those who not (Group 2-G2). We have found that obesity and Latin-American origin behave as risk factors: OR: 4.3; 95% CI: 1.4–13.2, and OR: 2.6; 95% CI: 1.1 − 6.2, respectively. Among the 23 patients that delivered with active SARS-CoV-2, the overall rate of cesarean section (CS) and preterm birth were 52.2% and 34.8%, respectively, but we observed that the rate of CS was even higher in G1 compared to G2: 81.8% versus 25%, $p = .012$. However, prematurity was equally distributed in both groups and only one preterm delivery was determined by poor maternal condition. There were no deaths among the patients neither their newborns.

Conclusion: In conclusion, the results of our cohort reveal that SARSC-CoV-2 infection may not behave as mild as suggested during pregnancy, especially when factors as obesity or Latin-American origin are present. No evidence of late vertical transmission was noticed but prematurity and high CS rate were common findings, although it is difficult to establish any causality between these conditions and COVID-19. Further evidence is required to establish if pregnancy itself can lead to severe forms of COVID-19 disease and whether risk factors for the general population are applicable to obstetric patients. Until larger studies are available, pregnant women should be monitored carefully to anticipate severe complications.

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SARS-CoV-2; COVID-19; pregnancy; pneumonia; risk factors; vertical transmission

Introduction

Currently, there is limited evidence on the particularities of the novel SARS-CoV-2 infection in pregnant women, its effects on the pregnancy course, or how pregnancy status and maternal characteristics could influence the evolution of the disease [1–3]. Largest reports in obstetric patients have described a wide spectrum of manifestations, varying from asymptomatic to severe forms of the disease [4,5]. Advanced age, male sex and preexisting conditions, especially obesity and hypertensive disorders have been proposed as risk factors for COVID-19 severity in general population, but there is scarce information about the

CONTACT Patricia Barbero patricia.barbero.casado@gmail.com Perinatal Medicine Unit. Department of Obstetrics and Gynecology, Hospital Universitario "12 de Octubre", Avda. de Córdoba, s/n, Madrid, 28041, Spain

Supplemental data for this article can be accessed here.

Due to the urgent and developing nature of the topic, this paper was accepted after an expedited peer review process. For more information about the process, please refer to the Instructions for Authors.

baseline characteristics or clinical features that may contribute to an increased risk among obstetric patients [6]. When considering the perinatal outcomes, a higher percentage of premature rupture of membranes (PROM), preterm delivery and fetal distress have been reported, while late vertical transmission seems to be an unlikely fact [7,8].

In the present study, we analyze the maternal characteristics and clinical presentation of SARS-CoV-2 infection in pregnant women during the 12 weeks that followed the diagnosis of the first case in our department, aiming to identify specific features associated with an increased need for hospitalization due to COVID-19 as a surrogate of severity. In addition, we compared the perinatal outcomes between hospitalized and non-hospitalized women by COVID-19 with the objective to determine if the severity of the infection may affect the pregnancy course.

Methods

Study design and patients

This observational retrospective cohort study included all women diagnosed with SARS-CoV-2 infection during pregnancy or postpartum period ($\leq$40 days from date of birth) from 3 March to 31 May 2020 in our tertiary care center.

Pregnant women presenting at the hospital (including Labor and Delivery Unit, Obstetric Emergencies Department and pregnancy consultations) with SARS-CoV-2 infection symptoms were tested with Reverse Transcription Polymerase Chain Reaction (RT-PCR) in nasopharyngeal (NP) swab. These symptoms included fever ($\geq$37.8 °C), dry cough, shortness of breath or dyspnea, chills and myalgia, headache, coryza and new onset of loss of taste or smell [9]. Chest X-ray with abdominal lead shields was performed in case of acute respiratory symptoms or oxygen saturation $<$95%. SARS-CoV-2 infection was diagnosed when the RT-PCR test resulted positive or if the radiological findings in chest X-ray highly suggested COVID-19 despite of two consecutive negative RT-PCR test performed 24 h apart [10]. Complementary to the diagnosis of symptomatic cases, screening with NP swab of asymptomatic patients admitted to hospital for scheduled procedures was started on 31st March 2020 and extended to all patients admitted to the OB/GYN department on 8th April 2020.

All patients were examined by an OB/GYN consultant. The initial assessment included vital signs (temperature, blood pressure, heart rate, respiratory rate and oxygen saturation) and lung auscultation. Laboratory tests including hemogram, C-reactive protein (CRP) and hepatorenal function were recommended only if the initial examination was abnormal. Ultrasound assessment of fetal vitality and, in addition, fetal heart rate monitoring in the 3rd trimester was performed.

The need for hospitalization as well as the type of treatment administered were consulted with our hospital's COVID-19 support team and depended on the hospital protocol at the time of diagnosis. Pneumonia itself was not a reason for hospitalization and complementary criteria as respiratory rate $>$30 rpm and basal oxygen saturation $<$95% were used [11]. Out-patient follow up included daily telephone contact to assess the evolution of symptoms and new onset of alarm signs.

Iatrogenic decision to deliver in COVID-19 patients was limited to women with severe clinical deterioration, mainly when respiratory condition did not improve despite therapy and oxygen support. Vaginal delivery was attempted whenever there were no contraindications for it.

All mothers received exhaustive information about skin-to-skin contact and breastfeeding, including preventing measures to avoid neonatal contagion, in order to facilitate their informed decision-making and avoiding routine separation of the mother and the healthy newborn. In order to assess the possibility of vertical transmission, NP swab was performed in neonates born from mothers with active infection 2 h after delivery. The neonates whose mothers were diagnosed during the puerperium underwent NP swab immediately after such diagnosis. All neonates were clinically followed during the first 14 days by the infectious diseases pediatric team.

Data collection and statistical analysis

Hospitalization due to COVID-19 was considered the dependent variable and patients were divided into two groups depending on if they were admitted because of COVID-19 (group 1-G1) or not (group 2-G2). G2 included out-patients and women who required hospitalization for obstetrical reasons. Independent variables analyzed were divided into baseline characteristics, obstetric conditions, presenting symptoms and complementary test results at diagnosis. Data were retrospectively gathered from our hospital's Health Care Information System (HCIS). Our local Research Ethics Committee approved the study (PI20/180). Verbal informed consent was obtained from all women but written informed consent was omitted considering the restrictions associated with the lockdown ordered by our government.

Continuous variables were expressed as means (standard deviations [SD]) or medians (interquartile ranges [IQR]) and compared using Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical variables were summarized as counts and percentages and examined with the chi-squared or Fisher's exact test. The statistical analysis was performed with SPSS for Windows version 22 (SPSS, Chicago, IL, USA) software.

Results

A total of 91 patients were included. Most (83, 91.2%) tested positive for SARS-CoV-2 in NP swab, six patients (7.7%) were negative and two early pregnancies were not tested, but their radiological findings were highly suggestive of COVID-19.

Most women suffered the infection during the 3rd trimester (40, 57.1%), with a mean gestational age (GA) of 28 ± 8 weeks, while four patients were diagnosed in puerperium (range 1–6 days).

COVID-19 symptoms were the main reason to consult in 56 patients (61.5%), while 30 women (33%) were identified to have at least one of the possible clinical features of COVID-19 when they came to the OB/GYN emergency department consulting for obstetrics reasons or during their pregnancy follow-up. Coinciding with active SARS-CoV-2 infection, 14 patients (15.4%) required admission for obstetric reasons, of which five were already hospitalized for obstetric complications before developing COVID-19 symptoms: 3 preterm PROM (PPROM), 1 monoamniotic twin pregnancy admitted for fetal monitoring and 1 threatened preterm labor. Only in one case the symptoms appeared within the first week of admission. Five women (5.5%) were diagnosed as part of the screening of asymptomatic patients admitted to the hospital, although three of them reported mild recent symptoms after knowing the result. One experienced respiratory deterioration within the first postpartum day.

At diagnosis, 34 (37.4%) women met admission criteria. Ten out of the remaining 57 patients were referred to the hospital for reevaluation in the following days (range of referral 2–5 days) and eight (14%) were finally hospitalized after respiratory deterioration. Therefore, the final number of patients in G1 was 42 (46.2%).

Risk factors for hospitalization due to COVID-19 in obstetric patients

When comparing baseline characteristics between the two groups, patients in G1 were significantly older and have a higher pregestational body mass index (BMI) compared to G2: 34.5(11) versus 32(9) years, $p = .034$, and 27.9 ± 4.7 versus $24.5 \pm 4.0\ kg/m^2$, $p = .001$, respectively. The need for hospitalization for COVID-19 was 4-fold increased among women with obesity (OR: 4.3; 95% CI: 1.4–13.2) and almost 3 times increased in Latin-American women (OR: 2.6; 95% CI: 1.1 − 6.2). Previous comorbidities and pregnancy aspects did not differ among the two groups.

Women that presented fever at the moment of diagnosis had a risk 3.3 times higher (95% CI: 1.3–8.6) to be admitted to the hospital. As expected, striking dyspnea was more frequently present in patients in G1 (30.1% versus 2.0%). Regarding the complementary tests performed, C-reactive protein (CRP) was significantly higher in G1 (6.3 ± 4.4 versus 2.7 ± 2.6 mg/dl) as well as elevated liver enzymes, that were present in 73.8% of COVID-19 admitted patients. Radiological findings at the moment of diagnosis showed a higher percentage of pneumonia in women of G1. Table 1 summarizes the main information regarding comparisons among the two groups.

Maternal treatment and follow up

G1 patients were treated with 400 mg single dose of hydroxychloroquine and then 200 mg/12h for 5–10 days, which was combined with azithromycin (500 mg/24h for three days) in 21 patients (50%) or broad-spectrum antibiotics in 17 patients (40.5%). In four cases (9.5%) antivirals as lopinavir/ritonavir or remdesivir were added to the hydroxychloroquine regime. 26 (61.9%) women needed oxygen support, with high flow requirements (≥10 L/min) in 10 cases (23.8%), of which nine also received immunomodulatory treatment with 400 mg single dose of tocilizumab.

Radiological findings consistent with pneumonia were present in 37 (88.1%), being bilateral in 32 and unilateral in 5 cases. ICU admission was limited to four women (4.4%) that required invasive mechanical ventilation (MV). Of note, two of them suffered from preeclampsia during their pregnancies. The most important characteristics of these four patients are summarized in Supplementary Table 3. There were 3 (6.1%) cases of unilateral pneumonia among G2 patients.

Prophylactic anticoagulation with low-molecular-weight heparin was administered to all women in G1 while they were hospitalized and to 19 (38.8%) women in G2. Heparin was maintained from two to four weeks depending on the severity of the disease.

Table 1. Comparison among patients hospitalized due to COVID-19 (G1) and those who did not required admission for COVID-19 reasons (G2).

	G1 42 (46.2%)	G2 49 (53.8%)	*p*
Baseline and obstetric characteristics			
Age, median [IQR]	34.5 [11]	32 [9]	.034
Origin [*n* (%)]			.178
Latin-American	30 (71.5)	24 (49.0)	**.029**
Caucasian	9 (21.4)	23 (46.9)	
Others	3 (7.1)	2 (4.1)	
Comorbidity [*n* (%)]	7 (16.6)	5 (10.2)	.363
Asthma	4 (9.5)	1 (2.0)	
Diabetes	2 (4.8)	0	
Chronic hypertension	0	2 (4.1)	
Others	1 (2.4)	2 (4.1)	
Pregestational BMI, kg/m^2 (mean ± SD)	27.9 ± 4.7	24.5 ± 4.0	**.001**
Obesity (BMI ≥ 30)	15 (35.7)	5 (10.2)	.009
Primiparous	16 (38.1)	19 (38.8)	.946
Singleton	42 (100)	46 (93.8)	.246
GA, weeks; median [IQR]	29 [9]	26 [18]	
Gestational trimester [*n* (%)]			.292
First	2 (4.8)	7(14.3)	
Second	16 (38.1)	19 (38.8)	
Third	23 (54.7)	20(40.8)	
Puerperium	1 (2.4)	3 (6.1)	
Pregnancy complications [*n* (%)]	7 (16.6)	6 (12.2)	.547
Preeclampsia	3 (7.1)	0	
Gestational diabetes	2 (4.8)	1 (2.0)	
Others	2 (4.8)	5 (10.2)	
Presenting symptoms [*n* (%)]			
Dry cough	37 (88.1)	33 (67.3)	.082
Fever	34 (80.9)	27 (55.1)	**.008**
Myalgia	19 (45.2)	16 (32.6)	.218
Headache	13 (30.9)	10 (20.4)	.248
Dyspnea	13 (30.1)	1 (2.0)	**<.001**
New loss of taste and/or smell	5 (11.9)	8 (16.3)	.547
Coryza	3 (7.1)	9 (21.4)	.114
Diarrhoea	1 (2.4)	4 (8.2)	.368
Asymptomatic	1 (2.4)	4 (8.2)	.368
Laboratory findings (at diagnosis[a])			
Performed [*n* (%)]	42 (100)	22 (44.9)	
CRP, mg/dl (mean ± SD)	6.3 ± 4.4	2.7 ± 2.6	**.004**
Lymphocyte count (mean ± SD)	997 ± 479	1122 ± 523	.344
↑ liver enzymes [*n* (%)]	31 (73.8)	7 (14.3)	**<.001**
Radiological findings (at diagnosis[a]) [*n* (%)]			
Performed	38 (90.5)	16 (32.7)	
Normal	4 (10.5)	9 (56.2)	**<.001**
Slight GGO	5 (13.2)	4 (25)	.424
Pneumonia	29 (76.3)	3 (18.8)	**<.001**
Bilateral	22 (57.9)	0 (0)	
Unilateral	7 (18.4)	3 (18.8)	

[a]Median symptoms 'onset – diagnosis 4(4) days' for both groups.
SD: standard deviation; BMI: body mass index; GA: gestational age; CRP: C-reactive protein; GGO: ground glass opacities.
Bold Values considered statistically significant.

There were no maternal deaths and all patients have been discharged from the hospital.

Perinatal outcomes

To date, 38 of the 87 women diagnosed during pregnancy have already delivered (43.7%). Among them, 15 patients were asymptomatic and had negativized RT-PCR in NP swab at the time of delivery.

We analyzed the perinatal outcomes among the 23 patients who delivered with active SARS-CoV-2 infection, founding a prematurity rate of 34.8% and a CS rate of 52.2%. Expediting delivery for worsening of the COVID-19 was needed in three cases, one of them in a very preterm pregnancy (28 weeks).

When comparing both study groups, a lower GA at delivery and a higher CS rate was observed in G1 compared to G2: 37(2.5) versus 39(5), $p = .036$, and 81.8% versus 25%, $p = .012$, respectively. Table 2 summarizes the main perinatal results of the two groups of the study.

All neonates tested with RT-PCR in NP-swab soon after birth were negative. Among the four babies whose mothers were diagnosed in the postpartum period, there was one positive result, diagnosed eight days after birth (the one whose mother was diagnosed in the 6th day of puerperium). The newborn showed

mild symptoms as tachypnea and vomits, with good clinical evolution. This transmission was more likely due to post-natal contact as no measures were initiated to avoid contagion until the mother was diagnosed. The clinical follow-up did not reveal suggestive symptoms in any of the other neonates.

Discussion

Results from our cluster of patients revealed a 46.2% rate of hospital admission, 44% of pneumonia and 5.5% of asymptomatic cases among obstetric patients infected with SARS-CoV-2. These data not just confronted with initial papers suggesting that pregnant women have a similar or lower risk for COVID-19 severity than the general population, but also doubles the hospitalization rate (15.8 – 21.9%) and ICU admission percentage (1.3 – 2.2%) reported for female patients in the same age range in Spain [12]. Therefore, obstetric patients could be considered as a risk group for COVID-19 severity, as expected, due to their susceptibility to viral infections and pneumonia development, although the ICU admission and mortality rates seem to be lower than SARS-CoV and MERS-CoV epidemics [13].

Aiming to find specific risk factors among pregnant women that could orientated clinicians to expect more severity in COVID-19 course, we obtained similar results than those published in the general population. Hospitalized patients were older and had a higher BMI, with an increased proportion of obese women that needed hospitalization. Latin-American women appeared to be not just over-represented among the total of infected patients (59.3%), but were also found to have an increased risk of developing more severe forms of COVID-19 that required hospitalization (71.5%). Although our hospital attends a multiracial population, data gathering from the deliveries assisted in 2019, revealed that 48.2% of the patients were Caucasian while Latin-American women represented 34.1% of the total. Similar findings regarding ethnicity differences have been described and hypothetical explanations are orientated toward socio-demographic circumstances, such as intergenerational cohabitation or cultural behaviors, rather than genetic or immunological particularities. Differential access to health-care services could explain severity disparities, with a delay in seeking medical care in patients who belong to ethnic minorities, whose follow-up in primary care is not guaranteed [14].

It was not possible to identify any obstetric feature that increased the risk of COVID-19 severe disease.

Table 2. Comparison of perinatal outcomes in patients that delivered with active SARS-CoV-2 infection.

	G1 11	G2 12	p^*
Delivery			
Symptoms-delivery interval(days), median [IQR]	2 [7]	0.5 [2]	.193
Labor onset [*n* (%)]			
Spontaneous	5 (45.4)	6 (50)	.827
Obstetric indication	3 (27.3)	6 (50)	
Covid-19 indication	3 (27.3)	0	
GA, weeks; median [IQR]	37 [2.5]	39 [5]	**.036**
Prematurity [*n* (%)]	5 (45.4)	3 (25)	.400
<32 weeks GA	2 (18.2)	1 (8.3)	
Reason for prematurity [*n* (%)]*			.764
Spontaneous	3 (60)	1 (33.3)	
Obstetric indication	1 (20)	2 (66.7)	
Covid-19	1 (20)	0	
Mode of delivery [*n* (%)]			
Cesarean section	9 (81.8)	3 (25)	**.012**
Covid-19	2 (18.2)	0	
Antepartum	1 (9.1)	2 (16.7)	
Intrapartum	6[a] (54.5)	1[b] (8.3)	
Perinatal outcomes, Newborns (n)	**11**	**13****	
Birthweight, grams (mean ± SD)	2698 ± 274	2876 ± 998	.655
Apgar-5, median [IQR]	10 [2]	10 [1]	.331
Arterial cord ph (mean ± SD)	7.28 ± 0.02	7.28 ± 0.02	.983
Delayed cord clamping	10 (90.1)	13(100)	.458
Room-in [*n* (%)]	5 (45.4)	8 (61.5)	.431
Breastfeeding [*n* (%)]	6 (54.5)	8 (61.5)	.551

IQR: interquartile range; SD: standard deviation; GA: gestational age.
*percentage among premature cases.
**1 pair of monoamniotic twins included.
[a]3 non-reassuring fetal pattern, 2 failed induction, 1 breech presentation.
[b]1 non-reassuring fetal pattern.
Bold Values considered statistically significant.

Regarding the fact that two of the four patients who needed ICU admission had been diagnosed with preeclampsia, it is difficult to establish whether this finding implies any correlation. Some situations involved in the pathogenesis of late-onset preeclampsia, as predisposing cardiovascular or metabolic factors for endothelial dysfunction, or a systemic hyperinflammatory status have also been described as triggers of COVID-19 severity [15].

Among the presenting symptoms and complementary tests related to a higher risk of hospitalization in our study, fever and CRP have been previously described to have a high consistency of association with COVID-19 severe forms [16]. Regarding dyspnea, previous publications have suggested its presence in 60–70% of healthy pregnant women, therefore distinguish whether it is a physiological event or a pathological finding in these patients may be essential in the severity assessment [17].

This study has no intention to analyze the treatments administered to pregnant women with SARS-CoV-2 infection, which were consulted to COVID-19-specific team. Tocilizumab has been proposed to mitigate the hyperinflammatory response related to severe cases. However, the safety profile during pregnancy is still unclear and its use in pregnant patients remains controversial [18]. On the contrary, low molecular weight heparin has demonstrated to be safe during pregnancy and its use with prophylactic purposes is widely recommended due to concerns regarding increased thromboembolic risk in SARS-CoV-2 obstetric patients [19].

Our perinatal results are consistent with previous reports. The data confirm the high prematurity rate in this cohort of patients, although we found no differences between COVID-19 hospitalized and non-hospitalized women. Some have suggested the possibility that COVID-19 infectious environment may cause preterm delivery [20]. Although our numbers are small, we noted that most preterm births were more likely related either with associated obstetric complications or with preexisting conditions that may trigger delivery, and not with the COVID-19. Furthermore, four patients already admitted to the hospital for obstetrical complications could have been infected during their hospital stay, pointing the fact that universal screening policies at the moment of admission may be considered during epidemic outbreaks to increase prevention measures, allow patients' adequate segregation and decrease in-hospital contagions.

Most publications described a high rate of CS in women affected by SARS-CoV-2 infection [5,7], that rose up to 81.8% in the patients with active disease at the time of delivery that belonged to G1, with a high proportion of them performed intrapartum. A plausible explanation for this finding is that the lapse of time needed to put on the personal protective equipment could increase the decision-to-incision time and the staff, concerned about this delay, may be more proactive when indicating a CS, as example, in a suspicious trace [21].

There were no cases of transmission among neonates born from mothers infected during pregnancy, supporting the fact that most reports have not shown evidence of intrauterine exposition to the virus [22,23]. However, the possibility of vertical transmission, although unlikely, cannot be completely ruled out, since a throughout examination of the placenta, umbilical cord or membranes was not routinely made [24,25]. In this sense, despite there is no solid evidence on recommending immediate cord clamping for neonates born from SARS-CoV-2 infected mothers, some authors advocated this attitude in terms of prudence [26]. Skin-to-skin contact and direct breastfeeding have been also considered as potential risk factors for transmission from the mother to the infant [27]. To our knowledge, this is the first series of newborns showing that delayed cord clamping can be safely performed, with no cases of neonatal transmission. Also, mothers of healthy term babies were encouraged to breastfeed, and they received support to initiate and establish lactation if they wish to, following WHO recommendations [28]. This information could be used to support the practices mentioned above with appropriate prevention measures.

To conclude, the results in our cohort of patients reveal that SARSC-CoV-2 infection may not behave as mild as suggested during pregnancy, especially when factors as obesity or Latin-American origin are present. No evidence of late vertical transmission was noticed but prematurity and high CS rate were common findings, although it is difficult to establish any causality between these conditions and COVID-19. There is an urgent need to analyze larger databases to identify the particularities of SARS-CoV-2 infection during pregnancy and whether it exists any obstetric factor that increases COVID-19 severity. Some national and international initiatives are working in this direction but, in the meanwhile, conclusions from small studies must be applied with extreme prudence.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Patricia Barbero http://orcid.org/0000-0002-6261-8450

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