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## Sterility Special Interest Group position paper on ART treatments and COVID-19 pandemic

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### ABSTRACT

COVID-19 pandemic caused a huge overload of healthcare systems worldwide. For such reason, in a preventive manner, governments and scientific societies recommended to stop any elective medical or surgical treatment in order to reduce the eventual burden on hospitals. Fertility treatments have since then been reserved only to urgent cases as oncologic patients asking for fertility preservation. However, the relevance of such policy on natality rate and on ovarian aging has soon induced the main scientific societies to ask for a fast return to action, considering that infertility should be treated as an urgent condition. In this regard, phase 2 recommendations have been issued to ensure working requirements to be settled in the safest way possible. Therefore, the Special Interest Group on Sterility (GISS) of the Italian Society of Gynecology and Obstetrics (SIGO) and its federates released their guidelines as Italy has been one of the first Western countries to face the phase 2 restart of treatments.

### SOMMARIO

La pandemia dovuta al COVID-19 ha causato un imponente sovraccarico dei sistemi sanitari di tutto il mondo. Per questa ragione, in maniera preventiva, i governi e le società scientifiche hanno raccomandato di interrompere ogni trattamento medico o chirurgico elettivo per ridurre l'eventuale peso sugli ospedali. Da quel momento, i trattamenti per la fertilità sono stati riservati solo a casi urgenti, come pazienti oncologici che richiedevano procedure di preservazione della fertilità. Pertanto, la rilevanza di questa politica sul tasso di natalità e sull'invecchiamento ovarico ha presto indotto le principali società scientifiche a spingere per un rapido ritorno all'attività, considerando che l'infertilità dovrebbe essere trattata come una condizione urgente. A tal proposito, sono state rilasciate le raccomandazioni di fase 2 per assicurare che i requisiti lavorativi fossero organizzati nella maniera più sicura possibile. Quindi, il Gruppo di Interesse Speciale per la Sterilità (GISS) della Società Italiana di Ginecologia e Ostetricia (SIGO) e le sue federate hanno rilasciato le proprie linee guida, dato che l'Italia è stata una delle prime nazioni occidentali ad affrontare l'inizio dei trattamenti in fase 2.

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## INTRODUCTION

The Sterility Special Interest Group (GISS) of the Italian Society of Gynaecology and Obstetrics (SIGO) and its federated associations (AOGOI – Italian Hospital Obstetricians and Gynaecologists Association), (AGUI – Italian University Gynaecologists Association), (AGITE – Community Gynaecologists Association), wishes to contribute to the establishment of the methods, times and conditions by which the ART (Assisted Reproductive Technology) Centres will be able to operate after the general *lockdown* phase (phase 1), guaranteeing the highest possible degree of safety for the couples and operators (phase 2). With regard to ART treatments, on 18th March, our GISS and the entire SIGO made the following statements:

1. the movement of people and their access to the clinical facilities must be avoided to reduce the risk of contagion. The exponential increase in the number of COVID-19 cases, in spite of the precautions taken in application of the Government decrees (Prime Minister decrees DPCM dated 8, 9 and 11 March 2020), increases the risk of contamination of infertile patients and the personnel of the assisted reproduction centers;
2. it is ethically important to avoid creating any situation that may result in patients having to go to First aid departments or be admitted to hospital after an ART cycle. To reduce the risks of having to occupy beds in hospital, operating rooms or intensive care units, as a result of complications related to the performance of assisted conception programmes, is a duty towards the population and colleagues involved in a fight at the limit of human and economic resources;
3. in conclusion, the GISS feels that the only exceptions to the suspension of activities are represented by stimulation cycles already started and fertility cryopreservation procedures in cancer patients, which will be guaranteed by the designated facilities, considering their urgency and undeferrability.

## Key words:

COVID-19; assisted reproduction technologies; pandemic; in-vitro fertilization; poor prognosis; position paper.

Our suggestions for avoiding the spread of contagion were in line with the recommendations of the main international scientific societies, all of which have underlined the need to refrain from initiating assisted reproduction treatments during the rise to the peak of infection to avoid spreading contagion. All the societies agreed that the treatments should be postponed to the fall from the peak, forecast over a period of time of no more than two or three months (1-3).

The Italian Prime Minister himself has tried to divide the long period for which the coronavirus will be present in Italy into phases: a first phase (the current lockdown phase), a second phase (which we will enter when the number of people testing positive decreases with a consequent reduction of the number of deaths) and a third phase (the return to normality with large groups of immunized people).

A premise to every subsequent organizational phase is the fact that, according to the currently available literature and also the large number of cases collected from our hospitals, there seems to be no or negligible vertical transmission of COVID-19 from mother to child (4). In fact, most mothers found to be COVID-19 positive during delivery have given birth to negative babies. Only three cases of babies born positive have been reported so far.

No health authority of any country has issued indications or recommendations to the population discouraging women from becoming pregnant in this period.

For this reason, we believe that, as long as there is no scientific evidence that advise against starting a pregnancy, the need to suspend ART treatments is technically and scientifically unfounded.

The purpose of this document is to prepare for the complete resumption of the reproductive medicine activities following the start of the second phase, to eliminate the latency times between the start of the second phase and the resumption of the clinical and care ART activities at full rhythm. This document is therefore aimed at defining the

path to be followed to promptly resume the treatments for our patients as soon as the start of the second phase is officialised.

Sterility treatment is considered a right of couples with reproduction problems; this is underlined several times in law no. 40, confirmed by the Constitutional Court in its changes to the law and, finally, implemented by the Ministry of Health as ART treatments were added to the List of Minimum Healthcare Provisions (5).

Our country has an infertile population among the oldest in the Western world (6), with the first treatments administered to couples in which the women have an average age of 37 years and, in a third of the cases, the woman is aged over 40 years. Excessive delays in treatment may significantly reduce the possibility of success for these couples. It is therefore necessary to resume these treatments as soon as the general lockdown phase is terminated, bearing in mind that every month of inactivity in Italy means about 7,500-8,000 fewer treatments administered with a potential monthly loss of about 1500 births (7).

When the second phase begins, one of the most important reasons for deciding to suspend the activity during the first phase of the epidemic, that is the need to avoid overloading the emergency health facilities with possible problems related to the performance of ART cycles, will no longer be valid. In fact, in the second phase, there will be no overcrowding of the emergency departments so all other healthcare activities will return to their normal rhythm and the ART activity must also be resumed.

In addition, it should be taken into consideration that the ART centres handle their procedures autonomously, and with an extremely low risk of infection, in that the authorized centres are classified as Tissue establishments, and thus have certified procedures and facilities. In addition, the surgical complications that may occur and require a visit to a First Aid department are extremely limited: 0.13% of haemoperitoneum after the oocyte retrieval, 0.04% of pelvic abscesses or infections and 0.35% of hyperstimulation syndromes (2019 Ministry of Health report to the Parliament) (8).

The procedure that we recommend be followed at the ART centres for the resumption of activities is set out here below.

## RECOMMENDATIONS ON THE SIMULTANEOUS MANAGEMENT OF THE ACCESS AND CIRCULATION OF PATIENTS AT THE FACILITIES WHERE THE ART PROCEDURES ARE CARRIED OUT

### *Remote management of patients*

In the new scenario, the occasions on which the couples have to leave their workplaces will have to be reduced to a minimum, both due to the predictable difficulties of the Economic System but above all to reduce the risk of spreading the virus by limiting the circulation of the couples at the health facilities.

In this sense, we agree with the fifth statement made recently by the ASRM (effective from 30 March - 13 April 2020) (9), which identifies the use of TeleMedicine (TM) tool as a solution to the need to guarantee the greatest possible “distancing of the patients from the operators”.

The need to use this tool has been confirmed on a national level by members of the GISS (10,11).

TM should be used for the following services:

- remote consultation;
- remote diagnostics;
- remote monitoring.

The supply of these services by “e-health” would reduce to a minimum the time spent by patients in waiting rooms and outpatient departments.

As the data transferred by TM are extremely sensitive, the use of certified platforms for the production and protection of this data is recommended.

This innovative approach requires institutional recognition (establishment of an Operating Procedure and Public accreditation).

Its efficacy can be assessed by adopting the NIMM (NHS *Infrastructure Maturity Model*) adopted in Great Britain.

It should be pointed out that the TM tool has already been indicated in the 2017 Guideline elaborated by the Ministry of Health, which indicated “e-health” as one of the priority areas for the development of interventional policies in the healthcare sector.

The SIGO is ready to stand by the institutions in designing a certified and recognized method on an institutional level.

As legislative decree no. 40/2004 is still in force, some provisions laid down in the law should be

adapted to this innovative procedure, making them “not face to face”. This would not interfere with the relationship of trust between the couple and the Centre’s team. On the contrary, the use of TM would enable medical consulting and checks of the progress of the treatments to be distinguished better and conducted at a distance, also through interviews with the nursing support staff who could deliver documents certified by the medical team.

### Access to treatments

Every ART centre is a tissue establishment that operates in a protected environment and setting and should constantly safeguard both the patients and the operators. Symptomatic SARS-COV-2-positive patients with a COVID-19 diagnosis must be excluded from all ART treatments. Similarly, infected operators or operators suspected of carrying the infection must be isolated from the ART centre.

Treatment should not be given to patients at a high risk of COVID-19 infection/complications due to existing clinical conditions, for example, kidney disease, diabetes, hypertension, liver disease, heart disease and all disorders that cause immune impairment, such as AIDS or malnutrition.

Prior to the ART pathway, the patient’s medical history should be drawn up with particular reference to the risk of exposure, and a preliminary clinical assessment should be made. To do this, an initial telephonic triage form should be filled in (**figure 1**). This approach would enable the health-care operator to formulate the questions appropriately and assess more directly the adequacy of the answers given. The triage questionnaire should, in any case, be sent also by e-mail to enable the couple to fill in, sign and return it. The best time to give the questionnaire to the patient is 7-10 days before the start of the ovarian stimulation cycle or, for Frozen Embryo Transfer (FET), the start of the endometrial preparation cycle.

The contents of the triage form will be updated periodically on the basis of the information that becomes available about the spread of the virus, the mobility directives and the latest provisions laid down by the competent bodies.

The transmission of the triage form 7-10 days before the presumed date of the start of controlled ovarian stimulation (COS) not only guarantees a preliminary assessment of the couple’s eligibility for the ART cycle, it also provides two fundamental advantages:

- a) the possibility of offering extensive and exhaustive counselling on the preventive measures to be adopted in the period immediately before the ART procedure and for its entire duration;
- b) the availability of a window period in which to stratify the patient’s risk status better, that is, to observe the onset of any symptoms (if the medical history is positive for a risk of exposure) and/or carry out any necessary diagnostic tests, such as the rapid immunoglobulin test (which can be repeated 7 days after resulting negative, if appropriate) or the swab (in patients with significant symptoms).

On the basis of the pre-ART triage result, various scenarios are possible (**figure 2**).

#### Scenario 1

Patient and partner with no symptoms and a negative triage result. Counselling will be given on preventing the risk of exposure and the ART procedure will be carried out using the standard methods used at the health facility.

#### Scenario 2

Patient and/or partner with positive triage result but only a risk of exposure and/or mild non-specific symptoms.

In this scenario, a reassessment will have to be made by triage on the second day of menstruation or the day planned for the start of controlled ovarian stimulation. In the interval of 7-10 days between the two triage procedures, infectious disease consulting can be requested or appropriate diagnostic tests can be ordered directly.

If, during the window period, no symptoms develop and/or the diagnostic tests or consultant examinations conducted do not reveal signs of recent infection, the situation would be equivalent to “scenario 1” and the couple would start ART treatment in accordance with the standard procedures.

**ACCESS TO TREATMENTS**

**First triage by phone:** 7-10 days before the initiation of COS or endometrial preparation for ET

**Second triage:** on the second day of menstrual cycle, or first day of COS or endometrial preparation for ET

**Additional check point:** on the day of ovulation triggering or first day of progesterone administration in endometrial preparation for ET cycle

Figure 1. Check points at crucial steps of IVF programs COS, controlled ovarian stimulation; ET, embryo transfer.

The couple should be informed of the risk of a cancellation of the cycle if evidence of an infection in progress appears.

#### Scenario 3

Patient and/or partner with manifest symptoms and/or a positive test. Under such circumstances, ART treatment must be deferred, and the couple must be directed towards an appropriate diagnostic pathway at the competent facilities. All couples that passed the initial triage should be subjected to another check at the end of the stimulation cycle, preferably on the day of ovulation triggering or at the start of supplementation with progesterone in the case of endometrial preparation for FET. The aim is to detect any risk factors and/or symptoms that appear during the stimulation or endometrial preparation procedure. This assessment can be made using a triage form similar to the previous one. Even in this case, the 3 scenarios described above could arise.

#### Scenario 1

Patient and partner with no symptoms and a negative pre-triggering/FET triage result. Oocyte retrieval and the frozen embryo transfer will be carried out regularly unless significant symptoms appear after the questionnaire has been given.

#### Scenario 2

Patient and/or partner with positive pre-triggering/FET triage result, even if only with a risk of exposure and/or mild non-specific symptoms. In these cases, a rapid test should be carried out, which will be decisive as to whether the cycles can be continued or have to be suspended.

#### Scenario 3

Patient and/or partner with manifestly positive pre-triggering/FET triage result. Under such circumstances, oocyte retrieval or the frozen embryo transfer will have to be deferred, and the couple will have to be directed towards an appropriate diagnostic pathway (infectious disease/pulmonary consulting examination and diagnostic laboratory tests). The only possible exception is for oocyte retrieval in patients with a high risk of developing severe ovarian hyperstimulation (**figure 3**). For deferred treatments, the possibility of carrying out the ART procedure in the subsequent cycles will be considered, upon exhibition of documenta-

tion certifying the patient's negative infection test result.

#### Management of access to the Centre and organization of the various phases

##### Premises of the ART centre

Cleanliness must be guaranteed in accordance with documented sanitization protocols that take account of the recommendations of the competent authorities. Reference must be made to good clinical practice and the infection mitigation guidelines.

##### Personnel and organization of the ART centre

All the staff (medical, embryological, nursing, psychological support and secretarial) must receive training on the risks of COVID-19 infection and the safety measures to be taken. Specific instructions that can be modified according to the scientific knowledge that becomes available must be prepared and distributed.

Emergency plans for managing potential shortages of staff and equipment, and undesired exposure of the members of staff to the risk of COVID-19 infection must be elaborated. If the staff is sufficient in number, several rotating work groups should be organized to limit the spread of the virus in case of contagion in one group only.

As indicated in the Disaster Plan procedures in force, an agreement must be stipulated with another centre to guarantee continuity of care for the couples under treatment if the centre cannot complete a treatment cycle. Similarly, the emergency procedures should be revised or new procedures implemented, by finding equally competent doctors and embryologists from outside the centre to

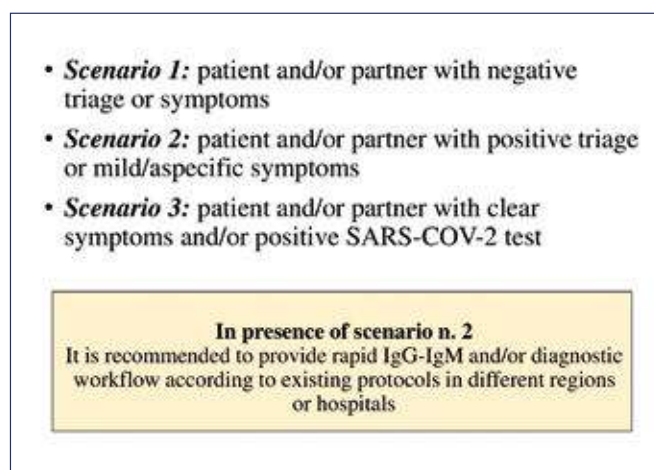


Figure 2. Delineation of different scenarios after triage.

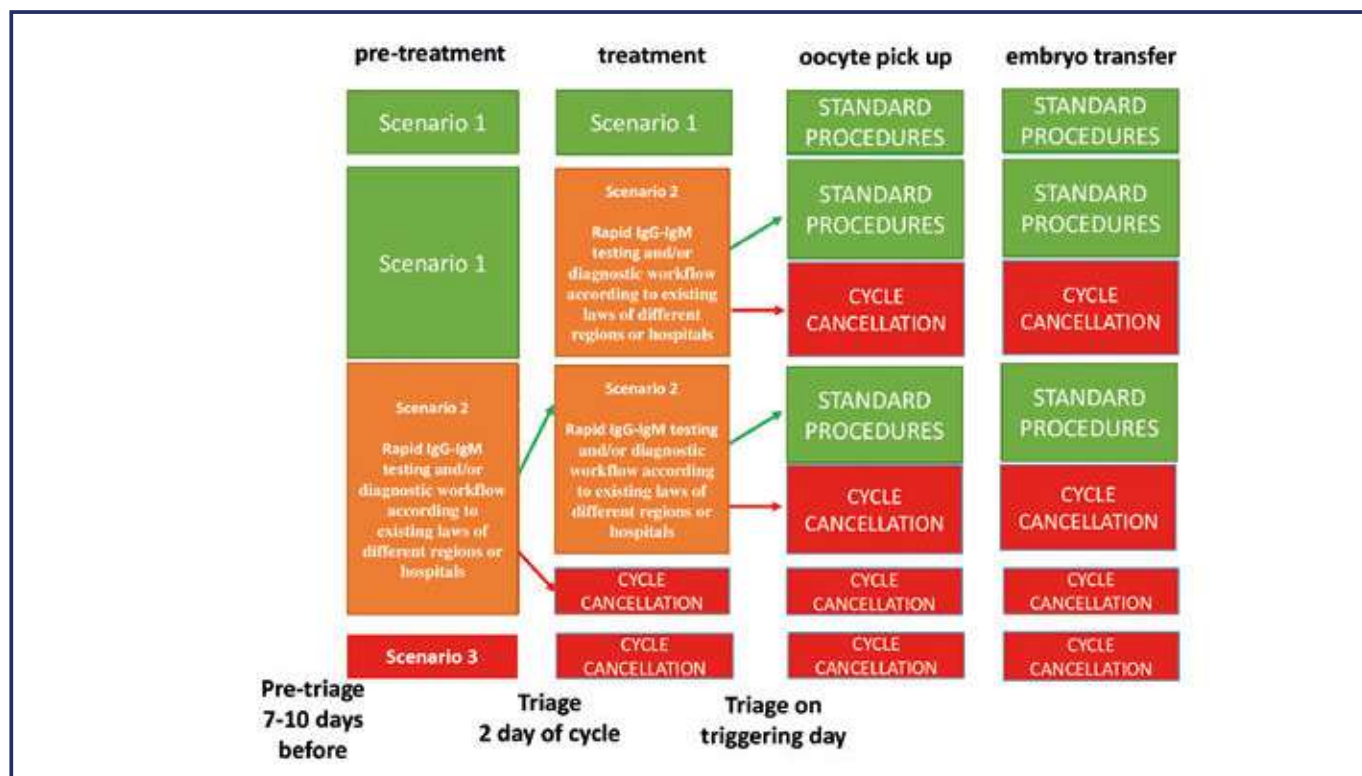


Figure 3. Summary flow chart for the management of ART treatments according to different scenarios.

replace the laboratory staff if the entire centre has to be put in quarantine.

*Access procedures*

The number of people present at the ART centre at the same time should be reduced to a minimum. The administrative staff must minimize contacts with patients and work behind screens when serving the public.

With a view to gradually resuming activities staggered in time, to avoid crowding at the single centres, priority of access will be given to couples with a diminished ovarian reserve, in accordance with the common classification systems.

Until the pandemic has been completely resolved, all health operators must wear the PPE conforming to the guidelines in force, where indicated.

The partner’s presence must be limited to a minimum except for the day on which the sperm is to be donated. Nobody apart from the couple must be allowed into the centre.

The couple is requested to bring a face mask, alcohol hand sanitizers and /or gloves and shoe covers, which, if the couple has not managed to procure them, will be put at their disposal at the entrance to the ART centre.

When called to the centre on the telephone, the patients eligible to enter the facility for outpatient

check-ups (ultrasound monitoring, semen analysis) must be informed of the time of the appointment by the offices concerned and the doctors involved. This time must be respected in order to avoid overlapping and the patients must be instructed to come alone, their state of health permitting, to avoid crowding in the waiting rooms and exam rooms; so, the staff must make sure the indications are followed.

There must be a limit to the number of people allowed in the waiting room, according to its size, respecting the distance of 1 meter and when this limit has been reached, any other patients present due to delays in the examinations will be requested to wait outside.

As a general rule, the number of operators present during the procedures must be kept to a minimum.

*Monitoring*

The doctor must wear gloves during ultrasound monitoring operations. The transvaginal ultrasound probe must be washed with a suitable disinfectant every time it is used. The use of ultrasound probe covers does not justify abandonment of the disinfection procedures to which the reusable devices must be subjected. The sheath must serve as a barrier. Compared to the normal probe sheaths, condoms are more effective (their acceptable qual-

ity level is equivalent to that of surgical/medical gloves). The probe must be cleaned with a substance that does not damage it and that has a bactericidal, fungicidal and virucidal effect (for example, a product containing quaternary ammonium).

#### *Oocyte retrieval*

In the case of *Scenario 1* or *Scenario 2*, with a negative rapid test result, a standard oocyte retrieval is performed. If the patient and/or partner is suspected to or actually tests positive, the cycle will be suspended.

If oocyte retrieval is inevitable, due to a risk of OHSS, the patient will be put on the “potentially COVID-19 positive patient pathway”. This is a dedicated pathway, centred on observance of the general regulations and adoption of the strategies for access to the operating rooms, biocontainment and postoperative sanitization.

All the operators must therefore wear:

- shoe covers;
- first pair of gloves;
- disposable waterproof whitecoat;
- bouffant cap;
- FFP2 / FFP3 mask (according to the role);
- protective glasses/visor;
- second pair of gloves.

The operators must sanitize their hands, put on a disposable waterproof whitecoat, knee-high shoe covers and a bouffant cap, an FFP2 face mask and protective visor and two pairs of non-sterile gloves. At the end of the procedure, the material used must be deposited in the containers for infectious waste, and the stretcher, any other aids, the ultrasound scanner and aspirator must also be cleaned/disinfected.

The patient must enter the operating room directly with shoe covers, a disposable whitecoat, surgical mask and bouffant cap, washing his/her hands thoroughly with hydroalcoholic gel.

The preparation of the operating room must be organized using only the material strictly necessary for the type of operation to be performed and preferably using disposable material. All the material used must be handled and disposed of in such a way as to prevent any form of contamination of the environment, the operators and the other patients. The team of doctors and biologists will put on the protective clothing before entering the operating room, in accordance with the standard procedure for a surgical operation, replacing the surgical

mask with a FFP2 mask, glasses or protective visor and knee-high protective shoe covers.

Anaesthesiological procedures that limit the need for assisted ventilation are recommended, so as to reduce the risk of contagion for the operators to a minimum. In fact, some procedures may create spray and thus increase the transmission of the virus (tracheal intubation, non-invasive ventilation, etc.) and, in this case, an FFP3 mask must be worn. The entrance doors of the operating room must remain closed, thus reducing the movement of things and people to a minimum. During the surgical operation behind closed doors, the corridor will be sanitized for the first time and then subjected to a second in-depth sanitization procedure after the patient has been transferred to another room. The oocytes retrieved and/or the embryos will be cryopreserved for subsequent use.

#### *Transfer*

For ascertained or strongly suspected COVID-19 positive patients (severe symptoms), the transfer should be deferred and the oocytes or embryos frozen, segmenting the ART cycle.

Only if the patient’s negative result is certified by a diagnostic test (in accordance with the guidelines of the competent authorities) and the partner is negative, the transfer can be performed.

If the pre-FET triage form (administered at the start of supplementation with progesterone) reveals a “Scenario 3” (see “Access to the treatments”), the transfer should not be made. If it indicates a “Scenario 2”, the choice will be made after a rapid test has been carried out.

#### *Laboratory or preservation of embryos, oocytes and spermatozoa*

To date, there is no information in the scientific literature on whether the virus is present in the human reproductive system, the follicular fluid or the seminal plasma or whether it adheres to oocytes, spermatozoa and embryos. This presence is improbable due to the lack of a receptor for the virus on these cells. For the fluids associated with them (seminal plasma and follicular fluid), no information is available so an adequate number of gamete washing should be performed, as laid down for the use of gametes of people affected by other viral diseases.

With regard to the ART procedures, there is currently no available information, on the risk of contamination of the culture systems with the SARS-

COV-2 virus, or on the risk of interference with in-vitro embryo development. Studies on this subject are therefore necessary.

For the organization and implementation of the laboratory methods, the GISS intends to follow the recommendations of the Italian Embryology, Reproduction and Research Society (SIERR) (12). At the end of the lockdown period, all the staff at the centre (doctors, nurses, auxiliary staff) should receive training on topping up the cryocontainers in such a way as to preserve the cryopreserved material if the laboratory staff have to be put in quarantine. The cryobank management procedure should also be updated accordingly.

If electronic monitoring tools are not available, flexible procedures that minimize the presence of support staff without jeopardizing the efficacy of the process (e.g. other adequately equipped health operators or IT monitoring tools) should be elaborated. The laboratory environment and equipment must be sanitized with suitable detergents (quaternary ammonium solutions) at the end of every procedure or access to the environment.

If a treated patient is currently or subsequently found to be infected by COVID-19 (for example,

cancer patients undergoing fertility preservation procedures), the laboratory spaces and the equipment (laminar flow hoods, incubators, etc.) used to handle the samples must be carefully decontaminated with a validated product; the manufacturers' recommendations, including dilution, contact time and safe handling, must be followed. This cleaning procedure must be performed after use and before the equipment is put back into normal service.

An extraordinary test of the alarm systems remote control should be planned.

#### *Cryopreservation*

To date there is no information about the risk of cross contamination between SARS-COV-2 infected samples and uninfected samples stored in the same container. If patients potentially at risk are treated, the samples should be cryopreserved in "high-safety" devices.

#### **CONFLICT OF INTERESTS**

The author declare that they have no conflict of interests.

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**SARS-CoV2 containment during pregnancy: single Center experience and the unique Chinese reality in Prato**

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COVID-19; SARS-CoV-2; nasopharyngeal swab; antibody; pregnancy; delivery.

## TO THE EDITOR

On December 31<sup>st</sup>, 2019, Chinese health authorities reported an outbreak of pneumonia cases of unknown etiology in the city of Wuhan.

On January 9<sup>th</sup>, 2020, The Chinese Center for Disease Control and Prevention identified a novel coronavirus as the cause of these pathologies.

On February 11<sup>th</sup>, the World Health Organization announced that the respiratory disease has been called COVID-19 (CoronaVirus Disease), and the causing agent was identified as severe acute respiratory coronavirus 2 (SARS-CoV-2). Due to the rapid worldwide spread of the virus, the WHO declared the state of pandemic on March 11.

Following mainland China, Italy has been the second SARS-CoV-2-affected country and is currently one of the most affected European countries, with more than two hundred thirty thousand cases diagnosed and more than thirty-three thousand cases of COVID-19 associated deaths (data on June 2020), with a significant difference in case distribution among the various regions, with Lombardy, Piedmont and Emilia Romagna counting the three highest number of cases in the whole country; Lombardy reported an unfortunate record of infected people. The reason why some areas of Italy have been so severely affected is still not clear. In fact, the first cases occurred in those areas before social interventions took place due to the poor knowledge of the new coronavirus and its high contagiousness.

Italy was the first European country to adopt strict lock-down measures: on January 22<sup>nd</sup>, the Minister of Health assembled a task force to coordinate interventions in the country.

The Ministerial Circular of January 22<sup>st</sup> established the activation of a surveillance system for suspected cases of SARS-CoV-2 infection. The coordination of surveillance is entrusted to the "Istituto Superiore di Sanità", which collects the reports from all the Regions through a dedicated web platform.

On March 11, the Council of Ministers approved the Prime Ministerial Decree regarding the containment and management of the epidemiological emergency from COVID-19, applicable on the whole national territory, in which the closing of commercial activities and services to the person was arranged, with the exception of those activities considered essential for population livelihood.

From March 22, transfers between different Municipalities by public or private means of transport have been, exception made for proven work needs, absolute urgencies or health reasons.

In May 4, Phase 2 started, with the loosening of some social restrictions; however, the population was advised to keep staying alert, due to the possibility of the epidemic resuming.

In Italy, especially in some cities, the Chinese population is highly represented. Out of a total of 1,390,434 inhabitants residing in Milan, 40,438 are Chinese citizens while in Rome the Chinese are 22,815 out of a total of 2,844,395 inhabitants. The demographic data of Prato city on December 31, 2019, revealed a total population of 195,089 people of which 152,718 Italians and 24,906 Chinese (out of a total of 42,371 foreigners). Particularly, women were 100,395, 12,302 of which were Chinese.

On the occasion of the Chinese New Year, which was held on January 25<sup>th</sup>, a possible massive spread of the virus was feared, owing to many people coming back from their permanence in China, which was counted numerous COVID-19 cases.

In January, as already implemented in their country of origin, Chinese people living in Prato self-quarantined, largely anticipating Italian lockdown measures; they self-isolated and implemented social containment measures early, using face masks and closing commercial activities.

The purpose of this article is to document the experience of a unique Italian reality in Prato (Tuscany) characterized by the mixture of Italian and Chinese people and cultures. In this paper, we focused our experience in an II level obstetrical center.

The Santo Stefano Hospital in Prato adopted a series of safety measures promptly instituted as soon as the arrival of the infection in Italy has been ascertained.

Differentiated PPE (personal protecting equipment) according to the risk of each patient were promptly introduced. Patients were initially divided into different pathways based mainly on epidemiological risk criteria.

During SARS-CoV-2 pandemic, in Prato, all pregnant women chose the hospital setting for delivery. From January 1<sup>st</sup> to June 14<sup>th</sup>, we recorded a total of 902 deliveries, of which 193 (21.39%) by Chinese women, 175 (19.4%) by patients from other nationalities, and the remaining 534 by Italian women.

Among the pregnant women admitted to the obstetric unit in Prato for suspected COVID-19-related symptomatology, we registered 5 cases showing fever, all in the second or third trimester of pregnancy; all of them were tested through nasopharyngeal (NP) swab. Among them, 1 Italian woman at the 26th gestational week tested positive for SARS-CoV-19; she was affected by fever, cough, low oxygen saturation and was diagnosed with interstitial pneumonia on pulmonary ultrasound examination. As regards the remaining 4 women, 3 of them had fever and cough and tested negative for SARS-CoV-2, but 1 was positive for influenza B, and in the other 2 patients no viral factors were identified. The last patient, presenting only fever, was admitted to delivery and tested negative for SARS-CoV-2 and after delivery diagnosed with *E. Coli* chorioamnionitis.

Starting from April 4<sup>th</sup>, we performed universal molecular screening on women admitted for delivery by NP swabs. All the patients were asymptomatic, all of them declared to have respected COVID-19 containment measures and denied contacts at risk (with positive people). Only 1 woman tested positive at Real Time Polymerase Chain Reaction (RT-PCR) on NP swab: she was Italian and gave birth through vaginal delivery after PROM at 37 weeks of gestation.

Neither symptomatic or positive nor identified/detected with NP swab screening Chinese pregnant women have been reported.

We explained this very low rate by the containment measures rigorously applied in Prato, a unique Italian reality in which we observe a condition of existing at the same time of a multi-ethnicity and in which the high rate of Chinese people caused in advance a SARS-CoV-2 alert.

Tuscany, and particularly our town, witnessed an outstanding sense of responsibility by the whole population, whose self-isolation has permitted to avoid the massive spread of the SARS-CoV-2.

Pregnant women and other fragile categories were protected early, thanks to the isolation of people, the closure of Chinese businesses, the voluntary quarantine for all individuals from areas at risk or with risky contacts.

The close contact with the Chinese population probably contributed to raise awareness among the Italian population residing in Prato towards SARS-CoV-2 threat when the first case in Italy had not yet been registered.

This integration between cultures takes place in Tuscany, a region where territorial services are effective in the management of pregnant patients. The presence of a well-structured consultancy network help women to better orient themselves in the pregnancy care path, limiting hospital accesses to necessary cases, even before the COVID-19 spread. There is no doubt that the habits of the Chinese population, so widely represented in the city (16% of the entire resident population), has led to an integration of the daily life customs between Chinese and Italians starting from economic relations to important cultural implications.

Dedicated and preferential care pathways for pregnant women of any gestational age were promptly established at the Santo Stefano Hospital in Prato, which provided pregnant women not to wait in hospital areas common to other patients.

A universal SARS-CoV-2 screening for pregnant patients guaranteed the distinction of the pathways between pregnant patients safeguarding non-infected women and health care workers.

Considering that pregnant patients with COVID-19 are generally asymptomatic up to 87.9% reported in literature (1) and that the birth event represents a highly infectious moment for staff and other patients, childbirth in COVID-19 positive women provides for PPE and special containment measures for staff and newborn.

The epidemiological factor had initially weighed heavily on the diagnosis and surveillance of COVID-19. At the end of the pandemic this factor appears to be no longer decisive but the criteria for suspecting were anamnesis (contacts at risk), known symptoms, investigations (swab and serological tests).

In conclusion, the association between the preventive measures started by the Chinese population, the good local territorial health management of pregnancy in Tuscany and the organization of dedicated pathways for pregnant women at the Santo Stefano Hospital in Prato contributed to an effective containment of the spread of coronavirus, especially among pregnant women.

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## Maternal sepsis: a comprehensive review from definition to treatment

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### ABSTRACT

Maternal mortality is a worldwide alarming concern, and sepsis is the third most frequent cause for its occurrence. Pregnancy and the postpartum period are an intrinsically vulnerable period during women's life, which may make the mothers more susceptible to develop sepsis, due to the physiological and immunological changes that regulate host capacity to counteract pathogens infection, such as bacteria, viruses, fungi, and protozoa. The physiological adaptations of pregnancy could additionally mask signs and symptoms of infection and limit the sensitivity and specificity of the available scores. On this basis, the obstetric-modified quick SOFA and the Modified Early Warning System were proposed to overcome these issues. Early recognition and treatment are vital to prevent mortality. Nevertheless, the evidence guiding the current management of maternal sepsis are derived from the general population and do not take into account the physiological changes of pregnancy. In pregnant women early fluid resuscitation should be carefully addressed, and the management of the source of infection may require expedite delivery, making the management of sepsis particularly challenging during gestation. Further studies are needed to establish pregnancy-related diagnostic criteria and therapeutic protocols for sepsis and septic shock in the obstetrical population.

### SOMMARIO

La mortalità materna è indubbiamente un problema di rilevanza globale e la sepsi ne rappresenta la terza causa per frequenza. Durante la gravidanza e nel post-partum la donna è più suscettibile allo sviluppo della sepsi, in quanto i cambiamenti fisiologici e immunologici modulano la capacità dell'ospite di contrastare le infezioni da agenti patogeni, come batteri, virus, funghi e protozoi, rendendo le madri più vulnerabili. Questi adattamenti fisiologici possono inoltre mascherare segni e sintomi di infezione e limitare la sensibilità e la specificità degli score diagnostici disponibili, motivo per il quale è stato proposto il quick-SOFA ostetrico e il Modified Early Warning System. Il riconoscimento e il trattamento precoce sono vitali per ridurre la mortalità legata alla sepsi. Tuttavia, le evidenze su cui si basa la gestione della sepsi materna sono ricavate dalla popolazione generale, che non tiene conto del cambiamento fisiologico della gravidanza, quando la rianimazione emodinamica precoce deve essere affrontata con attenzione e la gestione della fonte di infezione può richiedere l'espletamento in tempi brevi del parto, rendendo particolarmente difficile la gestione della sepsi in ostetricia. Pertanto, sono necessari ulteriori studi per definire chiaramente i criteri diagnostici e i protocolli terapeutici per la sepsi e lo shock settico nella popolazione ostetrica.

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*organ dysfunction scores; pregnancy complications; maternal mortality.*

## INTRODUCTION

According to the latest declaration of the World Health Organization (WHO), maternal mortality still represents a an alarming issue worldwide (1). Maternal mortality is defined as the death of a woman by any cause related to or aggravated by pregnancy or its management, during pregnancy or within 42 days from delivery or termination of pregnancy. Deaths from incidental or accidental causes are excluded (2).

From 1990 to 2015, the global maternal mortality rate of 43.9% declined with a 2.3% annual reduction rate. In particular, the most relevant reduction of maternal mortality rate has been observed in Eastern Asia, while in the Caribbean the slowest decrease was registered. The only exception to this trend is represented by the United States (US), where a concerning 75% increase in maternal mortality was recorded in the last 25 years (3–5). In terms of deaths per livebirth, the lowest rate of maternal deaths occurred in developed countries, while the highest in sub-Saharan countries (1). More than 99% of the women who die from pregnancy-related complications are in low and middle-income countries (6).

The causes of maternal death are historically classified in direct (obstetric complications of pregnancy) and indirect (disease previously existing or developed during pregnancy, that are aggravated by the physiological effects of pregnancy) causes, leading to give lower attention to indirect causes of maternal death than direct ones (7). Nevertheless, in 2006 the first systematic review of the literature showed that the main cause of global maternal deaths in developing countries was haemorrhage (which accounted for 27% of maternal deaths), followed by hypertensive disorders (8–10), and sepsis (14% and 7% respectively) (11,12).

Sepsis is an indirect cause and is defined as a clinical syndrome caused by the excessive activation of immune and coagulation systems by infections (13). Infection is currently the leading indirect cause of maternal death in the United States and the second leading cause in the United Kingdom. In detail, pregnancy-associated severe sepsis (PASS) increased by 236% from 2001 to 2010 and still represents a problem of global concern (14). Therefore, the early recognition and treatment of maternal sepsis, such as any other pregnancy-related infection, should become a priority for obstetricians and for every health practitioners (15).

In the last years there were many attempts to find consensus about a new definition of maternal sepsis, with the aim to provide an easier and earlier diagnosis and a consequent more accurate management of patients.

The purpose of this review is to evaluate and compare the most recent definitions and guidelines for obstetric sepsis, trying to provide a global overview improving early diagnosis and adequate management. In addition, we describe the most important risk factors for sepsis in pregnancy and puerperium.

## DEFINITIONS AND NEW GUIDELINES FOR DIAGNOSIS

The historical definition of sepsis by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) from the early nineties appears nowadays obsolete (16,17) (**table I**).

In 2001, a group of experts revised the 1992 sepsis-consensus definition and found that, apart from expanding the list of signs and symptoms related to sepsis, there was no evidence to support any change in this classification. In addition, the PIRO scheme for hypothesis-guided diagnosis of sepsis was introduced. The intention was to stratify patients considering their predisposing conditions, the nature of the original cause (infection), the nature and level of the host response, and the degree of concomitant organ dysfunction (18).

In 2013, the SCCM and the European Society of Intensive Care Medicine (ESICM) organised a task force to assess revised definitions, that were published at the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (19). The consequence was the elimination of the terms “sepsis syndrome”, “septicaemia”, and “severe sepsis”. The underlining reason was that, according to the new definitions, sepsis was triggered by infection. This pathophysiological consideration lead to remove the systemic inflammatory response syndrome (SIRS) from the classification of sepsis, since a number of conditions other than infection may cause SIRS. Consequently, according to the latest Sepsis-3 statements, sepsis was defined as a life-threatening organ dysfunction due to a dysregulated host response to infection (20). Therefore, the Sepsis-3 definition of “sepsis” corresponded to severe sepsis contained in previous

**Table I.** Historical and most recent definitions of sepsis.

Society	Year	Definitions
ACCP/SCCM	1992	<ul style="list-style-type: none"> <li>Systemic inflammatory response syndrome (SIRS): inflammatory response to severe clinical insult defined by the presence of two or more of the following symptoms:               <ul style="list-style-type: none"> <li>Temperature &gt;38 °C or &lt;36 °C</li> <li>Heart rate &gt;90/min</li> <li>Respiratory rate &gt;20/min or PaCO<sub>2</sub> &lt;32 mmHg</li> <li>White blood cells count &gt;12000/dL or &lt;4000/dL or &gt;10% immature forms</li> </ul> </li> <li>Sepsis: SIRS with evidence of infection</li> <li>Severe sepsis: Sepsis with signs of organ dysfunction, hypoperfusion or hypotension</li> <li>Septic shock: Sepsis with persistent hypotension despite adequate fluid resuscitation or need for inotropic or vasopressor agents</li> </ul>
SCCM/ESICM/ACCP/ATS/SIS	2001	No essential change in definitions. PIRO scheme for guiding diagnosis with expanded list of signs and symptoms
SCCM/ESICM – Sepsis-3	2014-2015	<ul style="list-style-type: none"> <li>Sepsis: a life-threatening organ dysfunction due to a dysregulated host response to infection. Severity of organ dysfunction is assessed using SOFA score.</li> <li>Septic shock: Sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and a serum lactate level &gt;2 mmol/L (18 mg/dL)</li> </ul>
WHO	2016	Maternal sepsis is a life-threatening condition defined as organ dysfunction which occurs during pregnancy or postpartum

ACCP: American College of Chest Physicians. SCCM: Society of Critical Care Medicine. ESICM: European Society of Intensive Care Medicine. ATS: American Thoracic Society. SIS: Surgical Infection Society. WHO: World Health Organization.

consensus statements, as well as septic shock was described as sepsis with persistent hypotension needing vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg, and a serum lactate level >2 mmol/L (18 mg/dL).

The most recent sepsis definition is provided by WHO in 2016 (21). These new guidelines are in line with previous definition from Sepsis-3, but with the goal to point the attention to a more time effective and appropriate antimicrobial therapy and fluid support. Moreover, the perspective to include laboratory tests among the diagnostic criteria seems to offer new possibilities for the future definitions. As a result of the lack of gold-standard laboratory tests for sepsis diagnosis, the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score was introduced to better describe severity of organ dysfunction and to predict in-hospital mortality (22) (**table II**). The SOFA score was introduced in 1994 during the ESICM conference in Paris, with the intention not to predict outcome but to describe a sequence of complications. According to the Sepsis-3 new statements, organ dysfunction is determined by an acute change in total SOFA score of 2 points, resulting from the disseminating infection. Furthermore, unless patient has a pre-existing organ dysfunction, baseline SOFA score should be assumed to be zero.

Since calculating SOFA score outside of the Intensive Care Unit (ICU) may be not simply, the quick SOFA (qSOFA) was created to have a faster and easier method of evaluation (23,24). However, the

qSOFA score does not define sepsis; it is intended to rapidly recognise those patients at high risk for developing severe complications and who need a more robust treatment. The qSOFA score evaluates altered mental status, tachypnoea and hypotension, and it ranges between 0 and 3 points (**table III**). A total score of 2 points in infected patients is predictive of a greater risk of poor outcome, especially if calculated outside the ICU. Among non-ICU patients with suspected infection, qSOFA has a predictive validity for in-hospital mortality that is greater than the one related to the full SOFA score and to SIRS definition (area under the receiver operating characteristic curve -AUROC- 0.81 for qSOFA vs AUROC 0.79 for SOFA score vs AUROC 0.76 for SIRS). Otherwise, in the ICU the predictive validity for in-hospital mortality is lower if qSOFA and SIRS definition are used, compared to the full SOFA score (AUROC for qSOFA 0.66 vs AUROC for SIRS 0.64 vs AUROC for SOFA score 0.74) (25).

Considering that neither the existing sepsis definitions nor the current scores account for the typical physiologic changes of pregnancy, in 2017 the Society of Obstetric Medicine Australia and New Zealand (SOMAZ) proposed an obstetric-modified qSOFA (omqSOFA) (26). Because gestation influences some variables of the full SOFA score and of the qSOFA score, such as systolic blood pressure (which usually decreases of 5-10 mmHg during pregnancy), respiratory frequency, and creatinine level (which is significantly lower during pregnan-

**Table II.** SOFA score.

SOFA SCORE	+0	+1	+2	+3	+4
Respiration PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	≥ 400	< 400	< 300	< 200 with respiratory support	< 100 with respiratory support
Coagulation Platelets x 10 <sup>3</sup> /mm <sup>3</sup>	≥ 150	< 150	< 100	<50	<20
Liver Bilirubin, mg/dl (μmol/L)	< 1.2 (<20)	1.2- 1.9 (20-32)	2.0- 5.9 (33-101)	6.0-11.9 (102-204)	> 12.0 (204)
Cardiovascular Hypotension	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose) *	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Score	15	13 - 14	10 - 12	6 - 9	< 6
Renal Creatinine, mg/dl (μmol/L) or urine output	< 1.2 (< 110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) or < 500 ml/day	> 5.0 (> 440) or <200 ml/day

\* Adrenergic agents administered for at least 1 h (doses given are in μg/kg/mamin).

**Table III.** Quick SOFA score.

Clinical signs	Score
Respiratory rate ≥ 22 breaths per minute	+1
Systolic Blood Pressure (SBP) ≤ 100 mmHg	+1
Any change in mental status (GCS <15)	+1

GCS: Glasgow Coma Scale.

**Table IV.** Obstetric-modified qSOFA (omqSOFA).

Clinical signs	Score 0	Score +1
Respiratory rate	< 25 breaths per minute	≥ 25 breaths per minute
Systolic Blood Pressure (SBP)	≥ 90 mmHg	< 90 mmHg
Altered mental status *	Alert	Not alert

\* GCS is not typically assessed as part of routine clinical management in obstetric wards.

cy), the omqSOFA includes parameters adapted for the pregnant status. According to this modified score, maternal sepsis should be considered when 2 or more abnormal parameters are present, like systolic blood pressure <90 mmHg, respiratory rate ≥ 25/min, and altered mental status (**table IV**). Moreover, SOMANZ guidelines also include some changes in laboratory test ranges of the full SOFA score (for example, creatinine level is considered abnormal above a cut off of 1.02 mg/dL). The effort of SOMANZ guidelines is to reduce the rate of false-positive diagnosis caused by overlapping ranges between normal and abnormal parameters in pregnancy, and to avoid the underestimation of sepsis signs.

## EPIDEMIOLOGY

Sepsis is a very threatening occurrence during pregnancy worldwide (27-29). Since there is no global agreement about its diagnosis and definition, the incidence and prevalence of sepsis provided by different studies and societies seem inaccurate

(30,31). Moreover, lack of data from low-income countries makes the incidence in that regions even more difficult to be determined (32).

What is unquestionable is that sepsis mortality is currently still increasing, especially and surprisingly, in developed countries like UK and The Netherlands, where deaths caused by sepsis have nearly doubled over the past decade due to increasing infections caused by invasive group A streptococcus (33). In particular, UK absolute risk of death from maternal sepsis is relatively low (2.0/100 000 pregnancies), but the total amount of severe morbidity is nearly 50 times higher (34). The UK Obstetric Surveillance System (UKOSS), that retrieves data from obstetric departments about maternal deaths occurring in the ICUs (35), reports that sepsis represents the cause of 2-6% of maternal ICU admissions, confirming the great impact of infections and their consequences in maternal morbidity (36,37). Nevertheless, recent studies have shown an under-reporting of sepsis-related maternal deaths, due to the lack of clinical audit or confidential enquiries (34). Actually, only few countries have such a monitoring system acting

as a maternal mortality surveillance method and providing essential statistical data. Other than the UK, clinical auditing after every adverse event is offered also in Finland, France, the Netherlands, Slovenia, Australia and South Africa (38).

Furthermore, it is important to point out that 37.5%, 25.5% and 24.1% of pregnancy-associated sepsis happen during hospitalization for labour and delivery, the antepartum period and the postpartum, respectively (30).

## RISK FACTORS FOR MATERNAL SEPSIS

Pregnancy and postpartum represent an intrinsically vulnerable period during women's life, which may make mothers more susceptible to develop sepsis. Physiological and immunological changes during pregnancy have an impact on the immune response (especially T-cell mediated immunity), modifying the host capacity to counteract pathogens infection, such as bacteria, viruses, fungi, and protozoa (as in the case of dengue, yellow fever, Ebola, and malaria) (39–42). Moreover, physiological adaptations to pregnancy, such as plasma volume expansion, tachycardia, blood hypercoagulation, and lower oxygen reserve could mask signs and symptoms of infection, thus delaying sepsis diagnosis (43).

Onset of labour is known to alter physical antimicrobial barriers and caesarean section has frequently been shown to be a major risk factor for maternal morbidity, increasing the risk of developing severe infection such as endometritis (44–48). Indeed, endometritis, in association with pyelonephritis and chorioamnionitis, is the most significant cause of septic shock in pregnancy (49).

In developed countries, well-known risk factors for sepsis are prolonged rupture of membranes, retained placenta or conception products, preterm labour, history of pelvic or other infection, interventions like cerclage or multiple vaginal examinations, diabetes, and anaemia (50,51). Maternal age over 35 years (52) and assisted reproductive techniques (53,54) can also increase risk of sepsis-related morbidity (17). Obesity, defined as a body mass index (BMI) > 30, is as well an established risk factor for surgical-site and nosocomial infections; it seems to negatively influence pregnancy-related outcome and to have substantial effects on immune surveillance (55,56). It is usually associated with poor wound healing, mainly after

caesarean section, and genitourinary and uterine infections (57,58). What is alarming is that obesity rate is rapidly increasing in UK and in other developed countries, affecting also young women. In the mid-2000s, nearly 20% of pregnant women in UK were obese, and among extremely obese patients, almost 50% underwent caesarean sections. It is important to underline that 33% of maternal deaths correlated to sepsis occurring in UK between 2003 and 2005 were in obese pregnant women (59). At the same time, new studies revealed that bariatric surgery represents a risk for pregnant women who underwent this kind of operation before gestation. For example, previous gastric bypass, which is the most performed procedure in US, has been demonstrated to increase the risk of gastrointestinal complications which could lead to sepsis during the antepartum period. In addition, whilst bariatric surgery is not itself an indication for caesarean section, rates of caesarean delivery seem higher than average in women who had prior bariatric surgery, similarly to other extensive bowel surgeries (60–62).

By contrast, analysing the literature about maternal mortality from sepsis in low-income countries, the most relevant independent risk factor is poverty. Indigence results in a lack of healthcare facilities and appropriate resources, such as antibiotics and medications, and makes women give birth to their children in unhygienic conditions and without proper obstetrics assistance. Immunosuppression caused by HIV and chronic infections like tuberculosis also play a key role in increasing the risk of severe superinfections during the postpartum period. As a result of these data, targeting the interventions towards the most vulnerable populations appears essential, as well as monitoring governments' actions to reduce the disparity of maternal death (50,63).

## MANAGEMENT

The diagnosis and management of sepsis are particularly challenging during gestation and the postpartum period due to the physiological changes induced by pregnancy. The increase in blood volume and consequently in stroke volume and heart rate, as well as the increment in tidal volume (more evident in the first trimester) and in systemic vasodilatation, allow pregnant women to longer compensate before clinical deterioration become evident.

Changes in coagulation, fibrinolysis and blood cells count also play a key role in sepsis diagnosis retardation (49,64). On the other hand, the reduction in the expiratory reserve volume and functional residual capacity, and the decreased venous blood return (mainly occurring in the last trimester), reduce the ability of pregnant women to cope with chronic and acute stress deriving from sepsis (65).

Recently, many societies tried to provide early score systems to facilitate timely recognition of septic disease, such as Modified Early Warning System (MEWS) (66). Unfortunately, these scoring systems were found unsuitable to be applied in the obstetric population, because they do not consider maternal physiological changes which can mimic sepsis initial signs (67). Between 2003 and 2005, the triennial Confidential Enquiry into Maternal and Child Health (CEMACH) report strongly recommended the routine use of the Modified Early Obstetric Warning System (MEOWS), a scoring system adapted for the obstetric population (68–71). Meanwhile MEOWS was introduced in UK, in the US the National Council for Patient Safety proposed the use of the maternal early warning criteria (MERC) (72), another scoring system dedicated to obstetrics population, as well as the Maternal Early Warning Trigger (MEWT) screening, a pathway-specific tool that supported the recommendations from The Joint Commission and other relevant societies (73). MEWT system differs from MEOWS and MERC because it was developed to recognize the 4 major causes of maternal mortality which are sepsis, cardiovascular disease, pre-eclampsia and haemorrhage. Even if many were the efforts from different societies and working groups to develop and refine the maternal early warning scores, no universally scoring system has currently been validated, and no clinical trial has still assessed the impact of the use of such scoring systems on mortality reduction (74). Actually, these scores need further implementation to improve their capacity to early detect signs of early sepsis and consequently identify the risk of women clinical deterioration.

In the past decades, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine proposed a collaboration which resulted in 2002 in the institution of the Surviving Sepsis Campaign (SSC) (75). The goal was the reduction of sepsis mortality rate by 25% in five years. In doing so, according to the most recent available evidence, the SSC periodically published

guidelines with the newest updates and recommended the use of care bundles in the clinical practice (76). Sepsis care bundles are a group of the best evidence-based interventions that, when implemented, provide an impact greater than any single intervention alone and give maximum outcome benefit (77). The Royal College of Obstetricians and Gynaecologists (RCOG) endorses the use of the care bundles in the management of sepsis, showing evidence of greater survival rate following this guidance (78,79). In the US, sepsis bundles approach showed also a substantial cost saving, since the hospitals could save up to \$5000/patient using these kind of interventions (80).

The first Surviving Sepsis Campaign (SSC) guideline was published in 2004 and later revised in 2008, in 2012 and updated in 2016. Lastly, in 2018 a revised “hour-1 bundle” was settled (75,81–84). According to the first bundles from 2004, each recommendation carries a level of evidence (grades A, B, C, or D) that represents a grade of recommendations, assessment, development, and evaluation (GRADE). Initially, two sets of bundles were described: the group of the resuscitation bundles and the management ones, which were to be respectively accomplished within 6 hours and 24 hours from patient presentation (75,85) (**table V**).

The intent of the first bundles is to provide cardiorespiratory resuscitation and slow down the spread of infection. Resuscitation necessitates the use of intravenous fluids and vasopressors, and the use of oxygen therapy and mechanical ventilation, if necessary (86). The following SSC guidelines revised bundles criteria so that they at present include part of the original 6 hours bundles divided into two groups, the first is to be completed within 3 hours, the second one within 6 hours. The original 24 hours-management bundles were no longer recommended (85,87). In 2018, the latest SSC-bundles’ revision combined the 3 hours and the 6 hours bundles into a single “hour-1 bundle”; the intention was the immediate starting of resuscitation and sepsis management. In this way, the concept of “time zero or time of presentation” was introduced to refer to the moment that patient access and receive triage consistent with all sepsis or septic shock’s element determined through chart review (84).

Finally, it is important to mention that obstetric population was not specifically considered when establishing SSC guidelines and sepsis bundles, which refer to the general population.

**Table V.** Original bundles based on the 2004-Surviving Sepsis Campaign guidelines and latest bundles from the 2016-Surviving Sepsis Campaign and 2018-revised bundles.

<p><b>2004-Surviving Sepsis Campaign Bundles:</b></p> <p>Resuscitation Bundles (to be completed within 6 h)</p> <ul style="list-style-type: none"> <li>• Measure serum lactate concentration</li> <li>• Obtain blood cultures before antibiotic therapy administration</li> <li>• Provide broad spectrum antibiotic within 3 h of emergency department (ED) admission and within 1 h of non-ED admission</li> <li>• If hypotension and/or serum lactate &gt; 4 mmol/L:               <ul style="list-style-type: none"> <li>- Administer an initial minimum of 20 mL/kg of crystalloid or equivalent</li> <li>- Give vasopressors for non-responsive hypotension to maintain MAP &gt; 65 mmHg</li> </ul> </li> <li>• If persistent hypotension despite fluid resuscitation (septic shock) and/or lactate &gt; 4 mmol/L:               <ul style="list-style-type: none"> <li>- Achieve a CVP ≥ 8 mmHg</li> <li>- Achieve a ScvO<sub>2</sub> ≥ 70% or mixed SvO<sub>2</sub> ≥ 65%</li> </ul> </li> </ul> <p>Management Bundles (to be completed within 24 h)</p> <ul style="list-style-type: none"> <li>• Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for low-dose steroids based on the standardized protocol</li> <li>• Administer rhAPC in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC</li> <li>• Maintain serum glucose ≥ 70, but ≤ 150 mg/dL</li> <li>• Maintain a median IPP &lt; 30 cmH<sub>2</sub>O for mechanically ventilated patients</li> </ul>
<p><b>2016-Surviving Sepsis Campaign Bundles:</b></p> <p>Resuscitation Bundles (to be completed within 3 h):</p> <ul style="list-style-type: none"> <li>• Measure lactate level</li> <li>• Obtain blood cultures before antibiotic therapy administration</li> <li>• Provide broad spectrum antibiotics</li> <li>• Administer 30 mL/kg crystalloid over the first three hours for hypotension or lactate ≥ 4 mmol/L</li> </ul> <p>Resuscitation Bundles (to be completed within 6 h)</p> <ul style="list-style-type: none"> <li>• Give vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP &gt; 65 mmHg</li> <li>• If persistent hypotension (MAP &lt; 65 mmHg) despite volume resuscitation (septic shock) or if initial lactate ≥ 4 mmol/L, re-evaluate volume status and tissue perfusion and document findings</li> <li>• Re-measure lactate if initial lactate elevated</li> </ul> <p>Management Bundles (to be completed within 24 h) no longer recommended</p>
<p><b>2018-updated Sepsis Bundles:</b></p> <p>Resuscitation Bundles (the 3-h and 6-h bundles combined into a single 1-h bundle)</p> <ul style="list-style-type: none"> <li>• Same bundles as previously described in 2016 by SSC</li> </ul>

MAP: mean arterial pressure. CVP: central venous pressure. ScvO<sub>2</sub>: central venous oxygen saturation. SvO<sub>2</sub>: venous oxygen saturation. rhAPC: recombinant human activated protein C. IPP: inspiratory plateau pressure.

### Lactate levels

New SSC guidelines emphasized the importance of spot and serial lactate testing and suggested that they should be extended to the inpatient setting. Hypoxia is a well-known cause of increasing lactate levels, which have been demonstrated to be associated with significant morbidity and mortality (88). The explanation in lactate increase is that, during hypoxic conditions like septic shock, mitochondrial oxidative phosphorylation fails and shifts to anaerobic glycolysis that sharply increases cellular lactate production. Usually lactate levels of less than 2 mmol/L at least 2 hours apart are considered to be normal and evidence of adequate tissue oxygenation (89). If initial lactate level is found to be > 2 mmol/L, it should be repeated within 2-4 hours to guide resuscitation manoeuvre with the goal of lactate blood level normalization (90,91). Some studies report that in case of ICU's patient with lactate level at admission greater or equal to 3.0 mmol/L, its early monitor-

ing and dropping by 20% or more per 2 hours in the first 8 hours is able to reduce ICU length of stay and overall hospital mortality (90,92).

### Blood cultures before antibiotic therapy

Many studies demonstrated a significant reduction in sepsis mortality (especially in the 28-days mortality) using appropriate antibiotic therapy preceded by blood cultures (93,94). Sepsis bundles recommend obtaining blood cultures in any septic patient before the beginning of antimicrobial therapy, since only one appropriate antimicrobial dose is sufficient to sterilize cultures. Literature recommends two blood culture sets, taken from different sites at the same time. They should be collected, if possible, as soon as possible after spike of temperature. In routine practice, a set of blood culture consists of one aerobic and one anaerobic blood sample. It is important to note that, if the culture drawn through the vascular access device is positive earlier (> 2 hours) than the peripheral blood

culture, it may support the fact that the vascular access device is the source of the infection (95,96). However, it is important to avoid any potential delay of the treatments just with the aim to obtain blood cultures.

### *Antimicrobial therapy*

Recently, many Authors confirmed that starting an effective antimicrobial therapy as soon as possible after the onset of hypotension is critical in influencing septic shock mortality (97–99). Kumar et al. established that initiation of antibiotic therapy within the first hour, defined as “the golden hour”, following the onset of hypotension was associated with 79.9% survival rate. For every additional hour to delayed antimicrobial therapy initiation, survival rate were demonstrated to drop an average of 7.6% (100). Therefore an intravenous empiric broad-spectrum therapy should be started immediately for patient presenting signs of sepsis or septic shock. The initial antibiotic choice should be made in accordance with local guidelines and antimicrobial resistance profiles. Since pregnancy-related sepsis is mainly due to Group A streptococcus (GAS) and Escherichia Coli infections, empiric antibiotic coverage should include these organisms (17,26,101). Usually, standard therapy against GAS consists of high doses of  $\beta$ -lactam antibiotic; moreover, in association to penicillin, the new guidelines of the Infectious Diseases Society of America (IDSA) strongly recommends the combined use of the protein synthesis inhibitor like clindamycin. Patients with severe GAS infection hence should receive penicillin (2–4 million units every 4–6 hours intravenously) plus clindamycin (600–900 mg/kg every 8 hours intravenously) for at least 10–14 days. For penicillin-allergic patients, alternative protocol should include linezolid or the combination of clindamycin plus either vancomycin or daptomycin (102–104). Similarly, both clindamycin and penicillin are useful for coverage of susceptible enteric aerobic organisms, such as E. Coli.

Once specific pathogen is isolated from blood cultures, empiric antimicrobial therapy should be discontinued and antibiotic therapy with a restricted spectrum coverage should be started. Alternatively, therapy should be narrowed if patient does not have any infection. In case of patient proven to be unresponsive to first-line antimicrobial treatment, infectious disease specialist should be involved in

clinical management with the aim of optimizing antibiotic therapy targeting.

In addition to antimicrobial treatment, 2016-SSC guidelines also underline the importance of the so-called “source-control”, which refers to all physical and surgical measures used to control a focus of invasive infection and to restore the optimal function of the affected area. Examples of such procedures are drainage and debridement, that is the physical removal of solid necrotic tissue or of an infected device. Sometimes source control can also lead to delivery of the foetus (83,105). Recent studies about sepsis from intra-abdominal infection and correct time for surgical intervention, that is source control, advocate the need to anticipate the procedure as soon as possible, even if patient’s hemodynamic status is not still optimal. However, there is no definitive answer in the literature to the question of when source control in patients with septic shock should be started (106).

### *Intravenous fluid*

A correct fluid balance is determinant in influencing sepsis-related mortality. Many strong recommendations support the use of crystalloid fluids in the early resuscitation of patients with sepsis or hypotension and elevated lactate levels. Fluid restoration may require more than 1 hour to be completed, but initiation of resuscitation and treatment should start immediately after recognition of disease.

The 2016-SSC guidelines and the 2018-latest revised bundles endorse the use of crystalloid at an initial bolus of 30 mL/kg (83,84). This recommendation may result aggressive and potentially harmful in pregnancy, especially in patient affected by preeclampsia or pre-existing cardiac disorders or with concomitant use of oxytocin. The lower colloid oncotic pressure observed in pregnant women together with a persistent positive fluid balance can lead to fluids compartmentalization to the so-called third space, pulmonary oedema, and left ventricular diastolic dysfunction (107). For this reason, fluid resuscitation in pregnant women should be carefully managed and, after initial fluids administration, further eventual fluid therapy should be guided by dynamic measures of preload.

### *Vasopressors*

For those patients who result non-responder to initial fluid restoration or who are not eligible for fur-

ther fluid supply, vasopressors are recommended to maintain a Mean Arterial Pressure (MAP)  $\geq$  65 mmHg. Targeting an individualized MAP is essential since reaching a MAP of 65 mmHg may be excessive in a previously healthy woman. The mechanism of vasopressors is based on the correction of the pathologic vasoplegia that characterizes septic shock and the maintenance of blood perfusion to organs. Although both dopamine and norepinephrine are recommended as first-line vasopressor agents in septic shock, and there is no significant difference in the outcome between patients treated with the first or with the second, SSC guidelines suggest the use of norepinephrine since it is associated with a lower number of adverse events (84,108,109). There is a lack of high-quality studies about the effects of vasopressors during pregnancy-related septic shock; however, norepinephrine has been proven to be safe in pregnancy for both the mother and the foetus (110). Epinephrine or vasopressin might also be used in pregnancy, especially when initial norepinephrine administration fails to maintain an adequate MAP. Conversely, dobutamine, which has an inotropic function, should only be infused in the setting of myocardial dysfunction or continued hypoperfusion despite fluid and vasopressor therapy (83,111).

### *Other interventions*

In addition to the interventions above reported, other drugs and controls should be considered for the management of sepsis in pregnancy. Based on the clinical conditions, interventions such as hydrocortisone administration, blood and platelet transfusion, active glycaemic control, antithrombotic prophylaxis, and prophylaxis for gastric ulcers can be required to control the disease or prevent complications (26). Noteworthy, both pregnancy and sepsis are risk factors for venous thromboembolism, and prophylaxis with low molecular weight heparin (LMWH) has been reported effective in the prevention of venous thromboembolism in pregnancy and puerperium (112).

## **DELIVERY AND ANAESTHESIA CONSIDERATIONS**

Appropriate timing for foetus delivery should be dictated by obstetric indications. The presence of sepsis itself is not mandatory for immediate deliv-

ery, especially if patient appropriately responds to early resuscitation treatment. Indeed, unless some conditions like chorioamnionitis or septic abortion occur, there is no evidence that prompt delivery improves maternal outcomes. Furthermore, attempting delivery in women with septic shock who are hemodynamically not stable may influence negatively both maternal and foetal mortality rates (113). For this reason, taking into account gestational age, maternal and foetal clinical conditions, stage of labour, and the presence of chorioamnionitis should be an obstetrician's priority that has to lead and justify clinical decisions.

During maternal sepsis management and treatment, foetal wellbeing has to be monitored with the most appropriate method. If the risk of preterm birth occurs, corticosteroids should be considered for foetal lung maturation, but this decision should be balanced with the need of immediate delivery (114,115). Regarding this last point, it has to be stressed that in case of maternal sepsis, antenatal corticosteroids are not contraindicated and are one of the most important antenatal therapies available to improve new-born outcomes, even in case of sepsis (116,117).

Some studies point out how septic shock is highly associated with the necessity of urgent caesarean section and that it is more frequent in those women with respiratory complications such as ARDS disease, which can lead to a rapid deterioration in both the mother and the foetus (118).

If the uterus is demonstrated to be the source of infection and surgical intervention for source control is needed, the decision whether to proceed or not ultimately depends on obstetrician's choice. The anaesthesiologist may advise whether to undergo regional or general anaesthesia, but it primarily depends on the risk and benefits of each approach, that should be evaluated case by case. To the best of our knowledge, there are no trials which have answered the question whether is better to proceed with regional or general anaesthesia in case of maternal sepsis. Regarding regional anaesthesia, underlying sepsis is a risk factor for spinal cord infective complications, like meningitis or neurological deficit secondary to abscess compression (119–121). Even if neuraxial anaesthesia is generally considered to be relatively contraindicated in case of sepsis, the American Society of Anaesthesiologists (ASA) and the American Society of Regional Anaesthesia (ASRA) advocate the possibility of using an individualized and

history-based protocol of regional anaesthesia in case of septic patients.<sup>(122)</sup> When regional anaesthesia cannot be provided in safe conditions, the guidelines suggest the use of general anaesthesia. It is important to consider that pregnancy physiologically modifies pulmonary ventilation and cardiovascular capacity; these changes imply an increased risk of gastric aspiration, difficult intubation and aortocaval compression, especially during general anaesthesia. Obstetric anaesthesiologist should not underestimate pregnancy-related risks when approaching a parturient with sepsis who necessitates anaesthesia.

## NEW PERSPECTIVES

The crucial key message across all major societies' efforts is that mortality from maternal sepsis is preventable, and that early recognition and treatment is vital to achieve this outcome. To date, having large-scale randomized clinical trials (RCT) to develop guidelines for sepsis in pregnancy and puerperium results problematic, since pregnancy is an exclusion criterion for most of the studies due to obvious ethical reasons. To the present day, the available evidence for maternal sepsis manage-

ment are provided from RCT conducted on the general population and for this reason do not take into account any physiological changes of pregnancy. Therefore, recommendations are to follow the current guidelines for nonpregnant women while considering the ways in which pregnancy may change the goals of management. Further studies are needed to establish pregnancy-related diagnostic criteria for sepsis and septic shock in the obstetric population and to consequently develop specific protocols. These obstetric-specific guidelines may finally help in reducing mortality rate for sepsis and septic shock in pregnant population.

## CONFLICT OF INTEREST

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper. All the authors conform the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study, and gave approval for the final version of the article.

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## Clinical application of Lung Ultrasound for the management of pregnant women with suspicion of COVID-19: a review of literature

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### ABSTRACT

COVID-19 is an infectious illness caused by a virus named SARS-CoV-2. Recent studies underlined the need for chest computed tomography (CT) in COVID-19 patients to assess lung involvement. However, CT has a series of disadvantages, such as the need to move the patient from an isolation room to a Radiology Department, the difficulty in protecting and disinfecting the machine, the high cost of the equipment. These disadvantages apply especially to pregnant women, in particular because of the exposure to a significant amount of radiation to the fetus.

In order to avoid these disadvantages, a series of manuscript were published on the alternative use of Lung Ultrasound (LUS) during COVID-19 outbreak. Therefore, we carried out a review of the published studies and case reports, in order to underline the advantages, the correct technique, the typical LUS manifestations of COVID-19 and to help researchers in the diagnosis and monitoring of the disease, especially for obstetricians and gynecologists who already use ultrasound in their clinical practice.

### SOMMARIO

COVID-19 è una malattia infettiva causata da un virus chiamato SARS-CoV-2. Studi recenti hanno sottolineato la necessità della Tomografia Computerizzata del torace (TC) nei pazienti COVID-19 per valutare il coinvolgimento polmonare. Tuttavia, la TC presenta una serie di svantaggi, come la necessità di spostare il paziente da una stanza di isolamento a un reparto di radiologia, la difficoltà nella protezione e disinfezione della macchina, l'alto costo dell'attrezzatura. Questi svantaggi si applicano soprattutto alle donne in gravidanza, in particolare a causa dell'esposizione a una quantità significativa di radiazioni al feto.

Al fine di evitare questi svantaggi, una serie di manoscritti sono stati pubblicati sull'uso alternativo dell'ecografia polmonare (LUS) durante l'epidemia di COVID-19. Pertanto, abbiamo effettuato una revisione degli studi pubblicati e dei case reports, al fine di sottolineare i vantaggi, la tecnica corretta, le tipiche manifestazioni LUS di COVID-19 e di aiutare i ricercatori nella diagnosi e nel monitoraggio della malattia, in particolare per gli ostetrici e ginecologi che usano già gli ultrasuoni nella loro pratica clinica.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by a virus named SARS-CoV-2. The first case was reported in Wuhan (1), but rapidly the outbreak spread all over the world. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as pandemic (2) and 412,755 cases were confirmed from all over the world on March 25, 2020 (3).

The gold standard for COVID-19 diagnosis is real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acid. However, recent studies underlined the need for chest computed tomography (CT) in COVID-19 patients to assess lung involvement (4,5). Fang et al. reported the CT sensitivity as 98% in diagnosing of COVID-19 pneumonia (6). In addition, CT examination is important not only in diagnosing but also in monitoring COVID-19 patients (7). The typical CT-signs are bilateral distribution of ground glass opacities (GGO) with or without consolidation in posterior and peripheral lungs (8,9).

However, CT has a series of disadvantages, such as the high amount of radiation, the need to move the patient from an isolation room to a Radiology Department with the potential spread of the outbreak. In addition, the difficulty in protecting and disinfecting the machine, as well as the high cost of the equipment with the poor availability in developing countries have to be considered.

These disadvantages apply especially to pregnant women, in particular because of the exposure to a significant amount of radiation to the fetus.

In the last years, a series of studies have shown that Lung Ultrasound (LUS) is able to identify interstitial lung disease and acute respiratory distress syndrome (10-13), even during pregnancy (14). As a result, recent articles were published on the alternative use of LUS during COVID-19 outbreak.

Therefore, we carried out a review of the published studies and case report, in order to underline the advantages, the correct technique, the typical LUS manifestations of COVID-19 and to help researchers in the diagnosis and monitoring of the disease.

### Advantages

The use of LUS in the management of patients with COVID-19 has several advantages:

- *avoid moving the patient* (15). This aspect simplifies the management of unstable patients who

should be transported by an intensive care to a radiology department;

- *clinical examination and LUS execution by a single operator*. The exam can be performed directly at bed side by a single initial operator, reducing the risk of spreading the outbreak among health professionals (16);
- *establish the severity of the disease*. LUS can distinguish low-risk patients (negative lung ultrasound) from high-risk patients (with pulmonary ultrasound abnormalities), which may require second-level imaging or specific therapies (15);
- *home evaluation* (15). Thanks to the existence of portable ultrasound machines, ultrasound could be performed at home, avoiding hospitalization and overcrowding of hospitals already under pressure;
- *does not use ionizing radiation*. This advantage is particularly important in monitoring those patients who require serial exams (10);
- *less expensive than CT*. LUS is a cheaper than CT scan and more easily to use in developing country (15);
- *use in pregnant women*. LUS has proven to be a reliable method for diagnosing pneumonia in pregnant women, avoiding fetus radiation exposure (17,16).

### Disadvantages

A known limitation of LUS is that this technique is unable to find deep lung lesions. In fact, the anomalies must extend to the pleura to be detectable at ultrasound, otherwise the air blocks the transmission of the ultrasound, making the execution of the CT necessary to detect pneumonia (19).

Indeed, average diameter of SARS-CoV-2 is about 120 nm, which allows it to reach the terminal alveoli, determining a peripheral pulmonary pathology (20).

## METHODS

In order to allow researchers from all over the world to perform a systematic examination, Soldati et al. proposed a standardized method (21).

During the COVID-19 outbreak, LUS should be performed with a portable convex probe (3.5 MHz), connected wirelessly with a tablet. Although this device processes lower quality images than the new larger ultrasound machines, in this setting,

the wireless ultrasound machine is the most appropriate in order to avoid contamination of the machine and the operator. In fact, these devices can be easily wrapped in disposable plastic covers.

The first operator performs LUS while a second operator, placed at a safe distance from the patient, holds the tablet and freezes images or videos (16). The protocol (21) requires that the operator analyzes 14 areas for 10 seconds:

- posteriorly, along the paravertebral line and bilaterally, in the basal (above the “curtain sign”), middle (inferior angle of scapula) and apical site (spine of scapula);
- anteriorly, along the mid-clavicular line and bilaterally, above and below the internipple line;
- laterally, along the mid-axillary line, above and below the internipple line.

Furthermore, the scans must be:

- intercostals, in order to analyze a large area;
- with focal point set on the pleural line, to optimize the beam shape and to highlight more details;
- with a low mechanical index, to avoid damage to the lungs;
- free of saturation phenomena, due to high echo signal and determining completely white areas;
- without imaging modalities such as Doppler or Contrast;
- with a high frame rate;
- saved in DICOM or video format.

## NORMAL AND ABNORMAL LUS PATTERN

In a healthy patient, the only lung structure that can be viewed directly by ultrasound is the pleural line, represented by a hyperechoic horizontal line. This line has horizontal movements synchronized with breathing (“lung sliding”). In fact, the air determines a high acoustic mismatch: the ultrasound beam is reflected and the pulmonary parenchyma is not displayed. This reflection causes the formation of artifacts, called “A-lines” and represented by horizontal, parallel and hyperechoic lines (Figure 1). As a result, LUS can only evaluate lung disease that has an impact on the pleura (22-24).

In cases of diseases that cause partial loss of the peripheral lung, for example an interstitial pneumonia, the so-called “B-lines” are formed (Figure 2). They are represented by heterogeneous vertical artifacts probably generated by the variation of the acoustic impedances due to the disease (12,25).

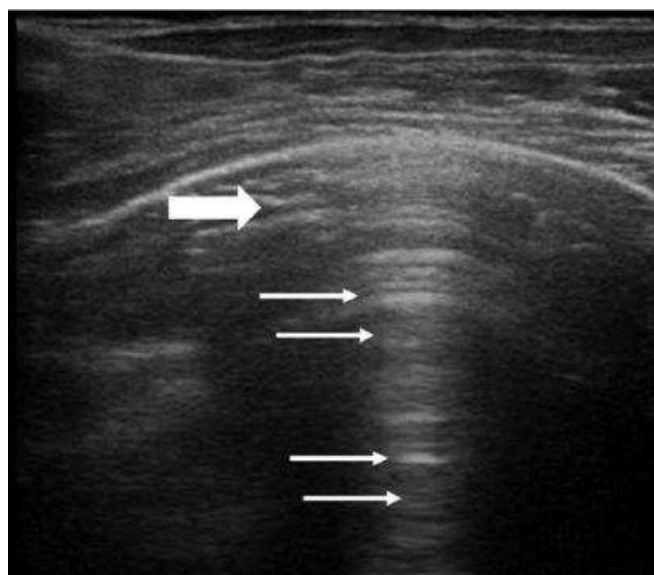


Figure 1. Lung ultrasound findings in a normally aerated lung. It is possible to see the pleural line (white thick arrow) and A-lines (white thin lines)

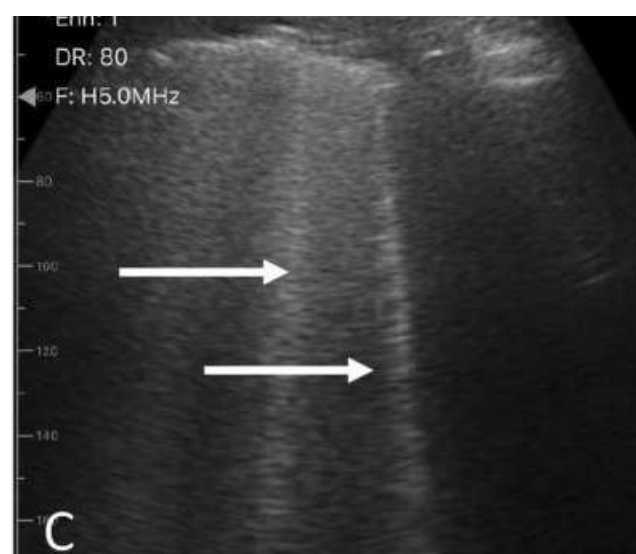
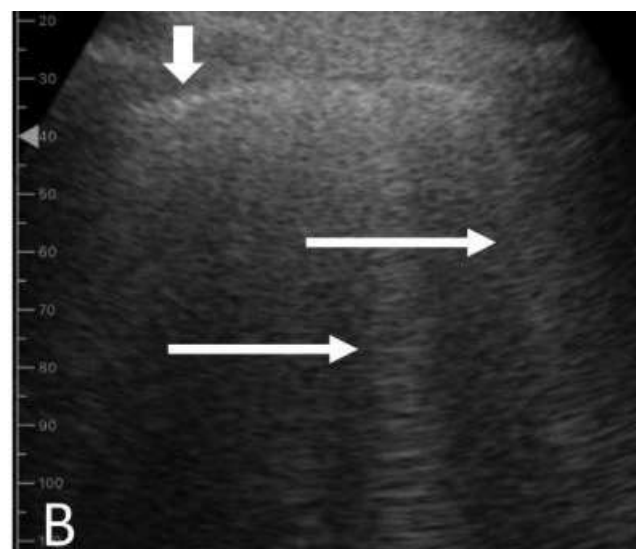


Figure 2. Lung ultrasound scan showing a vertical artifact (B-line, thin arrow) in the context of otherwise normally aerated lung with normal pleural line (white thick arrow)

On the other hand, if the density of the lung parenchyma increases without a consolidative state (12), for example in Acute Respiratory Distress Syndrome (ARDS), LUS highlights a white area in absence of A and B-lines (“white lung”) (Figure 3). When the lung collapsed, as in pneumonia or atelectasis, it appears as an irregular hypoechoic area, the *consolidation* (12,25), comparable to the liver (Figure 4).

Instead, the *pleural effusion* is due to collection of fluid in the pleura. It appears completely anechoic or with hyperechogenicity due to blood, pus, fibrin (26).

### LUS manifestations of COVID-19

Xu et al. reported that SARS-CoV-2 uses angiotensin-converting-enzyme-2 (ACE2) as the cell receptor, resulting in an interstitial lung damage (27). Table I shows the LUS manifestations of COVID-19 in the published articles. The lesions are found mainly in the posterior fields of both lungs (20). The findings identified were:

- B-lines;
- subpleural consolidations;

- thickening of the pleural line with irregularities or discontinuities, probably secondary to the reduced air content of the lung (20);
- regions of white lung;
- air bronchograms and pleural effusions are rare.

Since these findings are shaped following variations in acoustic impedance, LUS indirectly highlights the histopathological changes, which can also be recognized by CT (29).

Furthermore, the results are related to the severity of the disease (19).

Based on published articles (19,20,28), an irregular and rare distribution of B-lines and small white lung regions are found in the early and less severe stages of pneumonia COVID-19. Subsequently, these lesions involve an increased lung surface. Subpleural consolidations with associated areas of white lung appear in the more advanced stages. When these consolidations increase, located mainly in a gravitational position and possibly associated with air bronchograms, they indicate the evolution towards respiratory insufficiency.

Comparing ultrasound images with CT scans, Haung et al. found comparable findings. However, CT showed a superiority in displaying intrapulmonary and apical lesions, while LUS has a greater capacity to detect small peripulmonary lesions and pleural effusion (20).

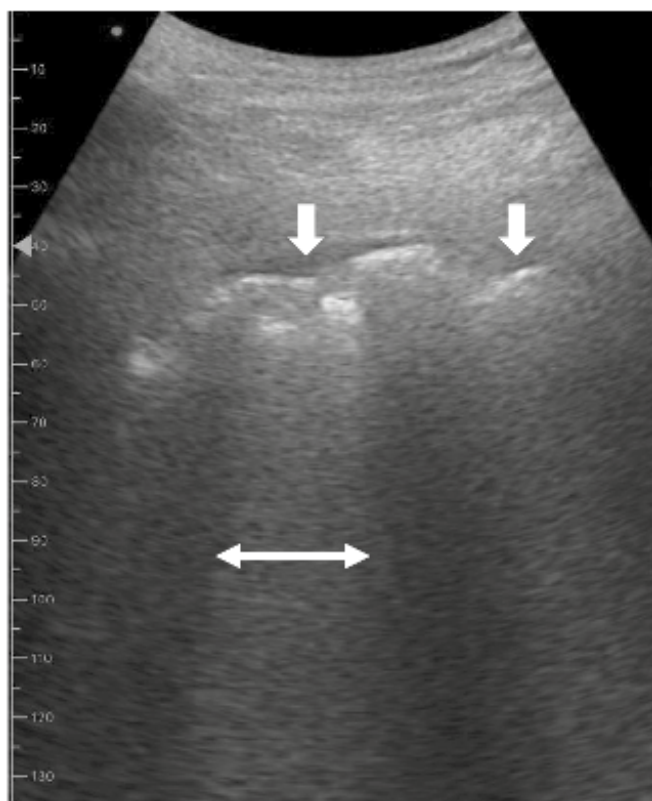


Figure 3. Lung ultrasound scan showing the small subpleural consolidations with areas of white lung. The pleura line is severely broken. Below the point of discontinuity, small consolidated areas (white thick arrow) appear with associated areas of white (double head arrow) in correspondence with the consolidations. The normal A-lines are not visible, nor single vertical artefacts. Conversely, a dense white area is visible below the pleural line (double head arrow).

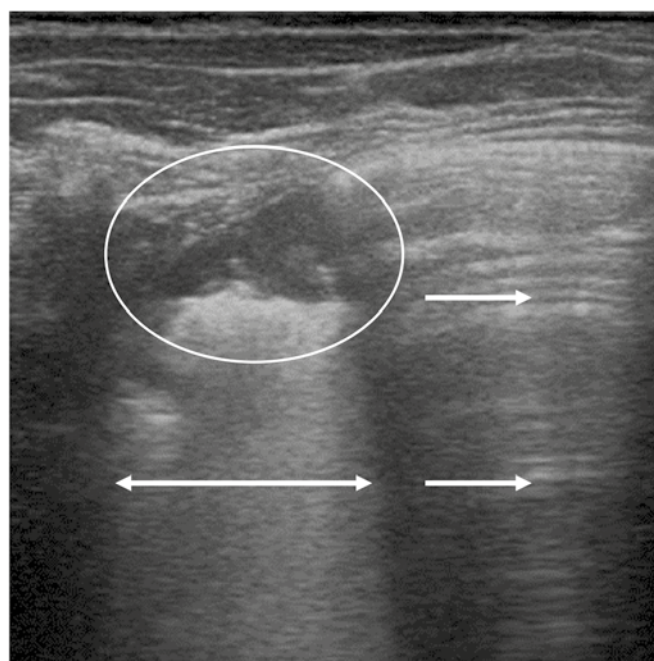


Figure 4. Lung ultrasound scan showing a subpleural consolidation (white circle), characterized by a hypoechoic area below the pleural line (white thin arrow). Below the point of discontinuity, large consolidated areas (white circle) appear with generalized white lung pattern (double head arrow). A-lines (white thick arrow) are visible in the close normal lung.

Table 1. LUS findings of COVID-19 currently described in literature

Authors	No. of patients	B-lines	White lung regions	Subpleural consolidation	Thickened pleural line	Air bronchograms	Discontinuous pleural line	Pleural effusion
Inchingolo et al. (16)	1	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	-	-	-
Poggiali et al. (27)	12	100% (1/1)	-	25% (3/12)	-	-	-	-
Huang et al. (19)	20 (examined 12 areas per patient, for a total of 240)	38% (91/240)		22% (53/240)	8% (19/240)	15% (37/240)	15% (36/240)	10% (24/240)
Peng et al. (18)	20	Yes	-	Yes	Yes	-	Yes	Uncommon
Buonsenso et al. (14)	1	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	-	100% (1/1)	-
Soldati et al. (20)	30	Yes	Yes	Yes	Yes	-	Yes	-

### LUS Score

In order to allow researchers from all over the world to obtain comparable data, Soldati et al. proposed a LUS score for COVID19- pneumonia (21):

- **score 0:** there are a **regular pleural line and A-lines**;
- **score 1:** presence of vertical artifacts. Due to the inflammatory processes and the consequent change in acoustic impedances, the **pleural line appears indented** and below it is possible to identify **B-lines** and **areas of white lung** (12, 13);
- **score 2:** presence of a **broken pleural line with dark and white consolidation areas** underneath. The first is related to the loss of ventilated tissue which is replaced by inflammatory tissue. The second is because of inclusions of air present in phlogistic process (12, 13);
- **score 3:** presence of a **dense and widely extended white lung**.

### CONCLUSIONS

Our review demonstrates that LUS is a reliable technique, useful in early diagnosis and monitoring, easier to perform, and less expensive than CT. In particular, LUS is a technique capable of diagnosing and monitoring COVID-19 pneumonia in pregnant women, avoiding excessive exposure to ionizing radiation of CT.

In addition, obstetricians and gynecologists who already use ultrasound in their clinical practice, represent a category of professionals who could easily examine the lung of pregnant patients, selecting those who need to be triaged for specialist care.

Given that COVID-19 is a global health challenge, a greater diffusion of this technique is needed in order to offer this diagnostic surveillance to as many patients as possible. The creation of a shared database is desirable, in order to create an algorithm able to identify the characteristic findings of COVID-19, developing a telemedicine program and sharing the results achieved.

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## Perinatal and post-partum infections in times of Coronavirus: are compliance with cautionary measures and safety protocols key factors in staving off litigation?

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### ABSTRACT

Several factors have been associated with increased risk of maternal and fetal peripartum and postpartum infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anaemia, bacterial vaginosis, and group B streptococcus infections) and unexpected or iatrogenic conditions during labour and childbirth, such as prolonged rupture of membranes (PROM) multiple vaginal examinations, manual removal of the placenta, and cesarean section. As such, the strategies to reduce maternal and fetal infections and their short- and long-term complications have been largely directed at preventive measures where such risk factors exist. In many cases of maternal and fetal infections, medical negligence may have played a role. In fact, a given infection may not have been detected during examinations, or proper treatment may not have been implemented in a timely fashion. In fact, some infections may become more severe if they are not properly treated as quickly as possible. The Authors have aimed to shed a light on the most common, and feared, childbirth-related infections, by means of a wide-ranging analysis of medical databases (Scopus, Pubmed, Embase, Research Gate, Web of Science), legal archives (Justia, Leagle, Lexis, Casetext) and recommendations issued by medical and scientific institutions (United Nations, World Health Organization, Centers for Disease Control and Prevention, National Health Service, etc...), spanning the 2004-2020 period. The inability on the part of physicians to thoroughly document the appropriateness of their interventions and the compliance with guidelines and best practices often results in claims being filed by damaged patients and/or their legal heirs. Litigation is typically complex in such cases, and likely to result in substantial compensatory damages being awarded to damaged patients. Currently, a higher standard for cautionary rules should be applied by practitioners and medical facilities to minimize the risk of claims being filed, particularly in tort courts. As a

### SOMMARIO

Numerosi fattori sono stati associati ad un maggiore rischio di infezioni materno-fetali peripartum e postpartum, tra cui condizioni materne preesistenti (ad esempio malnutrizione, diabete, obesità, anemia grave, vaginosi batterica e infezioni da streptococco di gruppo B) e condizioni inattese o iatrogeniche che insorgono durante il travaglio o al momento del parto (ad esempio rottura prolungata delle membrane, esami vaginali multipli, rimozione manuale della placenta e taglio cesareo). Pertanto, le strategie per ridurre le infezioni materne e fetali e le loro complicanze a breve e lungo termine sono state in gran parte rivolte ad implementare misure preventive in presenza di tali fattori di rischio. In molti casi di infezioni materne e fetali sono addebitabili a condotta colposa dei sanitari. Infatti, in alcune fattispecie, l'infezione potrebbe non essere stata rilevata durante gli accertamenti diagnostici previsti o qualora anche individuata, si potrebbero configurare casi di ritardato trattamento della stessa, che determina in molti casi un aggravamento del processo infettivo. Gli Autori si soffermano sulle infezioni peripartum considerate più comuni e pericolose, mediante un'analisi di banche dati mediche (Scopus, Pubmed, Embase, Research Gate, Web of Science) e di archivi legali (Justia, Leagle, Lexis, Casetext) effettuata per un arco cronologico compreso fra il 2004 e il febbraio 2020. Gli Autori hanno altresì analizzato le linee guida e best practices emanate da istituzioni mediche e scientifiche nazionali e sovranazionali (Nazioni Unite, OMS, Centri per il controllo e la prevenzione delle malattie, Servizio sanitario nazionale, ecc ...). Al verificarsi di eventi avversi in sala parto con conseguenze sfavorevoli alla madre e/o al feto/neonato, la condotta dei sanitari può essere chiamata in causa se i medesimi non sono in grado di comprovare il rispetto delle regole cautelari e che gli eventi in questione non siano riconducibili al loro operato. Da tali situazioni deriva un numero sempre crescente di contenzioso, di cui gli Autori hanno riportato esempi significativi, nell'ambito

matter of fact, the current global setting of Covid-19 pandemic crisis has engendered unique conditions. Hence, specifically targeted measures are needed in maternity centers in order to stave off the contagion of healthy patients, while at the same time providing the best possible care for Covid-19 positive parturients and their newborns. Compliance with directives and regulations issued by health care authorities, aimed at the implementation of adequate diagnostic pathways, isolation protocols and protection requirements, is undoubtedly crucial for preventing malpractice allegations and liability.

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## INTRODUCTION

Neonatal infections may be characterized as congenital (i.e. those which were present at birth and likely acquired in the maternal womb) or perinatal, that is acquired later in pregnancy or upon delivery. Outcomes for the neonate after infection can vary widely based on the organism involved, the time during gestation when infection occurs, and whether the mother has any protective antibodies that can provide the fetus with passive protection, reducing the disease severity for the infant. Transplacental spread of maternal infection is the common route by which the fetus acquires infection. Placental infection is often associated with systemic illness in the neonate; thus, molecular, microbiologic, and pathologic examination of the placenta is important in the critically ill newborn. In the perinatal period, acquired early-onset infection (before 72 hours) is almost always caused by organisms acquired in the maternal birth canal. After this period, most infections are acquired through close contact with members of the baby's environment and through human milk. The manifestations of infection vary with the infecting organism. The mechanism and dynamics relative to damage and response by the host and the stage of the pregnancy, determine the effects on the neonate. Some pathogens can trigger harmful effects throughout gestation. Fetal organogenesis is usually complete by 12 weeks gestation; thus, damage

del quale è sempre più difficile dimostrare l'estraneità della condotta dei sanitari al prodursi dell'evento infettivo e delle sue complicanze. Attualmente in tutto il mondo sono richiesti standard più elevati di misure cautelative per evitare addebiti di malpractice. Una condizione del tutto peculiare è quella del contesto epidemico attualmente vissuto in relazione alla infezione da Covid-19. Specifiche misure sono richieste nei punti nascita al fine di evitare il contagio di donne sane e di ridurre i danni per le partorienti infette e i loro neonati. L'aderenza alle disposizioni delle autorità sanitarie in termini di predisposizione di adeguati percorsi diagnostici, procedure di isolamento e sistemi di protezione è considerata decisiva per evitare addebiti di responsabilità.

### Key words:

*Childbirth infections; safety protocols; Covid-19; sanitation practices; claims.*

incurred during this period will likely result in anomalies (1). The mother does not transfer T-cell specific immunity, crucial in the control of many viruses, to the fetus. As for maternal Immunoglobulin G (IgG) antibodies, they are transferred to the fetus and reach one-half the normal serum concentration by approximately 30 weeks' gestation, and more normal values at term. Furthermore, the transferred antibodies need to have a certain degree of concentration to be protective. In some bacterial infections, the mother might not have enough antibodies in her system, and this factor is complicated by the newborns inability to rely on an antibody response to polysaccharide antigens, such as those found on bacterial capsules such as those of group B Streptococcus. Newborns who experience a sufficient period of antigenic stimulation (usually 7-14 days) will exhibit an identifiable and measurable Immunoglobulin M (IgM) response to some viruses and parasites, which has diagnostic value. Moreover, antigen-specific T-cell responses are significantly reduced or delayed in neonates, and this also contributes to delaying B-cell and antibody responses. Still, it is worth stressing that the pathogenesis of neonatal infection is not yet fully understood (2). Globally, the most common intervention for preventing morbidity and mortality related to childbirth infection is the use of antibiotics for prophylaxis and treatment. However, the misuse of antibiotics for obstetric conditions and procedures that are thought

to carry risks of maternal infection is common in clinical practice. Such inappropriate use of antibiotics among women giving birth has implications on global efforts to contain the emergence of resistant bacteria strains and, consequently, on global health. The WHO global strategy for containment of antimicrobial resistance underscores the importance of appropriate use of antimicrobials at different levels of the health system to reduce the impact of antimicrobial resistance, while ensuring access to the best treatment available. Therefore, appropriate guidance for health professionals and policy-makers on the need for antibiotics and the type of antibiotics for the prevention and treatment of maternal peripartum infections would align with the WHO strategy and, ultimately, improve maternal and newborn outcomes (3,4).

Various definitions and terms have been proposed for childbirth-related infections, but none are used universally. A WHO technical working group has outlined the concept of puerperal sepsis as infection of the genital tract, happening any time between the onset of rupture of membranes or labour and the 42<sup>nd</sup> day postpartum; two or more of the following signs are observed: pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odour discharge or delay in uterine involution. While this definition captures well the characteristics of infections related to giving birth, the use of the term puerperal suggests that the onset of infection is only limited to the puerperium. Patients are at a higher risk of urinary tract infection during the post-partum stages, and such complications might be linked to risk factors such as prolonged catheterization (catheters should therefore be promptly removed immediately when no longer needed), epidural anaesthesia and operative delivery; a study has found the incidence to be 2.8% after CS and 1.5% after vaginal birth (5). In addition, studies have pointed out that women with diabetes mellitus are at a higher infection risk, of the lower genital tract; significantly, those with poorly controlled diabetes appear to run the highest risk of contracting genital infections (6,7). It is worth noting that subclinical intraamniotic infection could lead to postpartum cardiovascular collapse and disseminated intravascular coagulation; such developments may be erroneously ascribed to other conditions, such as amniotic fluid embolism (AFE) (8), unrelated to infection. Patients diagnosed with AFE may therefore have infection/systemic inflammation

instead, a study has found. These observations have implications for the understanding of the mechanisms of disease of patients who develop cardiovascular collapse and DIC, frequently attributed to AFE (9).

## RISK OF LITIGATION ARISING FROM COVID-19 CASES AMONG PARTURIENTS

Pregnant women and their fetuses are undoubtedly high-risk population segments when outbreaks spread. Scientific studies have reported the outcomes of 55 pregnant women and 46 neonates who contracted COVID-19; still, no conclusive proof of vertical transmission has been found 10-11. Exposure and susceptibility to infections is affected and increased by pregnancy-related physiological and mechanical changes; that is particularly significant in Covid-19 cases: if the cardio-respiratory system is affected, such a scenario may lead to a rapid progression which can potentially trigger respiratory failure in pregnant patients (12). It is also worth noting that the pregnancy bias towards T-helper 2 (Th2) system dominance, which protects the fetus, could leave the mother more exposed to viral infections. Moreover, it is of utmost importance to put in place comprehensive safety measures based on principles such as consistent social distancing, workplace segregation, containment of cross-infection to health care providers, sensible and timely use of personal protective equipment and telemedicine (13). A rapid review has found that preterm delivery in 47% of women hospitalized with COVID-19 in the United Kingdom, which may put the nation's neonatal services under severe pressure, should the UK's reasonable worst-case scenario (80% of the population being infected) become reality (14). On 18th March 2020, the Royal College of Obstetricians and Gynaecologists (RCOG), in consultation with RCM, RCPCH, RCOA, OOA, issued guidance for delivery and neonatal care in COVID-19 affected pregnancies; among the recommendations, it is stressed that the delivery mode should be primarily determined by obstetric indication and that the separation of affected mothers from their babies is not advisable (15-17).

In addition, one of the most meaningful recommendations is that all patients who are admitted to maternity wards should receive screening for Covid-19, if they have distinctive symptoms, and

all women with symptoms should be considered potentially Covid-19 positive.

Evidence pointing to clusters and co-infections within households has led to the request for the implementation of preventive measures such as consistent hand hygiene and use of respiratory masks for asymptomatic family members who wish to access maternity units to attend delivery, whereas partners who tested positive are required to comply with quarantine protocols, and are therefore banned from the facilities.

The Royal Colleges also recommend that whenever gravidas are hospitalized due to the worsening of symptoms and suspected or confirmed Covid-19 infection, multidisciplinary assessment examinations must be carried out in a timely fashion, ideally with the involvement of infectologists, obstetrician/gynecologists, midwives, and delivery anesthesiologists. All such proceedings and their conclusions should be discussed with the patient, with a close focus on care priorities, the most suitable location (e.g. intensive care units, isolation rooms within infectious disease wards or elsewhere), the medical specialists who contributed to the process, the medical team's concerns about specific pregnancy aspects, particularly fetal conditions. Elective cesarean section is not recommended by currently available scientific evidence in such cases. All prescriptions about pregnancy and delivery progress as well as fetal health are therefore advisable (18). On the other hand, water birth ought to be advised against, due to evidence pointing to possible the possibility of a faecal-oral route of Covid-19 transmission. No scientific evidence currently recommends augmentation of labor in Covid-19 positive patients, and any decision to resort to peridural anesthesia should be discussed and agreed upon with all delivery team members (gynecologist, obstetrician and midwife), based on maternal and fetal clinical conditions. Access to obstetrical wards is not allowed to Covid-19 positive partners, who must abide by quarantine protocols. Such indications have been transposed into regulations by health care authorities in many countries. In Italy, for instance, the Ministry of Health issued a Covid-19 set of directives on 31<sup>st</sup> March 2020 ("Indicazioni per gravida-partoriente, puerpera, neonato e allattamento") (19). In the decree, the Ministry has codified the need for pregnant women to gain admission to "Punti Nascita" (Birth Centers) hubs, also denominated 2<sup>nd</sup> level birth centers, which must be set up by regional govern-

ments or autonomous provincial authorities based on population demographics for each specific area. The new regulations mandate that each birth center be tasked with outlining pathways aimed at the proper management of obstetrical care during labor and delivery for suspected or proven Covid-19 cases, for any situation in which patient transfer is contraindicated. Specifically, tenable procedures must be laid out for obstetric care in vaginal delivery or cesarean section and puerperium, which need to include thorough protective measures for all health care operators.

In cases of SARS-CoV-2 positive gravidas, strict measures need to be put in place in order to avoid the accidental transmission of the infection, either airborne or through contact with respiratory secretions. Newborns, the other hospitalized patients and health care personnel all must be safeguarded at all times. Confirmed Covid-19 cases should therefore be able to rely on single, negative-pressure isolation rooms whenever possible, with independent bathrooms and ideally, adjacent anterooms. Should such services be unavailable, confirmed cases should anyway be hospitalized in single rooms with bathrooms, to be transferred as soon as possible to facilities with higher safety standards. All procedures that could give rise to aerosol emissions have to be carried out in negative-pressure isolation rooms. Health care staff members who came into contact with suspected or confirmed Covid-19 cases must wear all proper Personal Protective Equipment (PPE), i.e. FFP2 respirator masks (FFP3 should be used for aerosol-generating procedures), facial protection, water-proof vests, gloves. The issuance of regulations by national health care authorities has a profound legal impact in terms of possible liability of health care operators and hospital management, when Covid-19 transmission is found to have occurred, as it would happen in any epidemic outbreak. As a matter of fact, the margin of appreciation granted to doctors, obstetricians, neonatologists and anesthesiologists is rather small: all procedures will in fact have to be carried out in strict compliance with official protocols, as laid out in policy papers issued by each regional health care bureau. Individual operators will be held liable only in cases of blatant failure to abide by the regulations issued by health care authorities (from which negligence liability may arise). Within the epidemic framework, hospital management may be called to answer for its acts as well, in light of its role as guarantor of in-

frastructure suitability, the implementation of adequate proceedings, the constant compliance with all measures aimed at the protection of patients and staff, and with the standards set by health care authority provisions. Although no jurisprudence has developed yet with regard to Coronavirus cases, precedents set in similar circumstances seem to show that the choice on the part of hospital managers or personnel to operate in conditions of sub-standard care does not rule out possible liability; such a choice is in fact bound to entail risks for professionals and patients alike.

### ***Delivery room malpractice: potentially catastrophic fallout***

Congenital and perinatal infections are undoubtedly major factors in determining permanent disability among children all over the world. Linked together by the acronym TORCH, denoting *Toxoplasma gondii*, rubella virus, cytomegalovirus, and herpes virus, congenital infections can result from only a modest number of human pathogens that cross the placenta and infect the fetus. Although congenital rubella syndrome has been eliminated in the Americas by immunization, no effective immunization exists yet against several pathogens, which cannot even be effectively treated by currently available antimicrobial drugs (20). Although expecting parents certainly experience great joy at the thought of their child soon to be born, quite frequently the path to motherhood entails risks that can result in damages and injuries to mothers and infants. As a matter of fact, several changes occur in the mother's system and body during pregnancy; The maternal immune system is complex and governed by multiple metabolic and hormonal factors, and during pregnancy, it adjusts in order to protect the mother, as well as her unborn child, from disease (21). During this process, some parts of the immune system are suppressed, while others are enhanced. This can put the pregnant mother at a higher risk of bacterial infections. The death rate of viral and bacterial infections is higher in pregnant women compared to non-pregnant women. The constant monitoring of women throughout pregnancy, and particularly delivery, is therefore extremely important in order to promptly identify any infection throughout pregnancy (22). Any failure on the part of doctors to identify infection in time and to select and administer suitable antibiotics in a timely fashion can jeopardize the lives of

mothers and unborn children alike. Such development can result in medical negligence litigation. Affected families can file lawsuits against the doctors involved if any malpractice is suspected (**table I**).

### **PROVIDING PATIENTS WITH THOROUGH INFORMATION IS KEY TO STAVING OFF LITIGATION**

The provision of thorough information to patients is undoubtedly a key factor. A 2009 survey of 606 Collaborative Ambulatory Research Network (CARN) members of the American College of Obstetricians and Gynecologists (sampled to demographically represent ACOG) found that a 67% majority agreed that informing pregnant patients about infection risk during pregnancy was prioritized in their practice. Still, although many specialists routinely counsel their patients on preventing toxoplasmosis (87.7%), hepatitis B virus (78.8%), and varicella-zoster virus (60%), less than half reported counseling patients on preventing less common conditions such as CMV, LCMV, and *Bordetella pertussis* infections. The majority reported counseling typically occurred at initial prenatal exams (30). Furthermore, throughout the process of communicating with the patient as well as the public at large, it is essential to tailor health messages to the appropriate literacy and language level. Hence, in order to tackle and minimize that issue, use of understandable, simplified language should be consistently encouraged on written documents, such as consent forms and patient instructions and in face-to-face counseling conversations. Moreover, patients and their families/legal guardians must be informed on any views or convictions held by their doctors, which may lead to a refusal, on conscience-related, religious or moral grounds, to provide certain forms of health care interventions (e.g. abortion procedures or administration of emergency contraceptives); a prompt referral to a non-objecting provider should be made in such instances, so as to make it possible for patients to undergo the procedure that they need or request within the bounds of the law (31,32). It is worth stressing that it is the patient's choice to have any tests or procedures performed. First and foremost, she needs to be provided with the tools to make a sensible and well-informed decision. All discussions of informed consent should be appropriately documented by the health care professional. If test-

**Table I.** Instances of childbirth infections and legal aftermath.

Patient, date and location	Course of events and type of infection	Medical consequences	Legal outcome
<p>Unnamed patient, May 5, 2004, Monmouth County, Freehold, NJ, USA</p>	<p>The child's mother was admitted to CentraState Medical Center in labor on May 5, 2004. The defendant obstetrician ordered Pitocin to augment the labor and the delivery of the baby. Plaintiffs' experts maintained that over the course of several hours, the obstetrician failed to appreciate evidence of a hostile uterine environment and fetal distress on the electronic fetal monitoring which should have prompted her physician to discontinue the Pitocin and call for an immediate emergency cesarean section earlier than she did. Plaintiffs' experts opined that the delay in calling for an emergency cesarean section resulted in the infant sustaining an acute asphyxic event in the minutes before his birth which left him with significant brain damage.</p>	<p>A neonatology expert for the defense also argued that the Plaintiff's neurological injuries were not caused by an acute asphyxic event, as the Plaintiffs' experts had argued, but by prolonged exposure to maternal chorioamnionitis, an infection of the placenta.</p>	<p>Attorney D. L. Z. obtained a multi-million settlement on behalf of a 6 year old boy with hypoxic ischemic encephalopathy and cerebral palsy. A portion of the settlement is being used to purchase an annuity, making the total value of the settlement \$3,715,000–\$9,625,000<sup>23</sup>.</p>
<p>Unnamed patient, August 2006, Brigham and Women's Hospital, Boston , MA</p>	<p>In August 2006, then 30 weeks pregnant plaintiff's mother was admitted to Newton Wellesley Hospital (NWH) for high blood pressure and preterm labor. After a 5-day admission, she was transferred to Brigham and Women's Hospital (BWH) because her labor was progressing. On admission to BWH, both babies had normal heart rates. Shortly after admission, the mother spiked a temperature to 102.3 and the babies' heart rates became tachycardic, ranging between 170-200 bpm. The babies' heart rates remained elevated for the next 3 hours. The defendant nurse notified the defendant OB/GYN resident and the defendant attending OB/GYN. After an examination, they determined that the mother had a kidney infection. The defendants planned to start antibiotics immediately, but they were not given for over an hour and a half.</p>	<p>Later that afternoon, the babies' heart rates started to show decelerations. The nurse called the resident, but the patient was not evaluated. Fifteen minutes after the first call, the nurse called the resident regarding an abnormal lab value, concerning for bleeding. Yet again, the resident did not evaluate the patient. Shortly thereafter, the patient started to shake and tremble. She then began to visibly bleed, an indication of a placental abruption. The defendant doctors were notified and delivered the twins by emergency cesarean section within 10 minutes. At delivery, the plaintiff was blue, limp, and did not have a heartbeat. The baby was admitted to the BWH neonatal intensive care unit (NICU) for 10 days, then transferred to the NWH NICU. At both hospitals, the plaintiff was noted to have normal neurological exams. At 23 days of life, the plaintiff was diagnosed with a blood infection. The infection was treated, but returned weeks later. At 4 months of age, the plaintiff was diagnosed with meningitis. At 8 months old, the plaintiff had an MRI that showed periventricular leukomalacia (PVL), a brain injury associated with prematurity. At 10 months of age, the plaintiff was diagnosed with cerebral palsy.</p>	<p>At trial, the defense claimed that the plaintiff's injuries were caused by prematurity and the multiple infections that the plaintiff had after delivery. After 11 days of trial, the case was settled for \$4,000,000.00 before closing arguments<sup>24</sup>.</p>
<p>Ms. H.C., August 18<sup>th</sup> 2011, St. Francis Hospital, Columbus, OH, USA</p>	<p>The newborn was infected with Group B Streptococcus, after the doctors failed to test the mother for the bacterial infection, which is quite frequently found in the vagina of gravidas. According to the family's argument, the standard of care applied to obstetricians requires Group B Streptococcus (GBS) culturing in the management of a pregnancy at that particular point in time. The mother was discharged after two days in the hospital, having received multiple courses of antibiotic treatment (Ampicillin, an antibiotic known to effectively treat GBS). A few days later, the mother went in for a routine prenatal appointment with Dr. D. E., another obstetrician employed by St. Francis Hospital, during which Dr. E. cultured her for Group B Streptococcus. The test came back negative, but despite that, the mother had been "colonized" by GBS: she had the infection, but the doctor's test failed to catch it.</p>	<p>Two weeks later, the woman went back to the hospital in labor. The medical operators, however, concluded that there was no need for antibiotics during labor, in light of the fact that GBS culture had been found negative. The child was delivered that evening, apparently healthy. A day later, the baby's temperature had alarmingly risen. Lab tests indicated the neonate to have an infection, and subsequent blood and spinal fluid tests confirmed that Gracie contracted Group B Streptococcus at birth, leading to meningitis. The child has since been diagnosed with cerebral palsy, cortical visual impairment, and generalized developmental delay</p>	<p>The family's attorneys argued that having knowledge of the fact that the patient had recently received antibiotics, Dr. E. should have figured out that a culture performed on that date could not be trusted to accurately reflect her GBS status. Case settled for an undisclosed amount<sup>25</sup>.</p>

Patient, date and location	Course of events and type of infection	Medical consequences	Legal outcome
Ms. H.N., 29-year-old woman, August 2013, Boston Hospital, Bangor, Maine, USA	The patient was admitted to Eastern Maine Medical Center on Aug. 1 2013 and gave birth to a baby girl 20 hours later. Her pregnancy had been uneventful till then. The woman underwent an episiotomy to expedite the childbirth. Once discharged, she experienced pain and swelling, which got worse overnight, so the first-time parents returned to the hospital the next day.	The mom contracted necrotizing fasciitis, a rare and quick spreading bacterial infection, and passed away on August 8 <sup>th</sup> , 2013.	The patient's family decided not to push charges against the doctors or the facility <sup>26</sup> .
Ms. O., 2015, United Kingdom	Ms O gave bore her daughter in June 2011. An instrumental delivery turned out necessary, which led to the patient suffering a torn cervix. Her doctor subsequently repaired the tear, inserted a vaginal pack and ensured that Ms O was administered antibiotics. Still, that did not prevent an infection from setting in. Hospital staff erroneously ascribed her symptoms to sciatica, although she had never suffered from it before. Blood cultures grew Group B Streptococcal bacteria.	Ms O started experiencing intense pain in her back, waist and buttocks, making her unable to walk. Ms O was then sent home, albeit she was by then unable to walk on account of the pain and unable to take care of her newborn baby. At home, however, she only got worse. She was only checked on by community midwives, but not referred to her general practitioner or back to the hospital. Ten days following delivery, the patient was again hospitalized with sepsis and renal failure. She was transferred to an Intensive Care Unit, but she was still in great pain with multi-organ failure. She was diagnosed as having suffered a reactive arthritis due to the severe infection, which had caused the pain, swelling and stiffness in her limbs and joints, particularly her left knee. X-rays showed that the reactive arthritis had resulted in rapid deterioration in her knee joint and severe osteoarthritis; she would need a total knee replacement, despite her young age. Due to the reactive arthritis, deterioration of her knee joint and mobility problems Ms O gained a significant amount of weight in a short time, adding to her musculoskeletal pain.	The patient could not go back to work as a cleaner and required care and help with any daily activity. The patient's attorney appointed a commission of experts to analyze the care that Ms O received. The expert witnesses pointed to the failure to administer antibiotics after repair of the cervical tear, the delays in identifying an infection and starting antibiotics and the decision to discharge Ms O from hospital in light of her state at the time. The hospital management made partial concessions: breach of duty related to the failure to administer antibiotics and prematurely discharging the patient. In addition, it was acknowledged that with the timely administration of antibiotics the infection would not have grown out of control. Two months before trial was due to begin, a settlement for £750,000 was negotiated <sup>27</sup> .
Unnamed patient, 2016, North Central Bronx Hospital, New York, USA	The pregnant woman was admitted to North Central Bronx Hospital for labor and delivery. The mother was full term, with no prenatal complications and had a spontaneous rupture of membranes while at home. For 50 hours, her labor failed to progress and she contracted an intra-amniotic infection (chorioamnionitis), due to prolonged rupture of membrane.	Despite the failure of her labor to progress, the presence of infection and repeated signs of fetal distress, Defendant hospital failed to perform a timely cesarean section. As a result of that failure, infant Plaintiff suffered a stroke and was subsequently diagnosed with cerebral palsy.	A settlement was reached on behalf of the Plaintiff for \$6,000,000 <sup>28</sup> .
Ms. Doe, April 2017, Roe Hospital, Michigan, USA	Doe was admitted to a hospital in pre-term labor at 29 weeks gestation. During her 39-hour admission, she received medication to prevent a premature delivery. The hospital staff then discharged her. One day later, laboratory results revealed that she had an E-coli urinary tract infection and that she was positive for Group B strep.	Within a week, she went into labor and delivered her baby by CS. The infant has been diagnosed with brain damage, resulting in cerebral palsy, developmental delays and learning disabilities. The untreated infection spread to D's uterus and caused premature cervical dilation. The defendant countered that antibiotic prophylaxis was not necessary.	The parties settled for \$5 million before the start of the trial <sup>29</sup> .

ing is declined by the woman, additional counseling should be offered to dispel any doubt and answer any other questions or concerns without ever resorting to coercion or pressure.

Rates of hand hygiene compliance vary in different parts of the world; 19.6% and 20% compliance have been reported from an Italian and a Spanish teaching hospital, respectively approximately 32% from an internal medicine ward of a University Hospital in Turkey, and 34% in health care workers from a Pediatric Hospital in Rio de Janeiro in Brazil. A study from Southeast Iran regarding compliance of HCPs working in hemodialysis centers revealed a hand washing adherence rate of 58.7%, while a study from Mashad, Iran, reported a hand washing rate in the health staff of a general hospital as 8.5%. A systematic review on hand hygiene compliance by the HCP reports a median compliance rate of around 40%, with the lowest rates found in ICU settings (33). The main aspects that make hand hygiene complex during delivery, especially if a birth attendant is attending alone, is that both the woman and her infant are in need of care at the same time, which can pose challenges in terms of effective infection prevention. Finally, a delivery involves large quantities of blood which easily contaminates the hands of the health care provider and the environment. Hand hygiene at the time of birth is especially important before a cesarean section or any other minor invasive procedure, such as an episiotomy. These are very direct routes for infection because hands are so closely in contact with patient blood (34). Cesarean sections are currently rising and in many countries account for as much as 50% of deliveries (35). Much of the global focus on preventing HCAs has concentrated on hand hygiene. This is an essential intervention but needs to be accompanied by a hygienic physical environment in order to break the transmission chain of infection. This is particularly important for clinical areas caring for patients at higher risk, and with vulnerable sites, such as delivery beds. In addition, the importance of the disinfection practices of health care personnel, instruments and patients has been evidenced by cases of legal relevance that have involved health care personnel and the problem of infections transmitted in the delivery room (36). A crucial enabling factor in the physical environment is the basic requirement for water and sanitation – a requirement that in low-income countries is inadequate compared to high-income countries. The reliance on visual cleanliness as a

substitute for ‘safety’ is currently widespread; national and international guidelines often view visual cleanliness and frequency of cleaning as indicators of the extent to which IPC standards are met. Still, visual assessment of cleanliness on maternity units alone is an insufficient basis on which to determine safety, in terms of the possible presence of potential pathogens. Therefore, improving the availability and knowledge of hygiene protocols, supervision and feedback, and initiatives aimed at quality improvement could be useful methods to improve compliance and cut maternal/neonatal infection rates. If infections do occur, it is extremely important to promptly and properly identify their symptoms and provide medical care. Most infections can be treated with relatively low risk of further complication, provided that they are quickly diagnosed.

## CONCLUSIONS

From a medico-legal perspective, not every case where a physician failed to diagnose a maternal infection will necessarily rise to the level of medical malpractice. In light of the considerable difficulties in demonstrating how the infection was transmitted, health care facilities are the most likely to be held liable. In fact, legal statutes in most countries, particularly under tort law, tend to prioritize protection and redress of those who suffered damages, by the application of “presumptive” criteria (such as the *res ipsa loquitur* legal principle, which infers negligence from the very nature of an accident or damage, even in the absence of direct proof as to how the defendant acted). Thus, the prevalent legal standard, which has become well-established in most judicial frameworks, indicates that any claimant who suffered damage due to an infection deemed to have been preventable, should be awarded compensatory damages, following a retrospective evaluation. Preventable infections, which were however not prevented due to organizational failure or individual errors by one or more operators, would generally result in compensatory damages for injuries or (wrongful death) for the plaintiffs. However, it is often quite challenging to identify when the failure/error took place, and who was liable for it, among the health care crew members; various care-related activities in fact have a potential to create a context in which infections may arise for any hospitalized patient. The most suitable and

broadly-applied standard for determining whether an infection was preventable is probability-based (preventability higher than 50%). It is safe to say that in cases of vertical infection transmission, from mother to fetus, courts will likely be more inclined to consider such outcomes as not preventable, thus unavoidable. Nonetheless, malpractice charges within a pandemic context constitute a different scenario altogether, such as the one that health care systems and operators have been fighting against

worldwide. Any activity within such a setting is in fact regulated by provisions issued by national governments, legislatures and health care authorities. Still, such factors do not fully shield health professionals from malpractice allegations. Any proven failure to comply with regulations or inappropriate clinical decisions, which might have exacerbated the patient's conditions or caused his/her death, will predictably still lead to claims under criminal and civil law statutes.

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## Anogenital distance and Gynaecological diseases: a narrative review

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### ABSTRACT

Anogenital distance (AGD) (i.e. the distance measured from the anus to the genital tubercle) is an androgen-dependent, dimorphic feature, which is dependent on the *in-utero* hormonal environment. Human studies have shown alterations in the AGD associated with reproductive health in adult individuals, both males and females. In particular, recent studies have investigated whether differences in AGD length could be associated with gynaecological diseases, such as endometriosis and polycystic ovary syndrome (PCOS), as in these conditions prenatal hormonal exposure could represent a risk factor for developing the disease later in life. In this narrative review, we aimed to review the most updated scientific evidence on the relation between AGD and the presence of endometriosis and PCOS. Studies suggest that a shorter AGD seems to be related to the presence of endometriosis, whereas a longer AGD seems to be associated with an increased risk of PCOS. In light of these findings, we discuss how AGD measurement in adult women could represent a novel, simple, and easily reproducible biomarker of endometriosis and PCOS. However, scientific evidence is limited, and further well-designed studies are needed to corroborate current findings.

### SOMMARIO

La distanza anogenitale (AGD) (ovvero la distanza misurata dall'ano al tubercolo genitale) è una caratteristica corporea androgeno-dipendente, che risente dell'esposizione ormonale intrauterina. Studi sull'uomo hanno evidenziato che alterazioni della AGD possono essere associate a malattie dell'apparato riproduttivo, sia negli uomini che nelle donne. In particolare, studi recenti suggeriscono una correlazione tra differenze nella lunghezza della AGD e presenza di patologie ginecologiche, come l'endometriosi e la sindrome dell'ovaio policistico (PCOS). In queste condizioni, infatti, l'esposizione ormonale prenatale (in particolare a ormoni steroidei) può rappresentare un fattore di rischio per lo sviluppo della malattia in età adulta. In questa review narrativa della letteratura vengono riportate le più attuali evidenze sulla relazione tra AGD e la presenza di endometriosi e PCOS. I risultati degli studi a disposizione suggeriscono che una AGD più corta possa essere correlata alla presenza di endometriosi, mentre una AGD più lunga ad un aumentato rischio di PCOS. Alla luce di questi risultati viene discusso il ruolo della misurazione dell'AGD in donne adulte, quale potenziale biomarker (semplice e facilmente riproducibile) di endometriosi e PCOS. Tuttavia, le evidenze scientifiche a disposizione appaiono insufficienti, e sono necessari studi per confermare i limitati risultati attuali.

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**Key words:**

*Endometriosis; anogenital distance; AGD; Polycystic Ovary syndrome; PCOS.*

## INTRODUCTION

Anogenital distance (AGD) is a sexually, androgen-dependent, dimorphic feature that represents the distance measured from the anus to the genital tubercle (1). There is considerable evidence in animal and human models that AGD represents a biomarker of the prenatal hormonal environment (2,3). During the prenatal and early human life, the endocrine system is involved in the formation and ensuring proper function of various systems, including the reproductive system, which is highly sensitive to steroids hormones. In males, the development of the reproductive system depends on *in-utero* androgen exposure, whereas in females on lack of androgen (4).

AGD has been shown to depend on androgen exposure, and it is approximately 50–100% longer in human males compared to females (5). In addition, observational studies suggest that AGD is one of the most sensitive biomarkers of in utero exposure to endocrine-disrupting chemicals, defined as an exogenous substance that alters functions of the endocrine system (6,7).

In rodents, AGD has been demonstrated to reflect the extent of androgen to which the female foetus is exposed during early in utero development. Thus, prenatal exposure of females to exogenous androgens ends in longer and more masculine AGD (8–10). Human studies have shown alterations in AGD associated with reproductive health. For instance, significantly shorter AGD has been reported in male with cryptorchidism and hypospadias (11–13), and in men with poorer semen quality (14) and reduced testicular volume (15) compared with controls.

Recent studies have investigated whether differences in AGD length could be associated with gynaecological diseases, such as endometriosis and polycystic ovary syndrome (PCOS). In fact, in both conditions, prenatal hormonal exposure could represent a risk factor for developing the disease later in life. In this narrative review, we aimed to review the most updated evidence, which suggests a link between AGD and the development of benign gynaecological diseases, such as endometriosis and PCOS.

## AGD AND ENDOMETRIOSIS

Endometriosis is an estrogen-dependent chronic inflammatory gynaecological disorder associated with pelvic pain symptoms and infertility (16), de-

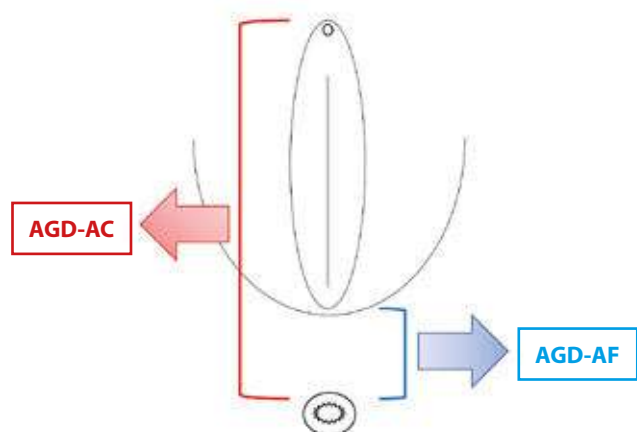
finied by histological lesions caused by the growth of endometrial-like tissue outside of the uterine cavity. Endometriosis affects about 5% of women of reproductive age (17). Endometriosis lesions could be schematically subdivided in peritoneal implants, ovarian endometrioma, deep infiltrating nodules or plaques, and extra-pelvic localizations (17). In the majority of the patients, pain can be managed via pharmacological inhibition of ovulation and menstruation (16,17), however, in some cases, a surgical approach should be considered, in particular in women with deep infiltrating forms (18,19).

The exact etiopathogenetic origin of the disease is still to be defined. The most widely accepted hypothesis is represented by the retrograde menstruation theory, characterised by the backward flux of menstrual debris that contains viable endometrial cells through the fallopian tubes into the pelvic cavity (20). However, some authors suggest an intrauterine origin of the disease (21,22), and the potential role of early-life influences, such as intrauterine hormonal environmental exposure to oestrogens or anti-androgens, are receiving growing consideration as a risk factor for endometriosis in adult life (23–29). In addition, accumulating evidence suggests that immune cells, adhesion molecules, extracellular matrix metalloproteinase and pro-inflammatory cytokines activate/alter peritoneal microenvironment, creating the conditions for differentiation, adhesion, proliferation, and survival of ectopic endometrial cells (30,31). Finally, a recent review (32) evaluated the potentially pivotal role of ion channel, in particular CFTR, AQP<sub>s</sub>, and ClC-3, in the etiopathogenesis of endometriosis.

As regards to the association between AGD and endometriosis, the hypothesis is that a prenatal estrogenic environment will result in a relatively shorter AGD, which may represent an indirect marker of higher risk of having endometriosis or developing endometriosis later in life.

In 2016, a Spanish control-study (1) assessed the relations between AGD measurements and the presence of endometriomas (OMA) and deep infiltrating endometriosis (DIE) in adult women. The investigators measured both AGD<sub>AC</sub> (i.e., the distance from the anterior clitoral surface to the upper verge of the anus) and AGD<sub>AF</sub> (i.e., the distance from the posterior fourchette to the upper verge of the anus) (**figure 1**). A total of 114 women with endometriosis ( $n = 82$  with OMA;  $n = 32$  with DIE) and 105 controls have been enrolled. AGD<sub>AF</sub> rather than AGD<sub>AC</sub> was associated with

### Anogenital Distance



**Figure 1.** Landmarks for two measurements of anogenital distance (AGD):  $AGD_{AC}$  from the posterior fourchette to the upper verge of the anus (right).

the presence of endometriomas and/or DIE. Considering the whole endometriosis group ( $n = 114$ ), women in the lowest tertile of the  $AGD_{AF}$  distribution, compared with the upper tertile, were 7.6-times (95% CI 2.8–21.0;  $P$ -trend  $<0.001$ ) more likely to have endometriosis. Among women with DIE, those with  $AGD_{AF}$  below the median, compared with those with  $AGD_{AF}$  above the median, were 41.6-times (95% CI 3.9–438;  $P$ -value = 0.002) more likely to have endometriosis. These results are in line with those of another Spanish unmatched control-study (33). Women with endometriosis had a significantly shorter  $AGD_{AF}$  compared to controls (23.5 mm [5.8] versus 27.3 [5.7];  $P < 0.001$ ).

In 2018, the same Spanish group (34) assessed the predictive ability of a combination of AGD and anti-Müllerian hormone (AMH) to diagnose the presence of endometriosis without surgery. A total of 57 women with endometriosis ( $n = 45$  with OMA;  $n = 12$  with DIE) and 93 controls were recruited. Women with endometriosis had significantly shorter  $AGD_{AF}$  ( $22.8 \pm 4.6$  vs  $27.2 \pm 5.7$  mm;  $P < 0.001$ ) and lower AMH levels ( $2.2 \pm 2.5$  vs  $3.3 \pm 1.9$  ng/mL;  $P = 0.003$ ). Women with serum AMH below the clinical cut-off (1 ng/mL) were 17.40-times more likely to have the disease (95% CI 5.64–53.82). The area under the ROC curve of combined AMH and  $AGD_{AF}$  was 0.77 (95% CI 0.70–0.85). The authors concluded that  $AGD_{AF}$  and serum AMH levels could be combined in a non-invasive model to predict endometriosis.

These results indicate a possible association between  $AGD_{AF}$  and presence of endometriomas and DIE, suggesting that the intrauterine hormonal mi-

lieu during prenatal life may play a central role in the development of the disease.

### AGD AND POLYCYSTIC OVARY SYNDROME

PCOS is one of the most common endocrine and reproductive disorders in reproductive age, with an estimated prevalence of 5–10% of women. However, the exact pathophysiology of this disease is still unclear. It has been proposed that environmental factors, such as excessive in utero androgen exposure, may play a fundamental role in the development of the disease (35). In fact, androgen excess is present in around 70% of women with a diagnosed PCOS (36). Moreover, clinical observations also support a potential foetal origin of PCOS. Women with foetal androgen excess disorders, including congenital adrenal hyperplasia or congenital adrenal virilising tumours, have an augmented incidence of PCOS during adulthood, despite the normalisation of androgen levels with treatment or removal of the neoplasia after birth (37–39).

Characteristics of the studies that analysed the association between AGD and PCOS are summarized in **table I**. The potential association between AGD and PCOS was firstly evaluated by Wu *et al.* (40) in a case-control study of 156 women with PCOS and 180 reproductively healthy women. In all patients, both  $AGD_{AF}$  and  $AGD_{AC}$  were measured. The authors demonstrated an association between longer AGD, in particular  $AGD_{AF}$  and the presence of PCOS. In particular, women with  $AGD_{AF}$  in the highest tertile were 18.8 times (95% CI 9.6–36.6;  $P < 0.001$ ) more likely to have PCOS compared with those in the lowest tertile. Women with  $AGD_{AC}$  in the highest tertile were 6.7 times (95% CI 3.7–12.1;  $P < 0.001$ ) more likely to have PCOS than those in the lowest tertile. In addition, the authors collected blood samples in order to analyse total testosterone, FSH and LH levels in all participants. In the PCOS group, multiple linear regression analyses revealed that both AGD measures were positively associated with total testosterone levels ( $\beta = 0.246$  for  $AGD_{AC}$ ;  $\beta = 0.368$  for  $AGD_{AF}$ ;  $P = 0.003$  and  $P < 0.001$ , respectively).

Another case-control study (41) confirmed the presence of longer AGD in Mediterranean women with PCOS. In this study, 285 women ( $n = 126$  women with PCOS;  $n = 159$  controls) were recruited. In bivariate analyses, women with PCOS showed significantly longer  $AGD_{AF}$  (27.8 versus

**Table 1.** Studies evaluating anogenital distance (AGD) in women with polycystic ovary syndrome (PCOS).

Source	Country	Study design	Number of patients enrolled	AGDAF and AGDAC (mm)	Outcomes
Wu <i>et al.</i> , 2017 (40)	China	Case-control	336 (PCOS $n = 156$ ; controls $n = 180$ )	AGD <sub>AF</sub> : PCOS: $26.6 \pm 4.0$ Controls: $22.0 \pm 3.7$ AGD <sub>AC</sub> : PCOS: $104.9 \pm 9.1$ Controls: $97.1 \pm 9.4$	Longer AGD was related to the presence of PCOS. In particular, women with AGD <sub>AF</sub> in the highest tertile were 18.8 times (95% CI 9.6–36.6; $P < 0.001$ ) more likely to have PCOS compared with those in the lowest tertile. Women with AGD <sub>AC</sub> in the highest tertile were 6.7 times (95% CI 3.7–12.1; $P < 0.001$ ) more likely to have PCOS than those in the lowest tertile.
Sanchez-Ferrer <i>et al.</i> , 2017 (41)	Spain	Case-control	285 (PCOS $n = 126$ ; controls $n = 159$ )	AGD <sub>AF</sub> : PCOS: $27.8 \pm 5.6$ Controls: $26.5 \pm 5.1$ AGD <sub>AC</sub> : PCOS: $80.5 \pm 11.3$ Controls: $76.0 \pm 10.4$	Women with PCOS showed significantly longer AGD <sub>AF</sub> and AGD <sub>AC</sub> compared to controls in bivariate analyses ( $P < 0.05$ ).
Hernández-Peñalver <i>et al.</i> , 2018 (42)	Spain	Case-control	285 (PCOS $n = 126$ ; controls $n = 159$ )	AGD <sub>AF</sub> : PCOS: $27.8 \pm 5.6$ Controls: $26.5 \pm 5.1$ AGD <sub>AC</sub> : PCOS: $80.5 \pm 11.3$ Controls: $76.0 \pm 10.4$	Women with PCOS showed significantly longer AGD than controls.
Simsir <i>et al.</i> , 2019 (35)	Turkey	Prospective cohort study	130 (PCOS $n = 65$ ; controls $n = 65$ )	AGD <sub>AF</sub> : PCOS: $23.0 \pm 6.0$ Controls: $21.0 \pm 5.0$ AGD <sub>AC</sub> : PCOS: $101.0 \pm 12.0$ Controls: $98.0 \pm 17.0$ Ratio AGD <sub>AC/AF</sub> : PCOS $4.4 \pm 1.0$ Controls $4.9 \pm 1.0$	No statistically significant differences in AGD <sub>AF</sub> and AGD <sub>AC</sub> measurements, although both measurements were longer in the PCOS group. The strongest predictor of PCOS is the ratio of AGD <sub>AC</sub> and AGD <sub>AF</sub> .

26.5 mm;  $P = 0.048$ ) and AGD<sub>AC</sub> (80.5 versus 76.0 mm;  $P = 0.001$ ) compared to controls. The authors further analysed data in tertiles and ORs, and in the final adjusted models, only AGD<sub>AC</sub> was associated with the presence of PCOS ( $P 0.002$ – $0.008$ ). Women with AGD<sub>AC</sub> in the upper versus the lowest tertile were 2.9-times more likely to have PCOS (95% CI 1.4–5.9;  $P$ , trend = 0.008). The correlation between AGD<sub>AC</sub> and PCOS was also demonstrated in another Spanish case-control study (42).

A recent prospective cohort study (35) of 130 Turkish women ( $n = 65$  women with PCOS;  $n = 65$  healthy controls) investigated the possible association between AGD and the presence of the disease. Unlike previous studies, Simsir *et al.* (35) also calculated the AGD Ratio (AGD<sub>AC</sub>/AGD<sub>AF</sub>). No statistically significant differences were found in AGD<sub>AF</sub> and AGD<sub>AC</sub> measurements, although both measures were longer in the PCOS group. However, the mean ratio of AGD<sub>AC</sub> to AGD<sub>AF</sub> for the PCOS and control group were  $4.4 \pm 1.0$  and  $4.9 \pm 1.0$ , respectively ( $P = 0.003$ ). Regression analysis demonstrated that this ratio positively correlates with the waist to hip ratio and negatively correlate with the

free androgen index. The authors suggested the use of AGD Ratio<sub>AC/AF</sub> instead of single measurements as a novel biomarker for PCOS.

A recent interesting Danish study (43) evaluated whether the presence of higher testosterone levels during pregnancy in women with PCOS is associated with longer offspring AGD. The study population included 139 mothers with PCOS and 1422 controls. Surprisingly, AGD measures were comparable in offspring of women with PCOS compared with controls, despite significantly higher maternal levels of total testosterone and free testosterone in women with the disease versus controls (both  $P < 0.001$ ). The authors suggested that longer AGD in adult women with PCOS could be the result of increased testosterone levels in puberty, perhaps in combination with weight gain. However, these results are not in line with previous finding. In 2018, Barrett *et al.* (44) reported that new-born girls of mothers with PCOS have a longer AGD than daughters born to women without PCOS, and the authors suggest that a longer AGD may be related to the presence of elevated exposure to intrauterine testosterone.

## DISCUSSION AND CONCLUSION

In recent years, AGD measurement in adult women has been receiving a growing amount of interests, due to its potential role as a novel, simple, and easily reproducible biomarker of different gynaecological diseases, such as endometriosis and PCOS.

Regarding endometriosis, shorter AGD<sub>AF</sub> seems to be related with the presence of endometriosis. However, we have to underline that all the available evidence derives from the same Spanish study group (1,33,34). Moreover, in all these case-control studies, women were not matched for age, BMI, and parity. Ideally, only nulliparous women should be included in order to avoid any bias related to changes in external genital anatomy after vaginal delivery and episiotomy. The authors suggested an association between shorter AGD<sub>AF</sub> and higher endometriosis risk, especially in case of deep infiltrating forms (1,33,34). As previously explained, prenatal exposure to androgens results in a longer AGD, whereas a prenatal estrogenic environment in a shorter one. Hypothetically, a shorter AGD, reflecting the intrauterine hormonal milieu, could represent an indicator of the presence of endometriosis and could suggest that endometriosis, espe-

cially deep infiltrating forms, might have a prenatal origin. However, studies investigating AGD in affected women are scanty, and further research from different study groups is needed to confirm the potential role of AGD as a biomarker of endometriosis.

Regarding PCOS, the strength of association between a longer AGD and the presence of the disease seems more reliable. Data derived from different study groups and the potential role of androgen in the pathophysiology of the disease has strong foundations. However, a recent Danish study (43) did not find an association between higher maternal testosterone levels and longer AGD in the offspring, questioning the impact of prenatal hormonal exposure on AGD length.

In conclusion, AGD could represent a cheap and easily reproducible biomarker of different gynaecological diseases, however further well-designed studies are needed to corroborate current findings.

## CONFLICT OF INTERESTS

All the authors declare that they have no conflicts of interest.

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**Role of Gross Examination of the specimen and ultrasound in Uterine Adenomyosis: case series with review of literature**

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**ABSTRACT**

**Background.** In times, Adenomyosis cannot be diagnosed accurately and differentiated from leiomyoma before histological assessment in a hysterectomy specimen. It can be suspected by gross pictures.

**Aim.** We aim to provide an assistance to pathological examination, proposing a role of ultrasound and gross examination of the specimen to be helpful.

**Case presentation.** We presented different cases with adenomyosis with different gross pathologies as trabeculation on external surface, small myometrial cysts, polypoidal adenomyosis and diffuse adenomyosis.

**Conclusions.** Adenomyosis cannot be diagnosed accurately before the pathological assessment of the uterus. It could be suspected from gross pathologies and ultrasound findings.

**SOMMARIO**

L'adenomiosi non può essere diagnosticata accuratamente e differenziata dal leiomioma prima della valutazione istologica in un campione di isterectomia. può essere sospettato da immagini grossolane.

**Scopo.** Ci proponiamo di fornire assistenza per l'esame patologico, proponendo alcune immagini grossolane ed ecografiche come supporto alla diagnosi istologica finale.

**Presentazione del caso.** Abbiamo presentato diversi casi di adenomiosi con differenti patologie lorde come trabecolazione sulla superficie esterna, piccole cisti miometriali, adenomiosi polipodiale e adenomiosi diffusa. La presentazione presenta diversi quadri grossolani di adenomiosi che possono sospettare l'adenomiosi.

**Conclusioni.** L'adenomiosi non può essere diagnosticata accuratamente e differenziata dal leiomioma prima della valutazione patologica dell'utero. Potrebbe essere sospettato da patologie grossolane e risultati ecografici.

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**Key words:**  
*Adenomyosis; cyst; uterus; polyp; hysterectomy.*

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## BACKGROUND

Adenomyosis is the presence of endometrial glands and stroma in the myometrium (1). When adenomyosis is focal, it is similar to a leiomyoma in being an intramural, space-occupying mass. It differs from leiomyoma in which the mass cannot be shelled out easily (2). Adenomyosis cannot be diagnosed accurately nor differentiated from leiomyoma before the pathological assessment of the uterus, at times it could be suspected from gross pathological that are presented here.

We aim to provide an assistance during surgery and before pathological examination as a guide and a preliminary diagnosis, proposing some gross pictures and ultrasound ones to be helpful as a support to the final histological diagnosis.

All cases did not have chronic illness. BMI of patients ranges between 25-30. The Second and third patient had history of one cesarean section while other patients surgical history is unremarkable. The complaints were not relieved by medical treatment combined of analgesics and hormonal treatment inform of pills and progesterone therapy. Patients refused mirena and continuing medication as they were putting on weight, they missed taking the pills and they developed unexpected bleeding. They were demanding a permanent cure - Patients underwent abdominal hysterectomy with bilateral salpingectomy. On pathologic assessment, the abnormality in uterus was adenomyosis. Microscopically, multiple irregular islands

of endometrial glands and stroma embedded in the myometrium and the entire uterine wall was identified. The myometrium surrounding were hypertrophic. The glands in the endometrial islands were of basalis-type endometrium in contrast to the early secretory glands in the endometrium (**table I**) (**figure 1-7**).

## DISCUSSION

Adenomyosis causes gross abnormality in advanced cases and the diagnosis is based upon microscopic findings. In Lev Gur's series (3), adenomyosis was present alone in the uteri smaller than 280 g. Reiter et al. reported six cases with a uterine weight of 320 g (4). A clinical diagnosis of adenomyosis can be confirmed by transvaginal ultrasonography and MRI, but specificity of these methods decreases when the uterine volume exceeds 400 ml (5,6).

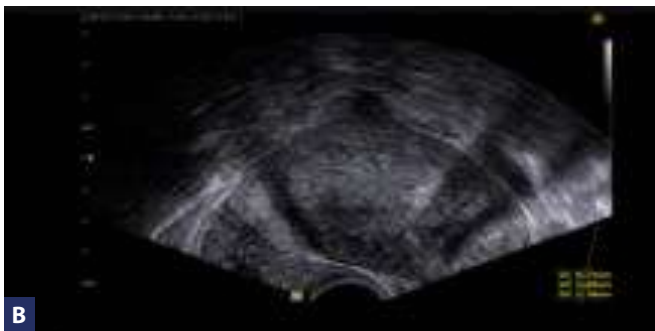
The MUSA (Morphological Uterus Sonographic Assessment) statement is a consensus statement on terms, definitions and measurements used to describe the sonographic features of the myometrium using gray-scale sonography, Doppler and three-dimensional ultrasound imaging. This Morphological Uterus Sonographic Assessment consensus is based on the opinion of clinicians with expertise including members from the IOTA (International Ovarian Tumor Analysis) and IETA groups (24). It describes criteria for diagnosing ad-

Table I. Case Presentation.

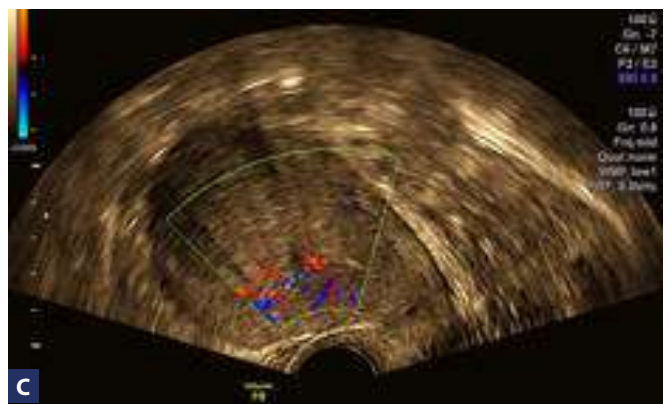
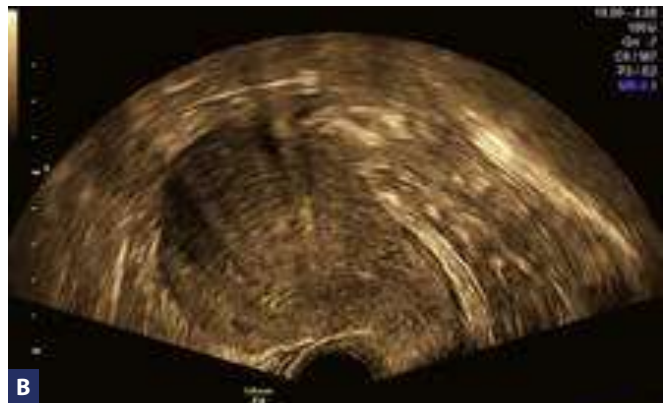
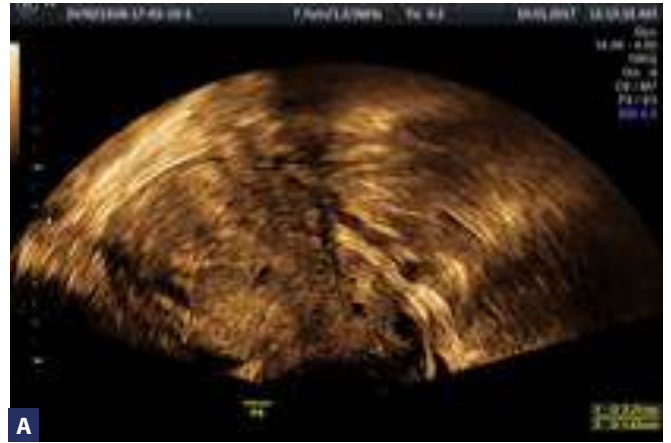
Case	Age	Complain	Gravidity, parity	Findings	Operative finding	Figure
1	40	AUB inform of menorrhagia	G3P3	Diffuse and Asymmetrical Thickening of uterine wall, enlarged uterus in size and volume, endometrial thickness is 8mm with ill defined endometrial myometrial junction	Diffuse adenomyosis With trabeculations and asymmetry between walls anterior and posterior	1, 7
2	45	AUB inform of menorrhagia	G1P1	Myometrial cyst, striation shadowing, heterogenous echogenicity, adenomyoma	Subendometrial Myometrial cyst	2, 3
3	47	Chronic PELVIC PAIN and low back pain	G2P1+1	thickened myometrium, polypi, myometrial cyst, asymmetrical diffuse wall thickening, thick endometrium and ill defined	Trabeculation on external surface of uterus, myometrial cyst bulging in cavity and multiple endometrial polypi	4, 5
4	42	AUB inform of menorrhagia	G3P2+1	Diffuse asymmetrical myometrial thickening, endometrial polyp, myometrial cyst and thick illdefined endometrium, echogenic spots	Trabeculations on the external surface, thickened myometrium with polypoidal adenomyosis and small myometrial cysts	6



**Figure 1.** Diffuse adenomyosis of the uterus (thickened walls with asymmetry and trabeculation all through).



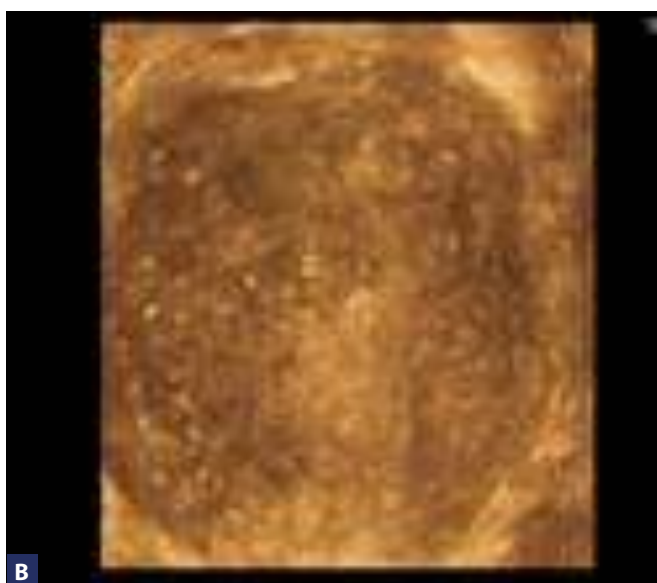
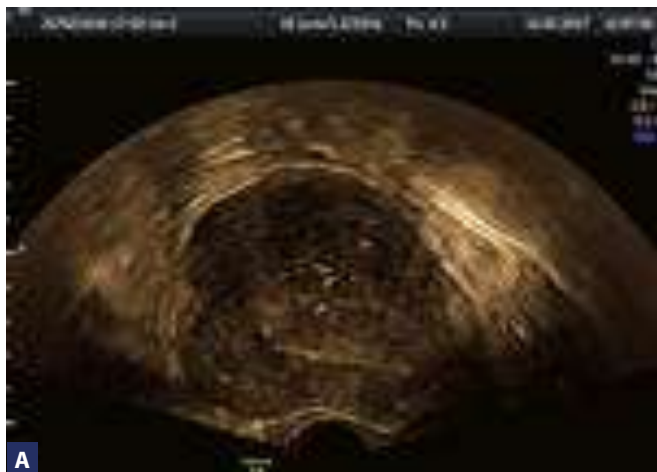
**Figure 2.** Myometrial cyst on ultrasound, an active recent lesion with echogenic wall (A), Ultrasound with illdefined endometrium with shadowing (B), Mottled heterogenous echogenicity of myometrium with subendometrial buds and lines (C).



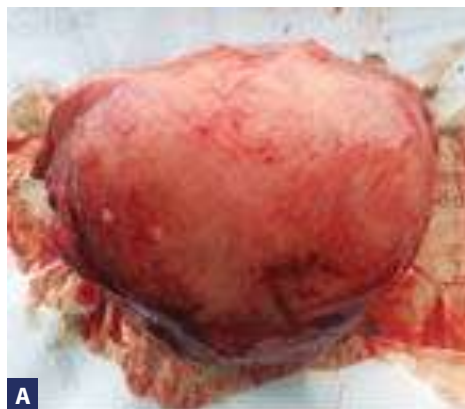
**Figure 3.** Ultrasound with adenomyoma in wall, (A) which is echogenic mass, ill defined considered as old lesion with fibrosis, shadowing fan shaped with intralésional vascularity, illdefined endometrium and junctional zone.



**Figure 4.** Subendometrial adenomyotic cyst with multiple adenomyotic polypi.



**Figure 5.** Echogenic spots in the myometrium associated with adenomyosis of old fibrosis hemorrhagic lesions and hyperechoic islands.



**Figure 6.** Enlarged uterus with small myometrial cyst with (B,C), thick wall of hyper-trophied myometrium and polypodal adenomyosiss (B).



**Figure 7.** Trabeculation over the external surface of uterus.

enomyosis and fibroids. Adenomyosis assessment on ultrasound include the following criteria for diagnosis as globally enlarged uterus, ill-defined lesion as in diffuse adenomyosis (adenomyoma may be well-defined) and Myometrial anteroposterior asymmetry. The mass lesion is characterized by ill-defined, irregular mass with no rim, no edge shadows but fan-shaped shadowing and mixed echogenicity. Myometrial cysts, hyperechogenic islands, subendometrial lines and buds, translesional flow, and thickened irregular or ill-defined interrupted JZ can be detected as shown on previous photos (7).

Polypoid adenomyoma, known as an adenomyomatous polyp, is an endometrial polyp in which the stroma is predominantly composed of smooth muscle. they are accounting for only 1.3% of all endometrial polyps (8-10). These tumors are of mixed epithelial and mesenchymal origin with typical and atypical variants (11-13). Most studies have focused on the clinicopathologic features of atypical polypoid adenomyomas because they are confused with malignant tumors. the transvaginal sonographic appearance has been described as a polypoid, hypoechoic or hyperechoic submucosal mass in the endometrial cavity, a large solid mass with multiple cystic areas, a mass with large cysts, and a polyp with small cystic spaces (11-13). Nasu et al. (14). reported a case of polypoid adenomyoma as a large solid mass with multiple cystic areas, similar to submucous leiomyoma with cystic degeneration. Furuhashi et al. (15) described a case in which a hyperechoic pattern changed to a vesicular one, similar to trophoblastic disease. Color Doppler has been used in the diagnosis of endometrial abnormalities by identifying vessels in the lesions.

Cystic lesions of the uterus are rare and are considered to be benign (16). Adenomyotic cysts are observed in parous women, and in association with diffuse adenomyosis uteri (17) isolated adenomyotic cysts may be detected (18,19). Adenomyotic cysts are seen in older ages but they may

be in adolescents (20). Small adenomyotic cysts that do not exceed 5 mm in diameter are found in 24% of hysterectomy specimens (21) but larger adenomyotic cysts are rare. Repeated surgical intervention might be a risk factor for adenomyotic cysts (22). Pelvic pain, dysmenorrhea, menorrhagia and large uterus are the most common features of adenomyosis. Urine retention may be the symptom (23). Pain or severe dysmenorrhea may be the main symptom in adenomyotic cysts. The pain of the adenomyotic cyst may be due to the increase in size of the mass, stretching of the endometrial cavity and cystic bleeding. Magnetic resonance imaging is important for the diagnosis of cystic adenomyosis especially when other imaging modalities are nonspecific (24). Magnetic resonance imaging can differentiate multiple cysts within the uterine myometrium, but hysterosalpingography may be useful for the differential diagnosis when magnetic resonance cannot differentiate isolated adenomyotic cyst from cavitated noncommunicating rudimentary horn. Imaging techniques are important in differential diagnosis of adenomyotic cysts and help us to choose the appropriate intervention. In young patients hormonal therapy is the first choice and can be accomplished by combined oral contraceptives or progesterone laden IUD as mirena. In the presence of severe symptoms that do not respond to medical therapy, a surgical intervention can be planned for excision (24). In older patients with no desire to preserve their fertility, hysterectomy can be performed.

## CONCLUSIONS

Adenomyosis cannot be diagnosed accurately nor be differentiated from leiomyoma before the pathological assessment of the uterus. it could be suspected from gross pathologies and ultrasound findings.

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## Malignant rhabdoid tumor of the peritoneum, mimicking an advanced ovarian cancer: a case report with literature review

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### ABSTRACT

**Objective.** Extra-renal malignant rhabdoid tumor is an uncommon neoplasm, more commonly occurring in pediatric aged patients. Despite current treatment options, prognosis and survival rate are poor. At present, there are only 20 published cases of primary malignant rhabdoid tumor of the female genital tract and peritoneum and, due to its rarity, there is no standard therapeutic guideline for appropriate treatment.

**Methods.** We report the case of a young female affected by this extremely rare tumor, who was surgically treated in our gynecologic oncology division and performed a systematic review of the English literature present in PubMed, SCOPUS and Web of Science. The systematic search was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO, no.: CRD 42019138911).

**Results.** Given the rarity of this tumor, only case reports' studies were available on this topic. A narrative description of the clinical characteristics, treatment and patients' status at last follow up has been carried out.

**Conclusions.** We believe that the best treatment option for patients with this type of tumor should be an aggressive debulking surgery in addition to prompt adjuvant treatment, especially in advanced cases.

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### SOMMARIO

**Obiettivo.** Il tumore rabdoide extra-renale maligno è una neoplasia non comune, che si verifica più comunemente nei pazienti di età pediatrica. Nonostante le attuali opzioni di trattamento, la prognosi e il tasso di sopravvivenza sono scarsi. Al momento, ci sono solo 20 casi pubblicati di tumore rabdoide maligno primario del tratto genitale femminile e del peritoneo e, a causa della sua rarità, non esistono linee guida terapeutiche standard per un trattamento adeguato.

**Metodo.** Segnaliamo il caso di una giovane donna affetta da questo tumore estremamente raro, che è stata chirurgicamente trattata nella nostra divisione di ginecologia oncologica. È stata inoltre eseguita una revisione sistematica della letteratura inglese presente in PubMed, SCOPUS e Web of Science. La ricerca sistematica è stata eseguita in accordo con le voci di segnalazione preferite per revisioni sistematiche e meta-analisi (PRISMA) ed è stata registrata nel registro prospettico internazionale delle revisioni sistematiche (PROSPERO, n. CRD 42019138911).

**Risultati.** Data la rarità di questo tumore, su questo argomento erano disponibili solo studi di casi clinici. È stata effettuata una descrizione narrativa delle caratteristiche cliniche, del trattamento e dello stato dei pazienti all'ultimo follow-up.

**Conclusioni.** Riteniamo che la migliore opzione terapeutica per i pazienti con questo tipo di tumore debba essere un aggressivo intervento di citoreduzione oltre al pronto trattamento adiuvante, specialmente nei casi avanzati.

### Key words:

*Malignant rhabdoid tumors of the female genital tract; malignant rhabdoid tumors of the peritoneum; systematic review.*

## INTRODUCTION

Rhabdoid tumor is an uncommon neoplasm characterized by a population of large, non-cohesive cells with vesicular nuclei and large nucleoli. They have been initially described as atypical and aggressive variants of Wilms tumors in early childhood (1). In 1978, Beckwith and Palmer first described a unique sarcomatous variant of the Wilm's tumor with very aggressive clinical behavior (2). Afterwards, Haas et al. reviewed these renal tumors and identified a distinct renal tumor in children, which they named "malignant rhabdoid tumor" (MRT) of the kidney because of its morphological resemblance to malignant tumors with rhabdomyoblastic differentiation (3). Several studies reported MRT in the central nervous system (4) and in various soft-tissues (5). Extracranial MRTs are rare and often occur in infants with an age standardized incidence ratio of 0.6 per million children in the United Kingdom (UK), with 61% of cases presenting in the first year of life (6) and are even rarer in the adult. The 1-year overall survival (OS) rate in the UK population-based National Registry of Childhood Tumors from 1993 to 2010, was only 31% (6). This poor survival rate was also reflected in the National Wilms' Tumor Study (NWTS) series, and in the Surveillance Epidemiology and End Results (SEER) program in the United States, with an OS at 4 years of only 23.3% and 33.0%, respectively (7, 8).

Given the rarity of extrarenal - extracranial MRTs, no standard therapeutic pathway exists to date, and there are no randomized or prospective trials examining the role of chemotherapy combinations or the addition of new existing agents in treating these tumors.

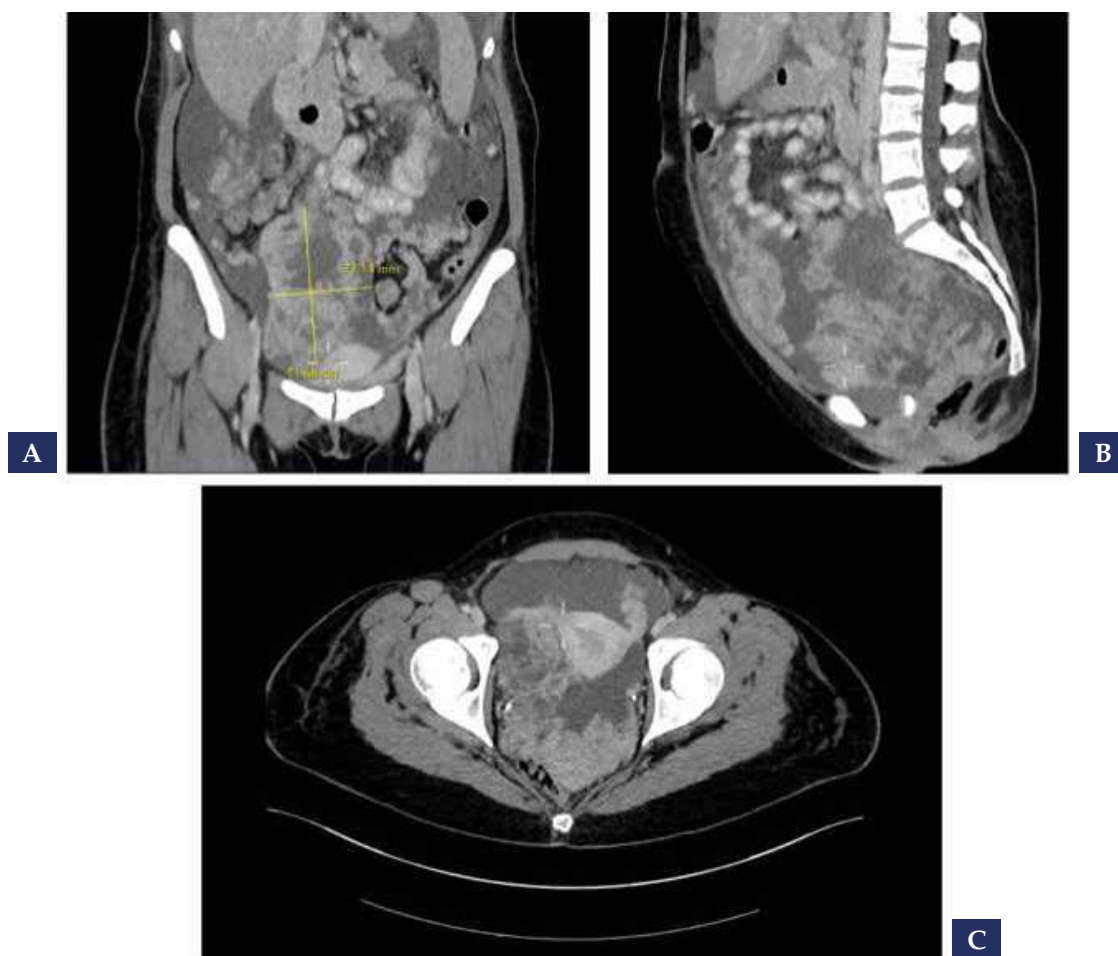
We report the case of a 32-year-old female patient with peritoneal rhabdoid tumor whose symptomatology mimicked that of an advanced ovarian cancer. We reviewed the pertinent medical literature to accompany this case.

## CASE REPORT

A 32-year-old woman, 0 gravida 0 para, was admitted to the emergency room of Policlinico Universitario A. Gemelli Foundation complaining of abdominal pain and dyspnea. Clinical examination showed a large abdominal mass.

Abdominal and pelvic computed tomographic scans revealed a large pelvic mass of 11 cm in the

right adnexal region, presumed to be of ovarian origin, omental cake and diffused carcinomatosis. No liver, splenic or renal metastasis were detected (**figure 1**). A chest CT scan showed an abundant bilateral pleural effusion but no pulmonary metastasis were evident. All pre-operative radiological exams and patient symptoms indicated advanced ovarian cancer. Considering the abundant pleural effusion and the patient's dyspnea, a pleural drain was placed before performing debulking surgery. We performed an initial diagnostic laparoscopy to assess the possibility of complete debulking surgery. More than 2000 ml of ascites fluid was drained. The laparoscopic examination of the pelvis confirmed an 11 cm peritoneal mass, infiltrating the right adnexa and rectum. Furthermore, widespread signs of carcinomatosis were distributed all over the pelvic, parietal and diaphragmatic peritoneum. Lab results of the frozen section revealed a malignant rhabdoid neoplasm. Unfortunately, despite the young age of the patient, the aggressiveness of the tumor coupled with the advanced stage of disease did not allow for a conservative fertility preserving approach and led our clinical judgment to opt for a demolitive surgery (9,10). Therefore, we decided for complete surgical tumor resection. After laparotomic conversion, an en-bloc resection of the uterus, adnexa, pelvic peritoneum, sigmoid colon and rectum was performed. To eradicate the tumor, the following procedures were performed: radical removal of the lesser and greater omentum, bilateral diaphragmatic peritonectomy, ileo-cecal resection plus anastomosis and radical lumbo-aortic lymphadenectomy. An ileostomy was performed to prevent anastomotic dehiscence. At the end of the operation, no gross residual disease was evident. There were only a few postoperative complications including anemia, fever and pleural effusion in the 9 days following surgery, and the patient was discharged in stable general condition. Histopathological examination revealed a high-grade neoplasm, consisting of large-sized epithelioid elements with nuclei and evident nucleoli and abundant eosinophilic cytoplasm of rhabdoid appearance. Immunohistochemistry showed positivity for vimentin, Estrogen Receptor (ER), focal positivity for EMA (Epithelial Membrane Antigen), Progesterone Receptor (PR) and negativity for Wilms' tumor 1 (WT1), S100 protein, myogenin, myoblast determination protein 1 (MYO D1), calretinine, Gross cystic disease fluid protein 15 (GCDFP 15), Human Melanoma Black 45 (HMB45), ERG, leu-



**Figure 1.** Computed tomography images showing a large pelvic mass of the right adnexal region, omental cake and ascites. A. Coronal scan B. Sagittal scan C. Transverse scan.

kocyte common antigen (LCA), desmin, caldesmon and Cytokeratin AE1 / AE3 (CKAE1 / AE3). Further investigations showed the loss of nuclear expression of integrase interactor 1 (INI-1). This type of histological profile is usually indicative of the progression of other malignant tumors but, in this case, a specific differentiation line was not provable and INI-1 was unequivocally lost (**figure 2**).

On histopathological examination, both ovaries measured approximately about 5 cm and were covered by multiple carcinomatous nodules as well as an “ab extrinseco” infiltration by the pelvic mass. Based on these findings, we diagnosed an extra-renal rhabdoid tumor, originating from the peritoneum.

In absence of clear guidelines for adjuvant therapy, and due to its sarcomatous disease similarities, we decided to treat the peritoneal MRT as a uterine sarcoma, administering a cycle of anthracyclines (Doxorubicin) + Olaratumab. The CT scan performed before chemotherapy (9 weeks post-surgery), showed extensive peritoneal and lymph

node recurrences and a hepatic metastasis of about 3 cm. The examination also depicted abundant ascites and neoplastic peristomal tissue.

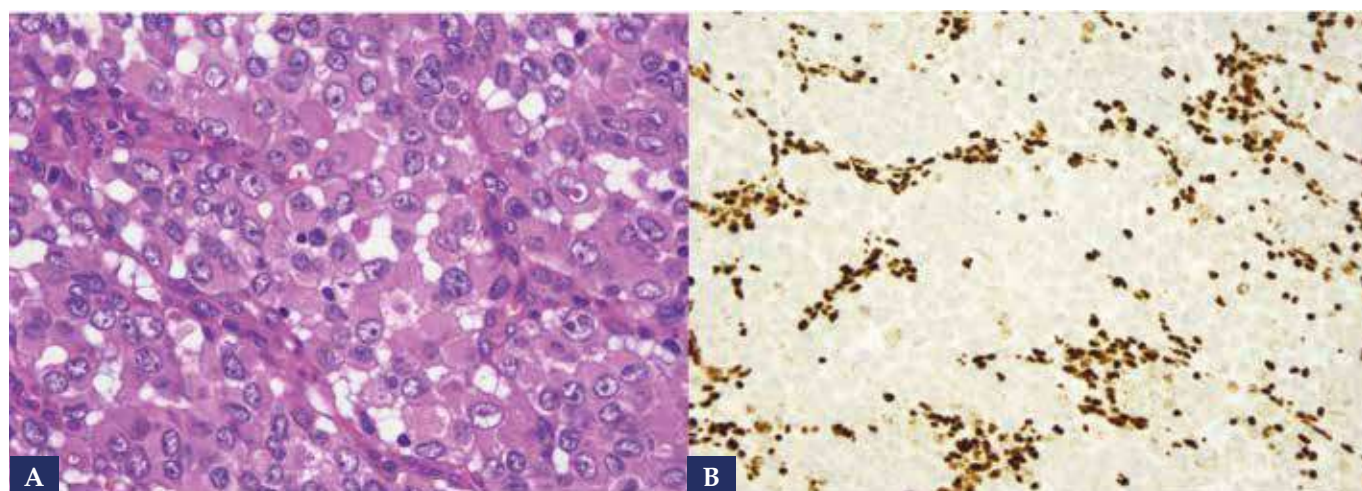
Chemotherapy was started 11 weeks after surgery in relation to the aggressive surgery performed and time required for histopathological results. According to RECIST criteria, the CT scan after 3 chemotherapy cycles revealed a progression of all the previous metastasis detected despite negative tumor markers results and good general patient conditions.

Therefore, we stopped the ongoing treatment with anthracycline and changed to trabectedin.

Unfortunately, the patient died due to disease progression 9 months after diagnosis.

## MATERIALS AND METHODS

We performed a systematic review of the English literature present in PubMed, SCOPUS and Web of Science, regarding cases of female genital tract and peritoneal MRT.



**Figure 2.** Histology is characterized by proliferation of “rhabdoid cells” with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm arranged in a discohesive solid growth pattern (a); immunohistochemical expression of INI-1 observed in endothelial and inflammatory cells, is loss in neoplastic cells (B). H&E (A), immunoperoxidase (B).

The systematic search was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11, 12), and was registered in the International Prospective Register of Systematic Reviews (available at <http://www.crd.york.ac.uk/PROSPERO>; CRD 42019138911).

The terms “malignant rhabdoid tumor of the ovary”, “malignant rhabdoid tumor of the uterus (corpus and cervix)”, “malignant rhabdoid tumor of the vulva”, “malignant rhabdoid tumor of the omentum” and “peritoneal malignant rhabdoid tumor” were used to search in the above-mentioned database. A hand search of the references of both potentially relevant articles and articles qualifying for inclusion was also performed. The exclusion criteria included duplicate publications, non-English language literature, papers based on animal models and laboratory studies.

No publication period restrictions were adopted. The search has been concluded in May 2019.

The titles and abstracts of studies retrieved using the search strategy, and those from additional sources, has been screened independently by two review authors (VV and LCT) to identify studies that potentially meet the inclusion criteria. The full texts of these potentially eligible studies have been then retrieved and independently assessed for eligibility by the two authors. Any disagreements between the two parties over the eligibility of particular studies have been solved through discussion with a third senior reviewer (BC).

The extracted information included tumor location and size, age of patients, presence of metastasis at

diagnosis, treatment approach, disease free survival and overall survival. Data supplied for included case reports have been checked by two researchers (VV and LCT) for: missing data; treatment and follow-up. Any discrepancies or unusual patterns have been checked with the study investigator (BC). Missing data have been requested from study authors when possible.

A narrative description of the findings from the included studies structured around treatment, disease free survival and overall survival of patients affected by malignant extra renal rhabdoid tumor originating from the female genital tract and from the peritoneum, has been carried out.

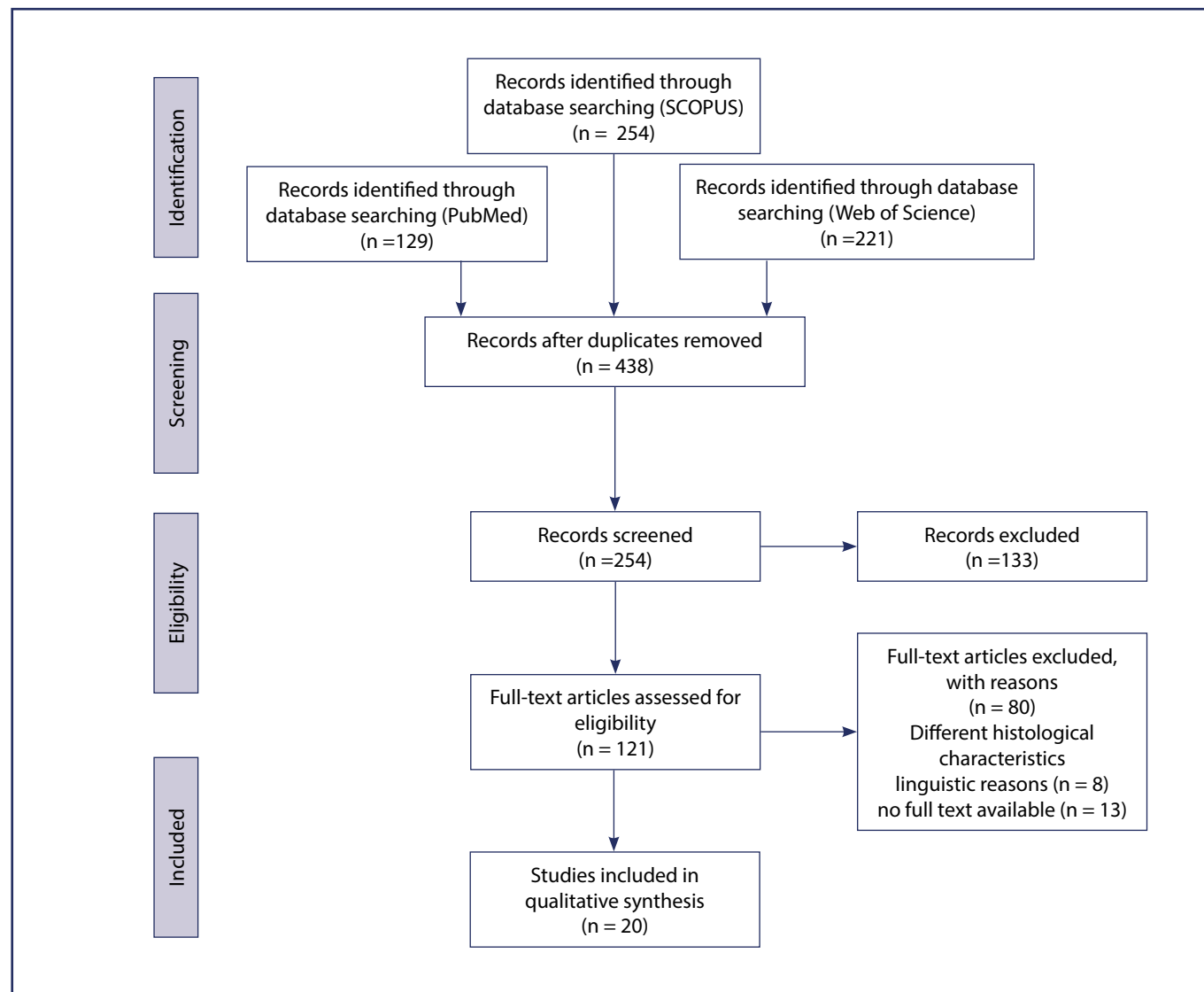
No statistical analysis or meta-analysis has been performed. The Cochrane risk of bias tool was not applicable to our review because the only studies available were case reports.

After a crossmatch research, 254 articles were screened. The number of full text articles assessed for eligibility was 121. Exclusion criteria were studies not in English language, the unavailability of full text article and non-pertinence with the present topic, as different genetic mutation, different histopathological characteristics or different site of localization of the tumor. Finally, 20 articles have been detected plus our case report (**table I**).

## RESULTS

We reviewed 10 MRT cases of the vulva, 4 of the uterus, 1 of the uterine cervix, 4 of the ovary and 1 of the omentum as well as our present case.

**Table I.** Study flow diagram of search results (up to May 2019).



**Table II** shows the clinical characteristics, treatment and the status of the patient at last follow up (dead of disease, alive with disease or no evidence of disease at last follow up) of the analyzed cases. Overall, surgery was the first treatment choice, usually followed by chemotherapy. Various combination of chemotherapeutic agents, such as ifosfamide - epirubicin - cisplatin (IEP), vincristine - doxorubicin - cyclophosphamide/ifosfamide - etoposide (VDC/IE) and carboplatin - etoposide - ifosfamide or cisplatin alone, were administered in advanced MRT cases as first line chemotherapy with little benefit. Doxorubicin or cisplatin have been used as second line therapy. Surgery plus adjuvant treatment (chemo- or radiotherapy) has been the treatment of choice in 11 out of 21 patients. Five patients were treated with radical surgery alone, two received chemo- plus

radiotherapy (one EBRT and one BRT) while just one patient received external beam radiotherapy as sole treatment. In 7 cases EBRT and/or BRT was administered alone or in combination with surgery and/or chemotherapy and just in one case with a palliative aim. In 1 case radiotherapy was provided at recurrence. No information regarding the treatment approach were available in the remaining 2 cases. The median survival, considering the different time of follow up, in patients receiving surgery as first treatment was 9 months (range 0.5 months to 61 months). Eleven out of 21 patients died of the disease, just 6 out of 21 had no evident disease at the time of publication of the case report and 2 had a stable disease. No information is available about the remaining 2 patients.

**Table II.** Literature review of genital tract and peritoneal malignant rhabdoid tumor.

Author	n of cases	Age (year)	Site	Size (cm)	Treatment	Metastasis At diagnosis	CHT	DFS	DOD/AWD/NED
#	1	32	Peritoneum	11	Surgery + Adjuvant CHT	Ovarian, diffuse peritoneal carcinomatosis	Anthracycline, trabectedine at recurrence	5 Mo	DOD 9 Mo
Dolanbay 2016 (13)	1	51	Vulva	3	EBRT	None	No	NA	NED 12 Mo
Rabinovich 2015 (14)	1	34	Ovary	12	Surgery + Adjuvant CHT	Omentum, Pelvic lymphnodes	IEP (ifosfamide, epirubicin, cisplatin) second line weekly doxorubicin	3 Mo	DOD 8 Mo
So-Hyun Nam 2014 (15)	1	10	Greater Omentum	9	Surgery + Adjuvant CHT	Diffuse peritoneal carcinomatosis	VDC/IE (Vincristine, Doxorubicin, Cyclophosphamide/ Ifosfamide, Etoposide)	4 mo	DOD 9 Mo
Venugopal 2014 (16)	1	17	Clitoris	5	CHT + RT	NA	NA	NA	DOD 6 Mo
H. Narendra 2010 (17)	1	50	Vulva	8	Surgery + RT	None	No	NA	NED 30 Mo
Banzai 2007 (18)	1	19	Ovary	14	Surgery + Adjuvant CHT CHT CHT + palliative RT	Lombo-aortic lymphnodes	IEP on recurrence ifosfamide and cisplatin on 2nd recurrence	2 Mo 9 Mo	AWD 18 Mo
Leath 2003 (19)	1	18	Ovary	NA	CHT	NA	NA	NA	DOD 2 Mo
Tzilinis 2002 (20)	1	63	Vulva	6	Surgery + BRT	None	No	NA	NED 30 Mo
Tsuda 2001 (21)	1	36	Cervix	7	Surgery + Adjuvant CHT	None	carboplatin, etoposide and ifosfamide	NA	NED 38 Mo
Sert 1999 (22)	1	NA	Vulva	NA	Surgery + RT + CHT	NA	NA	NA	DOD 8 Mo
Igarashi 1998 (23)	1	25	Vulva	6	Surgery + Adjuvant CHT	None	NA	8 Mo	AWD 8 Mo
Stastny 1996 (24)	1	36	Ovary	NA	Surgery	Pelvic	No	NA	DOD 0,5 Mo
Hsueh 1996 (25)	1	37	Uterus	10	Surgery + Adjuvant CHT	Lombo-aortic lymphnodes	Cysplatin	3 Mo	DOD 4 Mo
Lupi 1996 (26)	1	NA	Vulva	NA	NA	NA	NA	NA	NA
Matias 1990 (27)	1	45	Vulva	5	Surgery + Adjuvant CHT	None	NA	1 Mo	DOD 9 Mo
Perrone 1989 (28)	1	19	Vulva	NA	Surgery	None	No	26 Mo	NED 38 Mo
Cho 1989 (29)	1	46	Uterus	NA	NA	NA	NA	NA	NA

Abbreviations: # = present case, N= number, NA = not available, DFS= disease free survival, NAD= neo adjuvant, CHT= chemotherapy, RT= radiotherapy, AWD= alive with disease, NED= not evidence of disease,

DOD = dead of disease, EBRT= external beam radiotherapy, Mo= months

## DISCUSSION

MRT was first described as a distinctive, highly malignant round cell neoplasm of the kidney in children (1). Cytogenetic and molecular analyses showed abnormalities in the long arm of chromosome 22 (30,31) and alteration of the hSNF5/INI1 (SMARCB1) gene (located at 22q11.2) in renal, extrarenal and intracranial MRTs. This chromosome deletion led to the inactivation of a tumor-suppressor gene SMARCB1 (also known as INI1, BAF47, and hSNF5, a core member of the SWI/SNF chromatin-remodeling complex), involved in renal and extra-renal rhabdoid tumor pathogenesis (32). This characteristic implicates SMARCB1 as a tumor suppressor gene, as defined by Knud-

son in the “two-hit model” (33). The hSNF5/INI1 tumor-suppressor gene has been reported to modulate cell growth and actin cytoskeleton organization, through an ATP-dependent manner to remodel chromatin (34). These genetic aberrations have been regarded as specific for MRT. However, Modena et al. recently demonstrated that this gene is frequently inactivated in proximal-type of epithelioid sarcoma (35). Because of INI-1 gene alterations, immunohistochemical loss of the INI-1 (BAF47/SNF5) protein has been observed in MRT, whereas positive nuclear staining is preserved in other non-rhabdoid tumor cells. Therefore, immunohistochemical study for INI antibody is useful to confirm the histological diagnosis of renal or extra-renal MRT (36,37).

Recently, mutations in a 2nd locus of the SWI/SNF complex, the SMARCA4 gene, also known as BRG1, located at 19p13.2, were found in rhabdoid tumors with retention of SMARCB1 expression (38,39,40,41). The SMARCA4 mutation is typical for the small-cell carcinoma of the ovary, hypercalcaemic type (SCCOHT), a very rare and highly malignant ovarian tumor, considered a type of MRT (42). Familial cases may occur in a condition known as rhabdoid tumor predisposition syndrome.

Up to one third of patients with rhabdoid tumors harbor SMARCB1 germline inactivating mutations (43,44,45). MRTs are aggressive, often widely metastatic at diagnosis, respond poorly to therapy, and are uniformly fatal, except for localized disease, and for these reasons, most of the mutations described above seem to occur *de novo*. Furthermore, the diagnosis is difficult and is based on light microscopic findings with supportive immunohistochemistry. The first most common localization site after the kidney is the CNS. Other relatively frequent onset sites of this tumor are deep axial locations such as the neck, paraspinal region, perineal region, abdominal cavity or retroperitoneum and pelvic cavity. Extremities, especially the thigh, or cutaneous lesions are also well-documented. This tumor can also affect visceral organs such as the liver, thymus, gastrointestinal system and the genitourinary tracts (46).

In our case, the disease manifested itself mimicking the typical presentation of an advanced ovarian cancer, with acute abdominal distention, dyspnea, ascites and diffused carcinomatosis.

Surgery was deemed essential to obtain a histopathological diagnosis and to evaluate the possibility of complete excision of the disease.

Furthermore, based on the experience gained from the treatment of advanced ovarian cancer, we know that the complete disease removal (residual tumor RT=0) has the greatest impact on overall survival and progression free survival (47). This is particularly true for some ovarian cancer histotypes such as the Low-Grade Serous Carcinoma, whose response rates to chemotherapy are significantly lower than those of High-Grade Serous Carcinoma, and where complete removal of the disease

leads to decisively better oncological outcomes (48). This is also the case for ovarian carcinosarcoma where optimal debulking surgery can improve overall survival of these patients. The frozen section showed rhabdoid features, so considering the absence of clear guidelines and the scant benefit of a neo-adjuvant treatment, we decided to perform a highly debulking surgery notwithstanding the disease's widespread.

Due to the rarity of this disease and its difficult histological diagnosis, the patient was able to begin chemotherapy 11 weeks after surgery, unfortunately when the disease had already recurred with liver metastasis. Based on our results, that showed minimal benefits of treating patients with chemotherapy and radiotherapy alone, we believe that the best treatment option should be an aggressive debulking surgery plus a prompt adjuvant treatment, especially in advanced cases. Given the similarities of MRT to uterine sarcomas we choose doxorubicin as first line treatment.

## CONCLUSIONS

The rare occurrence of extra-renal MRT complicates adequate survival-improving protocols.

Generally, patients are very young with few comorbidities. Therefore, maximum surgical effort, in a specialized oncological surgery center with dedicated pathologists must be provided in order to deliver the best treatment options and obtain a timely histopathologic diagnosis.

Due to the rarity of extra-renal malignant rhabdoid tumors, prospective studies choosing the right therapeutic plan are difficult to perform. However, future patients presenting this disease should be routed to a single specialized center in order to find a personalized approach, which could ultimately lead to a better prognosis.

## CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interests.

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