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Original

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SARS-CoV-2 screening of asymptomatic women admitted for delivery must be performed with a combination of microbiological techniques: an observational study

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ABSTRACT

Introduction. The aim of this study is to assess the value of systematic screening in asymptomatic women admitted for spontaneous delivery with a combination of reverse transcription polymerase chain reaction (RT-PCR) and cycle threshold (Ct) and serum antibodies.

Material and methods. Since May 6 all women admitted for spontaneous delivery underwent RT-PCR in nasopharyngeal swabs and specific antibodies IgG of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in serum that were performed as part of routine clinical care in our institution. Ct of the PCR was recorded. We analyzed the first 100 women consecutively admitted for spontaneous delivery at our institution.

Results. Nine women were positive for SARS-CoV-2 in nasopharyngeal samples (9%) and 13 (13%) presented positive specific antibodies of the coronavirus. Overall, SAR-CoV-2 prior exposure was 15%. The Ct determination (RT-PCR test) of our 9 positive patients ranged from 36 to 41 cycles with a median of 40. Vaginal delivery occurred in 94% of the cases and only 6% underwent a cesarean section, always for obstetric reasons. No fetal transmission was observed and maternal and neonatal prognosis was excellent.

Conclusions. During epidemic episodes in asymptomatic women in labor, universal testing with RT-PCR (considering Ct determination), and the detection of antibodies, permits a better interpretation of the results and avoid unnecessary isolation procedures.

Key-words: SARS-CoV-2, RT-PCR, specific antibodies, cycle threshold, delivery, screening.

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El cribado de SARS-CoV-2 en mujeres asintomáticas admitidas en trabajo de parto se debe realizar con una combinación de técnicas microbiológicas: un estudio observacional

RESUMEN

Objetivo. El objetivo de este estudio es evaluar, en mujeres asintomáticas que acuden a urgencias en trabajo de parto, el valor de la detección sistemática con una combinación de reacción en cadena de la polimerasa con transcriptasa inversa (RT-PCR) y umbral del ciclo (Ct) y anticuerpos séricos.

Material y métodos. Desde el 6 de mayo, todas las mujeres ingresadas para parto espontáneo se sometieron a RT-PCR en hisopos nasofaríngeos y anticuerpos específicos IgG del síndrome respiratorio agudo severo por coronavirus 2 (SARS-CoV-2) en suero que se realizaron como parte de la atención clínica de rutina en nuestra institución. Se registró el Ct de la PCR. Analizamos las primeras 100 mujeres admitidas consecutivamente para parto espontáneo en nuestra institución.

Resultados. Nueve mujeres fueron positivas para SARS-CoV-2 en muestras nasofaríngeas (9%) y 13 (13%) presentaron anticuerpos específicos positivos del coronavirus. En general, la exposición previa a SARS-CoV-2 fue del 15%. La determinación de Ct (prueba de RT-PCR) de nuestros 9 pacientes positivos varió de 36 a 41 ciclos con una mediana de 40. El parto vaginal se produjo en el 94% de los casos y solo el 6% se sometió a una cesárea, siempre por razones obstétricas. No se observó transmisión fetal y el pronóstico materno y neonatal fue excelente.

Conclusiones. Durante los episodios epidémicos en mujeres asintomáticas en trabajo de parto, las pruebas universales con RT-PCR (considerando la determinación de Ct) y la detección de anticuerpos, permiten una mejor interpretación de los resultados y evitan procedimientos de aislamiento innecesarios.

Palabras clave: SARS-CoV-2, RT-PCR, anticuerpos específicos, umbral del ciclo, parto, valoración.

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INTRODUCTION

Existing information on SARS-CoV-2 infection during pregnancy and delivery is still scarce and fragmentary [1]. Isolated cases, or small series of women with upper respiratory tract symptoms are usually reported, and the general idea is that the situation does not significantly increase the risk for either mother or infant [2,3]

However, the situation may not be as favorable as it appears, and in a series of 23 pregnant women with COVID-19, 2 required admission to the Intensive Care Unit (ICU) and one ended in ECMO therapy. In a systematic review of 33 studies involving 385 pregnant women with COVID-19 infection, 3.6% were severe cases and 0.8% reached critical status, 17 women required mechanical ventilation and one died. [4]. Cesarean sections were performed in 69% of cases and vaginal deliveries in 31%. It is clear, therefore, that COVID-19 is far from being an innocent disease in pregnant women and its presence should be monitored [5]

On the other hand, the large majority of the information regarding SARS-CoV-2 and pregnancy has been generated from symptomatic women and there is doubt as to whether or not systematic screening of asymptomatic mothers admitted for natural birth delivery is adequate [6,7] The potential benefits for universal testing approach include the ability to use COVID-19 status to determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of personal protective equipment. The screening is usually performed with RT-PCR tests, and positive women are usually put on isolation [8]

The aim of this study was to describe the results of systematic SARS-CoV-2 infection surveillance, using both RT-PCR and detection of antibodies in 100 asymptomatic women consecutively admitted for delivery in our center.

MATERIAL AND METHODS

Location of the study. Hospital General Universitario Gregorio Marañón (HGUGM) is a general and reference hospital, of Madrid University (Complutense University), with 1,350 beds, serving a population of approximately 350,000 inhabitants in the southeast area of Madrid. The Centre performs highly complex surgery, attends to patients with malignant diseases of both solid and hematological organs, has a very active HIV and transplant program and is one of the major referral centers for Obstetrics and Gynecology in our country. The Clinical Microbiology and Infectious Diseases Service is a multidisciplinary unit with a long history of care, teaching and research.

Design and patients. We performed an observational, cohort study. Since May 6 all patients admitted for spontaneous delivery underwent RT-PCR in nasopharyngeal swabs and specific antibodies IgG of SARS-CoV-2 in serum that were performed as part of routine clinical care in our institution.

Since that date we analyzed the first 100 women consecutively admitted for spontaneous delivery at the Department of Obstetrics and Gynecology of our institution.

All women were screened on the emergency room for specific signs and symptoms of COVID-19 and previous contact with a COVID-19 positive patient. Patients admitted for induction of labor or elective cesarean section were exclude.

Patient's classification

Clinical situation at the time of the study of the participating individuals was finally defined as:

-Group A: all pregnant women with a PCR positive test, irrespective of the presence of antibodies.

-Group B: all pregnant women with PCR negative test and presence of specific antibodies.

-Group C: all pregnant women with PCR negative test and absence of specific antibodies

Study outcomes. The primary endpoint was to assess the SARS-2-CoV status by RT-PCR and specific antibodies of SARS-CoV-2 during an ongoing pandemic. The secondary endpoints were: maternal and neonatal outcomes of positive pregnant women by PCR or specific antibodies and the indirect assessment of viral load of the RT-PCR test in positive women.

Diagnostic techniques. Nasopharyngeal swabs in viral transport media was tested for the presence of SARS-CoV-2 RNA using real time RT-PCR detecting gen N and Orf 1a1b (Thermo Fisher®).

The Ct (cycle threshold) is defined as the number of cycles required in the PCR technique until a detectable amplicon was achieved. If a high viral load is assumed, the number of cycles required until detection will logically be less than if a low viral load is assumed, which requires a higher number of cycles until detection. Ct cycle determination of the gen N of the PCR test was systematically assessed.

Detection of serum IgG antibodies against the SARS-CoV-2 nucleocapsid protein was carried out in the Architect analyser using Abbott's SARS-CoV-2 IgG assay (Abbott, Abbott Park, IL, USA) following manufacturer´s instructions. The assay is based on a chemiluminescent microparticle immunoassay and determinations were considered negative or positive depending if results were <1.4 or ≥1.4, respectively (cut-off index value).

Venipuncture samples and nasopharyngeal samples were processed in the Microbiology and Infectious Disease Service of our institution.

Variables. Collected variables that included age, comorbidities, RT-PCR performed previously to admission, previous history of infection, disease or contact by SARS-CoV-2 and symptoms attributable to coronavirus at admission were added to an electronic database designed specifically for this study in a standard case report form. Maternal and obstetric variables were also included such as parity, type of pregnancy, gestational age, hospital visits, maternal RT-PCR status, maternal specific antibodies status, Ct determination and type of delivery. Maternal outcomes, neonatal RT-PCR status and

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Table 1	Baseline characteristics of pregnant women

Maternal and obstetrics characteristics	
Age-yr	
Median	32
Range	16-44
Parity - no. (%)	
Primiparous mother	48 (48.0)
No primiparous mother	52 (52.0)
Type of pregnancy - no. (%)	
Single	99 (99.0)
Multiple	1 (1.0)
Gestational age (weeks + days)	
Median	39+5
Range	33+3 - 41+2
Comorbidity - no. (%)	
No	100 (100.0)
Hospital visits-no. (%)	98
Group Aª+B: RT-PCR positive or serology positive	13/98 (13.3)
Median	2
Range	0-4
Group C: RT-PCR negative+serology negative	85/98 (86.7)
Median	1
Range	0-8
SARS-CoV-2 clinical characteristics	
Past history –no. (%)	
No previous history of SARS-CoV-2 infection or contact	86 (86.0)
Previous history of SARS-Cov-2 contact without infection	6 (6.0)
Probable infectionᵇ	6 (6.0)
Proven infectionᶜ	2 (2.0)
Current clinical situation at admission - no. (%)	
No signs or symptoms of SARS-CoV-2 infection.	100 (100.0)
Signs and symptoms of infectious disease no related to SARS-CoV-2.	0
Signs and symptoms compatible with SARS-CoV-2 infection.	0
Active and proven SARS-CoV-2 infection.	0
RT-PCR performed previously to admission- no. (%)	
No	79 (79.0)
Probable infectionᵇ or previous history of SARS-CoV-2 contact	8/79 (10.1)
Yes	21 (21.0)
RT-PCR performed by contact or clinically suspected SARS-CoV-2 infection	4/21 (19.0)
RT-PCR performed by institutional protocolᵈ	17/21 (81.0)
Negative test result	19/21 (90.5)
Positive test result	2/21 (9.5)

ªTwo patients have been excluded due to a prior positive RT-PCR.

ᵇProbable infection was defined as patient with signs and symptoms compatible with SARS-CoV-2 in the appropriate epidemiological context but who for some reason had not undergone PCR test prior to admission

ᶜProven infection by coronavirus was defined as patients who have had signs or symptoms compatible with SARS-CoV-2 and the existence of a positive PCR test in nasopharyngeal swabs at some point, prior to the moment of admission.

ᵈInstitutional protocol previous to external cephalic version, induction of labor and elective cesarean section

Abbreviations: no,: Number. %: Percentage. yr: year. SARS-CoV-2: Severe acute Respiratory Syndrome coronavirus 2. RT-PCR: Reverse transcription polymerase chain reaction

neonatal outcomes were analyzed only in RT-PCR positive pregnant women.

Hospital visits were considered: appointments to outpatients clinic, admissions to hospital, performance of blood tests, visits to the emergency room and antenatal fetal monitoring visits since March 14th, when lockdown was announced in Spain. Multiple visits performed the same day were considered only once.

Statistical analysis. Descriptive statistics were performed to assess baseline characteristics. Quantitative variables were expressed as mean and range. Categorical variables are presented by the frequency distribution and percentages (%). The Mann-Whitney U test is used to compare differences in medians. Differences with p<0.05 were considered statistically significant. All the statistical analysis was done with SPSS 25.

Ethical approval. The study protocol was approved by the Institutional Clinical Research Ethics Committee of University Hospital Gregorio Marañon on 3 June 2020 (act 15/2020).

RESULTS

Between May 6 and May 21, at a moment of decline of the COVID-19 epidemic in Spain, a total of 100 pregnant women were admitted for spontaneous delivery at our institution. Baseline characteristics are described in Table 1. None of them did have symptoms of SARS-CoV-2 infection at admission.

Nine women had nasopharyngeal swabs positive for SARS-CoV-2 (9.0%) and 13 women (13.0 %) presented positive specific antibodies against SARS-COV-2 (including 7 of the 9 PCR positive patients). The overall rate of patients with exposure to SARS-CoV-2 was 15.0%. The results of RT-PCR and serology are described in Table 2.

Only two of the nine RT-PCR positive patients had no specific antibodies. The first one had no contact or symptoms of SARS-CoV-2. The second one referred anosmia one month prior to delivery. Among seven RT-PCR positive women with specific antibodies against SARS-CoV-2 at admission, two of them had another positive RT-PCR for SARS-CoV-2 in the previous weeks. Of the remaining five patients, the first one had family contact seven weeks prior to delivery but she didn´t had symptoms in the past; another one had family contact and presented anosmia four weeks prior to delivery and in the last three patients there were no symptoms of infection neither close contact with positive cases. The situation of the nine RT-PCR positive at admission is summarized in Table 3

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Table 2	RT–PCR and serology results		
	SARS-CoV-2 antibodies (+) Number	SARS-CoV-2 antibodies (–) Number	Total number
Number of RT-PCR (+)	7	2	9
Number of RT-PCR (–)	6	85	91
Total	13	87	100

Table 3	Description and clinical evolution of RT–PCR positive women.						
RT-PCR positive women	Previous covid19 clinic/Family contact	Previous positive RT-PCR	RT-PCR positive test at admission	Ct	Specific antibodies	RT-PCR negative test date	Evolution
1	3-4 weeks before delivery/No	Yes	May 6th	41	Positive	Unrealized	Asymptomatic
2	No	No	May 6th	41	Negative	May 26th	Asymptomatic
3	4 weeks before delivery/No	No	May 9th	38	Negative	May 24th	Asymptomatic
4	No	No	May 10th	40	Positive	June 8th	Asymptomatic
5	No/7 weeks before delivery	No	May 10th	36	Positive	May 27th	Asymptomatic
6	4 weeks before delivery/Yes	No	May 14th	39	Positive	May 28th	Asymptomatic
7	No	No	May 17th	40	Positive	June 2nd	Asymptomatic
8	6 weeks before delivery/No	Yes	May 18th	41	Positive	June 5th	Asymptomatic
9	No	No	May 19th	36	Positive	June 4th	Asymptomatic

RT-PCR: Reverse transcription polymerase chain reaction. Ct: Cycle threshold

Among 91 RT-PCR negative women, six had specific antibodies against SARS-CoV-2.

The Ct determination of the PCR test of our 9 positive patients was assessed as a surrogate marker of the viral load. The Ct value was delayed (or very high) and ranged from 36 to 41 cycles, with a median of 40. The two RT-PCR positive women who had no specific antibodies had also delayed Cts of 38 and 41. These results and clinical evolution of the women are shown in Table 3.

In our series, if a previous history of contact with COVID-19 were used as a single indicator of COVID-19 testing we had lost 40.0% (6/15) of the patients with evidence of prior SARS-CoV-2 contact.

According to our predefined criteria, patients were classified in three risk categories regarding SARS-CoV-2 status: group A, 9.0%, group B, 6.0% and group C 85.0%. Excluding two patients with past history of positive RT-PCR test, we observed a non-significant trend towards an increase number of hospital visits in the group A+B compared to group C (median 2 versus 1; p =0.49).

Vaginal delivery occurred in 94.0% of the cases and only 6.0% underwent a cesarean section, always for obstetric reasons. None of the RT-PCR positive pregnant women required specific therapy against SARS-CoV2 o prolonged hospital stay. Maternal prognosis was excellent and they remained asymptomatic. No fetal transmission was observed and neonatal prognosis was excellent too. One newborn with a COVID-19 positive mother was admitted to neonatal unit due to prematurity. Type of delivery, maternal and neonatal outcomes is described in Table 4.

DISCUSSION

Our study shows that, during the COVID-19 pandemic, a high percentage (15%) of asymptomatic women in labor arrived at the hospital with evidence of past or present coronavirus infection. The simultaneous combination of epidemiological history, RT-PCR (Ct value) and antibodies allows a better classification of women by risk of transmission. During the follow-up time, all the women remained asymptomatic and also their newborns.

Pregnant women were not listed as a group at particular risk of poor outcomes for either mother or fetus in the earlier publications on COVID-19 [2,9-11], but more recent data are showing that this is not always the case and that COVID-19 in pregnant women are to be prevented and searched with care [1,12-17].

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Table 4	Type of delivery, maternal and neonatal outcomes.

	n (%)
Type of delivery	
Eutocic	82 (82)
Instrumental	11 (11)
Cesarean section	6 (6)
Breech delivery	0
Twin delivery	1 (1)
Maternal outcomes (if RT-PCR maternal positive)	
No treatment	9/9 (100)
Medical treatment	0/9
Admission for ICU	0/9
Death	0/9
Neonatal RT-PCR status (if RT-PCR maternal positive)	
Positive	0/9
Negative	9 /9 (100)
Neonatal outcomes (if RT-PCR maternal positive)	
No treatment	8/9 (88.9)
Admission to neonatal unit for SARS-2-CoV treatment	0
Admission to neonatal unit for other reasons.	1/9 (11.1)
Death	0

RT-PCR: Reverse transcription polymerase chain reaction. ICU: intensive care unit

Information at the height of the epidemic has come mainly from pregnant symptomatic population, where an etiological diagnosis was attempted only in hospitalized patients with physical complaints [12,18]. Reports are now appearing showing that more than 10% of symptomatic pregnant women may have severe forms of the disease requiring assistance in intensive care units. Cardiomyopathy, coagulopathy, premature rupture of membranes, preterm labor and fetal distress were the main prenatal complications reported [16,19,20]. Death from COVID-19 is extraordinarily rare in pregnant women but is no longer an unknown fact. In a recent systematic review, authors identified 33 studies reporting 385 pregnant women with COVID-19 infection: 14 (3.6%) were severe and 3 (0.8%) critical. Seventeen women were admitted to intensive care, including six who were mechanically ventilated and one maternal death occurred [4].

Our study evaluates the need of screening in asymptomatic pregnant women arriving for labor to the hospital, in order to properly classify patients and their offspring and direct them to the adequate hospital circuits.

The CDC and the ACOG Practice Advisory boards are not totally clear on the recommendation to screen asymptomatic women at the time of delivery [21], but others suggest that since there may be asymptomatic positive women, testing

should be considered at delivery [22]. Recently, Sutton et al [23], described a 13.5% positive RT-PCR test in asymptomatic pregnant women. A second report [24], also from New York City, showed an incidence of asymptomatic infection of 15.5 % among patients and 9.6% among support persons and another one, published on April 26, described an incidence of asymptomatic infection of 13% [25]. In all those series the detection was made only with PCR tests. The data is practically identical to our 9% PCR positivity and 15% overall positivity.

Our study is more comprehensive because we used not only RT-PCR but also IgG antibodies in all pregnant patients presenting for spontaneous delivery and an epidemiological questionnaire. This permits a better interpretation of the PCR test significance. Until relatively recently, a positive PCR test was considered equivalent to a risk of viral elimination and therefore associated with a potential for transmission. However, recent data have shown that it is extremely rare to transmit after day + 8 from the onset of symptoms and those patients who show elevated antibody titers are no longer transmitters [26-29]

The low possibility of viral excretion in our cases is further reinforced by the very high number of replication cycles (Ct) on the PCR tests of our patients (All Cts> 35) Recent studies show that the risk of transmission of the disease has to do with the excretion of live viruses and their quantity. A study carried out by Bullard et al showed that there was no viral growth in samples with a Ct > 24 [30].

With these results in hand, none of our 9 positive PCR women would had to be really isolated or directed to any special circuit, which means a considerable saving of resources for the patients and the health system. The evolution of them and their children, in the absence of any treatment, was excellent and there was no evidence of transmission either to the children or to the healthcare personnel associated with these cases.

The main strength of our study is the use of a combination of techniques to properly interpret the results of a positive RT-PCR in asymptomatic women entering the hospital for delivery. A history of disease of more than 10 days duration, the absence of symptoms, a delayed Ct cycle and the presence of antibodies are all highly suggestive of a low risk of viral shedding.

Our study has several limitations. First, these results come from a unicentric study therefore they must be taken with caution regarding the generalizability to other populations. Second, our study reflects the situation at a certain point in the epidemic wave and shows that screening makes sense at earlier phases of the wave but probably not when the large majority of the positive cases are really past infections without risks of further transmission.

We can conclude that universal testing with RT-PCR should be performed on all women admitted to delivery, at least while the pandemic is active, but the screening, if performed, must include not only a PCR nasopharyngeal test but also consider Ct amplification cycle and the presence of anti-

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bodies. With all the information, many unnecessary isolation procedures can be avoided.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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