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Prenatal screening diagnosis and management in the era of coronavirus: the Sardinian experience

https://doi.org/10.1515/jpm-2020-0208
Received May 14, 2020; accepted May 31, 2020; published online July 6, 2020

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus, was first identified in December 2019 in Wuhan, China and spread rapidly, affecting many other countries. The disease is now referred to as coronavirus disease 2019 (COVID-19).The Italian government declared a state of emergency on 31st January 2020 and on 11th March World Health Organization (WHO) officially declared the COVID-19 outbreak a global pandemic. Although the COVID-19 incidence remained considerably lower in Sardinia than in the North Italy regions, which were the most affected, the field of prenatal screening and diagnosis was modified because of the emerging pandemic. Data on COVID-19 during pregnancy are so far limited. Since the beginning of the emergency, our Ob/Gyn Department at Microcitemico Hospital, Cagliari offered to pregnant patients all procedures considered essential by the Italian Ministry of Health. To evaluate the influence of the COVID-19 pandemic on the activities of our center, we compared the number of procedures performed from 10th March to 18th May 2020 with those of 2019. Despite the continuous local birth rate decline, during the 10-week pandemic period, we registered a 20% increment of 1st trimester combined screening and a slight rise of the number of invasive prenatal procedures with a further increase in chorionic villi sampling compared to amniocentesis. Noninvasive prenatal testing remained unvariated. The request for multifetal pregnancy reduction as a part of the growing tendency of voluntary termination of pregnancy in Sardinia increased. The COVID-19 pandemic provides many scientific opportunities for clinical research and study of psychological and ethical issues in pregnant women.

Keywords: chorionic villous sampling; coronavirus disease 2019 (COVID-19); fetal cell-free DNA; non-invasive prenatal screening; nuchal translucency; prenatal screening diagnosis; quantitative reverse transcription polymerase chain reaction; severe acute respiratory syndrome coronavirus 2.

Introduction

Coronaviruses are enveloped, non-segmented, positive-sense ribonucleic acid (RNA) viruses belonging to the family Coronaviridae, order Nidovirales. They are named after the crown-like spikes on their surface, “corona” being the Latin for “crown”. Coronaviruses are common in several animal species; however, they can rarely evolve to infecting humans and then spread among people. The first ones were identified in the mid-1960s, while others have been detected only recently [1].

The most commonly prevalent are: 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus which causes the Middle East respiratory syndrome) and SARS-CoV (beta coronavirus that causes severe acute respiratory syndrome).

A new coronavirus strain that has not been previously identified in humans is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is now referred to as coronavirus disease 2019 (COVID-19). Epidemiological studies report a mortality rate of 4.08% [2], the estimate of morbidity has not yet been defined. According to the data available so far, patients with comorbidities are more susceptible to COVID-19 and the infection in these patients is more severe. Diabetes, chemotherapy, and chronic organ diseases, as well as a suppressed immune system are responsible for the high mortality and morbidity [3].

COVID-19 virus spreads primarily during close contact, via small droplets of nose discharge or saliva when coughing, sneezing, or talking. The severity of COVID-19 illness ranges from common cold to acute respiratory distress, kidney failure, and death.

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The most common symptoms are: fever, dry cough, and fatigue. Among the less common symptoms are: muscle and joint pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, skin rash, and discoloration of fingers or toes. The serious symptoms of this infection are: difficulty breathing or shortness of breath, constant chest pain or pressure, loss of speech or movement.

Universal testing for COVID-19 remains a topic of debate and its necessity is determined mainly by local health service protocols and the level of community spread of the virus.

The criteria for laboratory testing of patients with severe respiratory distress could also include a case-by-case clinical judgment based on national and international guidelines, such as the World Health Organization (WHO) recommendations for testing strategy and the European Centre for Disease Prevention and Control surveillance strategy. Typically, a suspected case should be tested for SARS-CoV-2 using available molecular tests, such as quantitative reverse transcription polymerase chain reaction (qRT-PCR) [4–7].

SARS-CoV-2 was first identified at the end of December 2019 by Chinese scientists in Wuhan City, Hubei province, China [8]. The initial outbreak in Wuhan spread rapidly, affecting other parts of China and cases were soon detected in many other countries. Outbreaks and clusters of the disease have since been observed in Asia, Europe, Australia, Africa, and the Americas. The epidemiology is constantly evolving worldwide.

In Italy, a surveillance network of the new Sars-CoV-2 has been implemented; clinical controls and screening have been activated under the coordination of the task force that meets at the Italian Ministry of Health to collaborate on all SARS CoV-2 pandemic issues. The situation is closely monitored by the Italian Ministry of Health which is in continuous contact with the international health authorities.

The Italian government declared a state of emergency on 31st January 2020, allocated the first funds and appointed an extraordinary commissioner for the emergency.

On 11th March 2020, WHO officially declared the COVID-19 outbreak a global pandemic.

COVID-19 in pregnancy

The emerging data, both in terms of infection and lethality rates, highlights sex and gender differences in the context of the COVID-19 pandemic [9].

From what is known and can be hypothesized so far, it is essential to carry out specific studies to evaluate the role of immune responses and sex hormones in the gender differences found during this pandemic and to understand the role of genes that escape the inactivation of one of the two X chromosomes in female cells and their regulators, such as microRNAs.

Understanding the gender related mechanisms associated to the pandemic should not be considered an additional research option but a fundamental aspect which will guarantee appropriate and effective global health interventions for each individual.

The SARS-CoV-2 genome does not differ from other coronaviruses responsible for previous epidemic outbreaks, such as SARS-CoV and MERS-CoV. Studies of both the SARS and MERS epidemics, the first occurring in the years 2002–2003 and the second in 2010, report a higher incidence, a more severe course and a higher lethality rate in men than women, especially in the older age groups [10–12].

Data on COVID-19 during pregnancy are so far limited. Pregnancy is a physiological state that predisposes women to respiratory complications due to viral infection. Pregnancy results in a modification of the woman's immunological state, useful for developing tolerance towards the fetus [13]. Therefore, pregnant women are more likely to develop a severe illness after infection with respiratory viruses [14]. However, pregnant women do not appear more likely to contract the infection than the general population, and although data are limited, clinical and laboratory findings are similar to those reported in nonpregnancy.

In order to understand the COVID-19 mechanism in pregnant women, considering the current paucity of data, analogies with SARS-Cov-1 (about 79% of nucleotide identity) and MERS-CoV (about 50% of nucleotide identity) were made [15].

The existing data on these other severe coronavirus infections (SARS or MERS) suggest that clinical findings during pregnancy can range from no symptoms to various severe conditions and death [16]. Manifestations are similar to those seen in nonpregnant patients with SARS or MERS. Pregnancy outcomes vary by gestational age of presentation for both of them. In the first trimester, spontaneous abortion, pregnancy terminations for economic and social reasons such as apprehension and anxiety related to COVID-19 but also delivery of full-term healthy newborns have been observed. Cases of preterm delivery have been reported after 24 weeks of gestation. Additionally, SARS-CoV and MERS-CoV are both known to be responsible for severe complications during pregnancy, including the need for endotracheal intubation, admission to an intensive care unit, renal failure and death [17, 18].

Currently, however, there is no evidence that pregnant women are more susceptible to SARS-CoV-2 or that those infected with it are more prone to developing severe respiratory tract complications [19–21].

Case reports from early pregnancy studies with SARS and MERS do not demonstrate a convincing relationship between the infection and the increased risk of miscarriage or second trimester fetal loss. Now, during the COVID-19 pandemic, the most prominent national and international scientific societies have had to collaborate by providing universal clinical practice guidance for health professionals caring for pregnant women and assisting in childbirth [9].

According to the international scientific societies, any suspected case should be tested for SARS-CoV-2 using available molecular tests, such as qRT-PCR.

Chest imaging is essential for evaluation of the clinical condition of the pregnant woman with COVID-19. A chest Computerized Tomography (CT) scan may be considered as a primary tool for the detection of COVID-19 in pandemic areas because of its high sensitivity (97%) [22–24]. The ultrasound examination of the lungs together with the obstetric scan of the pregnant woman with suspected COVID-19 has been proposed. Maternal vital signs and oxygen saturation level should be monitored vigilantly, arterial blood gas analysis should be performed and particular attention should be paid to fluid and electrolyte balance.

The Royal College of Obstetricians and Gynaecologists has released its guidelines on SARS-CoV-2 pregnancy infection for healthcare professionals based on a combination of available evidence, good practice, and expert advice [25].

These instructions aim at managing the emergency more efficiently; however, the information they contain is contextualized to the United Kingdom scenario and this may differ from what is applicable in the rest of the world. In addition to a brief introduction summarizing the available evidence on the virus, its ways of maternal-fetal transmission and the effects of the infection on mother and newborn, these guidelines offer information to pregnant women and healthcare professionals on the management of SARS-CoV-2 in both suspected or confirmed cases. The guidelines include instructions on transfer, admission, and hospitalization for women with suspected or confirmed SARS-CoV-2 infection and those who have recovered from it.

The document contains further recommendations on the information that healthcare professionals can give to pregnant women in terms of possibility of travelling, virus exposure concerns, procedures for quarantine, and access to diagnostic testing. These guidelines end with a flowchart of assessing COVID-19 risk in maternity unit attendees.

The Italian scientific community of obstetricians, perinatologists, neonatologists, paediatricians and midwives have joined the working group created by the Italian National Institute of Health and coordinated by the National Centre for Disease Prevention and Health Promotion, which has the task to review and disseminate scientific literature updates on COVID-19 in pregnancy, childbirth, and breastfeeding. The checklist developed by the The Italian Society of Infective and Tropical Diseases (SIMIT-2) is the first step in classifying patients to be managed according to the SIMIT-1 flowchart and by applying all the appropriate infection control procedures. In this scenario, the management of pregnant women should follow the same procedures as that of the general population.

Prenatal screening diagnosis before coronavirus era in Sardinia

Our Department of Maternal-Fetal-Perinatal Medicine is a referral center in Sardinia, a Mediterranean island with a population of 1,600,000 inhabitants. It has been offering a highly efficient program for prenatal screening and diagnosis of beta thalassemia since 1977 [26, 27].

The field of prenatal screening and diagnosis for birth defects has been largely modified in the last years by various economic, social, cultural and technological advancement factors [28–33].

These exponential changes are due both to physician expertise and advances in molecular methodologies and technologies.

The new approaches depend on new screening methods, ultrasound fetal abnormalities, obstetrician and laboratory experience, earliest prenatal diagnosis, low fetal loss risk, analysis accuracy, molecular genetic diagnosis, laboratory availability, legal aspects, ethics, public/private healtcare issues, ethics, costs and patient choices [28, 29, 34–38].

Although in the beginning of its activity, our center offered prenatal screening in the second trimester, much like all other centers in the rest of the world, the major part of screening nowadays is performed in the first trimester through fetal nuchal translucency (NT) measurements, ultrasound soft markers [39–41], combined with serum analytes such free beta human chorionic gonadotropin, and pregnancy-associated plasma protein A [42–44].

Our experience complies with all the relevant national regulations, institutional policies and in accordance with

the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board.

The recent introduction and rapid diffusion of noninvasive prenatal screening (NIPS) [45] into obstetrical care, using fetal cell-free DNA (cfDNA) detected from maternal blood, have coincided in centers where invasive procedures are not widely available [46, 47] with the decline of invasive prenatal procedures [48, 49]. However, in our experience, the introduction of first trimester combined testing remains the cornerstone of prenatal screening which reversed the traditional prenatal care pyramid [50].

Indeed, ignoring the ultrasound screening for the evaluation of any fetal malformations is impossible. It still is the starting point which any complex prenatal care algorithm stems from. In fact, the ultrasound screening and the combined test remain extremely significant and are far more widely applied in our prenatal center, compared to NIPS. This is due to various reasons: the high-level sonography expertise of the operators in our center which is equipped with the most technologically sophisticated ultrasound tools, including 3D-4D imaging [51, 52], the considerable detection rate of fetal malformations as early as the first trimester [53, 54], the substantial costs of NIPS (400–700 euros), or because Sardinian women are already familiar with invasive prenatal diagnosis and have grown accustomed to it due to its frequent application for thalassemia and other high-risk genetic pathologies [27, 50].

Prenatal screening diagnosis and management during coronavirus era in Sardinia

Although the COVID-19 incidence remained considerably lower in Sardinia than in the regions of North Italy, the field of prenatal screening and diagnosis was partially modified in the last months because of the emerging pandemic (from 10th March to 18th May 2020).

Since the beginning of the emergency, our referral center offered to pregnant patients all procedures considered essential, in compliance with social distancing (at least 1 m distance between people) and the constant airing of all room environments. It is also important to point out that the whole staff was being periodically tested for COVID-19 by nasopharyngeal swabs in order to esclude the risks of infection and all resulted negative.

In agreement with the Medical Administration Office of our hospital and according to the recommendations issued by the National Ministry of Health and the scientific societies, we performed a double triage in order to prevent infection and to slow down the transmission of COVID-19. According to the flow chart SIMIT-1, we adopted the following procedure: first, contact of patient via telephone or e-mail while booking the visit and a second, one upon accessing in our department. Both the telephone check and the prehospital triage were performed by trained midwives. Before accessing the hospital, all pregnant women had to undergo an additional triage procedure in a specially equipped medical tent where all demographic and medical history data were registered, body temperature was measured, and personal means of protection were supplied (Figure 1).

The tent space was divided in three rooms: one for triage and registration of patient medical history, one for sonograph screening, and one for invasive prenatal procedures if the patient was confirmed as COVID-19 positive. To access the department, all patients had to use a face mask, wear two pairs of gloves, have eye protection, if possible, and disinfect scrupulously the hands with an alcohol-based sanitizer. An obstetrician was involved whenever supervision is needed or COVID-19 is suspected.

In cases of absolute urgency, such as voluntary termination of pregnancy with gestational time limit expiration, high-risk results of first trimester screening, fetal malformations, multifetal pregnancy reduction and selective feticide in multiple pregnancies, complications in monochorionic twin pregnancies, etc., the visit and/or the procedure were performed inside the medical tent according to the protocols.

For example, in this specific medical tent, invasive prenatal procedures were being performed on patients coming from high risk COVID-19 areas who could not stay in quarantine because essential treatment was required and due to gestational time limit expiration. These patients were tested by a nasopharyngeal swab, and if the result

Figure 1: Specially equipped medical tent for pre-triage at Microcitemico Pediatric Hospital in COVID-19 period.

was negative, the invasive prenatal procedure was performed, thus bypassing the waiting time which the quarantine would usually impose. In several cases, when the patient had difficulty to travel to our center, her attending physician forwarded to us via telemedicine the sonographic scans in order to perform the obstetrics counseling.

Since the outbreak of COVID-19, we have had an increasing request for multifetal pregnancy reduction [55] and selective feticide [56] in multiple pregnancy cases. In April 2020, we performed eight of these procedures. Six of these were tested by a nasopharyngeal swab because they were coming from a region at high epidemiological risk. Two other patients from the local region required selective feticide because of fetal malformations in twins (one case of holoprosencephaly and one case of acrania), to whom, considered the urgency, it was impossible to apply preventive procedures. Patients had access to the service through reserved and pre-established paths, following the protocols. All the medical staff involved used individual protection devices and performed the procedure after finishing the pre-established worklist. Sanitization of the premises took place after each invasive procedure.

Another activity of our center which was greatly influenced by the changes during the COVID-19 period is tutoring of foreign and Italian fellows, continuing education, scientific update and assisted reproductive techniques, (ART) and preimplantation genetic diagnosis (PGD).

In fact, due to the impossibility to organize congresses and courses, global setting with TC-based conferencing with satellite transmission had to be adopted [57]. Due to the cancellation of regular airfare transport services and the travel limitations, we were forced to interrupt the tutoring in invasive prenatal procedures that we continuously offered to fellows [58, 59].

Also, in compliance with the COVID-19 Pandemic Emergency Decree issued by the Italian Ministry of Health during this period, we performed only two urgent PGD procedures for thalassemia and six ART procedures for preserving the fertility of oncologic patients who had to initiate chemotherapy [60].

To evaluate the influence of the COVID-19 pandemic on the activities of our center, we compared the number of procedures performed from 10th March to 18th May 2019 with those of 2020 (10 weeks). Generally, we perform 50% of first trimester combined screening in Sardinian population [46] and this activity increased by further 20% during the COVID-19 period, in comparison with the same period in the previous year. This is probably due to the reduction or suspension of the activity in other Sardinian outpatient clinics which could not apply the necessary rules of social distancing, sanitation, and disinfection.

The number of second and third trimester screenings remained almost unvariated; however, it should be considered that our department is a secondary and tertiary level center which only treats pregnancies at high risk of malformations and cases with suspected and/or confirmed fetal pathology during these two trimesters.

We also had a slight increase in the number of invasive prenatal procedures during this 10-week pandemic period. Comparing the 2019 data with 2020 (Table 1), we could observe a further increase in chorionic villi compared to amniocentesis, supporting what we reported in a previous study [46, 48]. Whether this increase in invasive procedures is an actual trend or results from the modified risk perception of women because of the pandemic generated apprehension is challenging to understand.

These data are surprising, especially if we correlate it to the number of births. In fact, there has been a continuous birth rate decline in Sardinia during the last years. From 10th January to 18th May 2020, there has been further 13% decrease, compared to the same period of the previous year. Although this decline can surely not be attributed to the COVID-19 pandemic, we hope that the consequences in terms of birth rate next year will not be too harsh. Unfortunately, this hypothesis is to be taken into consideration, especially given the three crucial factors such as economic precariousness, wedding ritual blocking, and increase of voluntary termination of pregnancy. This last one has increased in Sardinia by 30% during the pandemic period.

The number of NIPS performed at the Microcitemico Hospital remained unchanged while in the rest of Sardinia there was a notable decline in its demand because women generally prefer Chorionic Villous Sampling (CVS) to NIPS [50]. There could be various reasons for it: the necessity of couples to be more comprehensively reassured regarding their pregnancy in the recent turbulent period and, surely, the considerable financial cost in these times of particular economic instability.

These motivations could be also valid for the increase of multifetal pregnancy reduction cases which is a part of the increase of voluntary termination of pregnancy cases in Sardinia.

Table 1: Number of prenatal invasive procedures pre and during COVID-19 period.

Prenatal invasive procedures	2019 (10th March–18th May)*	2020 (10th March–18th May)[a]
Chorionic villous sampling	105	118
Amniocentesis	41	32

[a]10 weeks.

The psychological state of the pregnant woman during a pandemic is certainly an important and compex factor to consider, not only in terms of the major issues related to pregnancy and its course but also regarding some minor aspects, such as the discomfort of not being able to be accompanied by the partner during the obstetrical visits. Also, the obligatory use of a face mask for all the medical staff modifies the physician–patient interaction by making it more impersonal and psycologically implying less empathy.

The current pandemic is an opportunity for considerable scientific studies. It must be considered that the last pandemic occurred in the early years of the 20th century when no means for carrying out mass studies were available and when no particular attention to the psychological effects of the precarious state induced by the health emergency was paid.

Acknowledgments: The authors of this manuscript would like to thank the Regional Civil Protection Department and Mr. Antonio Belloi; CEO AO Brotzu; Fondazione di Sardegna; Boyana Petrova Tsikalova, MA in English Philology for editing assistance.

Research funding: None declared.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: Authors state no conflict of interest.

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