REVIEW

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Impact of COVID-19 on fertility and assisted reproductive technology (ART): a systematic review

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Abstract

The appearance of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a major obstacle for the performing of current medical activities throughout the world. COVID-19 has affected humanity in many ways, thus causing a great medical, social, economic, and political instability. The aim of this study was to make an analysis of the scientific data obtained by so far to highlight the impact that COVID-19 has had on fertility and assisted reproductive technology (ART). Infection with SARS-CoV-2 alters the normal immune response by local and systemic damage to tissues and organs. After the virus enters the body, the first lesions are produced in the respiratory tract. Extrapulmonary lesions specific to COVID-19 include acute renal lesions/acute kidney damage, hepatocellular lesions, neurological diseases, myocardial dysfunction and arrhythmia, gastrointestinal diseases but also genital impairment. The possible impairment of the male reproductive system is because angiotensin-converting enzyme 2 (ACE2) receptors are in an increased number in the testes, seminiferous duct cells, spermatogonia, Leydig cells and Sertoli cells. Many published studies to date have pointed out that COVID-19 could also affect female fertility and disrupt the functions of the female reproductive system. The theory that this virus can also be transmitted sexually and can cause infertility or testicular damage is supported by the fact that the virus can be isolated in the semen of COVID-19 patients but only during the disease. Choosing the best method of treating infertility during the COVID-19 pandemic is multifactorial, but the risk of infection and compliance with specific ART hygiene protocols must always be considered. Currently, there is no scientific basis regarding the fact that the COVID-19 vaccination would influence fertility.

Keywords: COVID-19, fertility, ovaries, reproduction, SARS-CoV-2, testes.

Introduction

Coronaviruses (CoVs) are a group of ribonucleic acid (RNA) viruses belonging to the *Nidovirales* order, the *Coronaviridae* family and the *Coronavirinae* subfamily. The first CoVs that infected humans and affected their respiratory tract were discovered in 1960 and were represented by the HCoV-229E strain. One year later, it was reported the presence of another strain, HCoV-OC43, in the human upper respiratory tract. Patients infected with both strains, identified between 1960 and 1961, showed classical symptoms of a cold (the headaches, the sneezes, and the sore throat) [1]. This type of virus is 26–32 kb long and has numerous spiny extensions, as seen under the electron microscope, which has also entailed its name "*corona*" meaning "crown" in Latin [2].

So far, modern medicine has recognized a total of seven kinds of CoVs that can infect humans [3]. Severe acute respiratory syndrome (SARS) caused an endemic outbreak with a mortality rate of 9% between 2002 and 2003 when about 8000 people were infected worldwide and then in 2012 Middle East respiratory syndrome (MERS) caused another CoV outbreak but with a mortality rate of over 35% [4]. There are also other four related viruses, but they

have little impact on people. SARS-CoV-2 is similarly to SARS-CoV and has a lower mortality rate comparing to the other types, but its rate of transmission and contagion is much, much higher by comparison with them [5].

The first infection with SARS-CoV-2 was made public in the end of 2019 in China, and the disease was named COVID-19. At the time of writing this article, the SARS-CoV-2 has already affected more than 200 countries and territories around the world. On June 17, 2022, the number of the people infected was 545 068 408 (some people have been infected several times) out of which 6 345 128 was the number of reported deaths [6].

Because there was limited information about this virus, the emergence of the COVID-19 has been a major obstacle for the performing of current medical activities throughout the world. Over time, thanks to the research carried out assiduously in this direction, new elements were brought to light, the main goal of these years being the discovery of a specific treatment. This is the reason that clinical trials have been intensified. It can be considered that no other disease, up until this point, has benefited from such an extensive research work meant not only to establish a method of diagnosis and prevention but also to obtain an adequate treatment [5].

COVID-19 has affected humanity in many ways, thus causing a great medical, social, economic, and political instability, as well as leading to major changes in the health field around the world [7].

As a result of the imposition of medical and social restrictions during the current pandemic, many people diagnosed with essential diseases, but without being considered medical emergencies, have been suffering worldwide. The diagnosis and treatment of infertility is one of these problems. Infertility is a condition characterized by a high sensitivity in time and as a matter of fact the longer it is left untreated properly, the lower the chances are that the patient should become a biological parent [8].

Aim

The aim of this study was to make an analysis of the specialized literature and of the scientific data obtained by the medical community so far since the beginning of the pandemic to highlight the impact that COVID-19 has had on the male and female reproductive system, as well as on fertility and assisted reproductive technology (ART).

Materials and Methods

This study was based on extensive studies of specialized literature using *PubMed*, *Google Scholar*, *Scopus*, and *MEDLINE* databases to highlight the influence of SARS-CoV-2 on the reproductive system, on fertility and on assisted human reproductive techniques. The key words used were 'SARS-CoV-2', 'COVID-19', 'testicles', 'ovaries', 'fertility', 'assisted human reproduction', and 'vaccine'. We have analyzed papers published from February 2020 to June 2022, and we have included mainly case reports, case-control studies, cohort systematic studies and reviews.

We identified in this way around 2400 articles. After this search, we made a screening of titles and abstracts. Relevant information has been extracted from 57 articles for this review.

Etiology and pathogenesis of COVID-19

The origin of this virus has been and still is the subject of great controversy. It is considered that SARS-CoV-2 could come from bats or pangolins, and then after undergoing several mutations, it became able to infect people as well [9]. Therefore, CoVs are a family of viruses that passed the barrier between species thus becoming human pathogens [3].

COVID-19 has spread in the whole world, unlike any other virus encountered by most people in their lifetime [10]. Each person infects about 2.2 people compared to 1.3 people in the case of seasonal flu, and the mortality rate of this virus has been estimated somewhere between 0.5% and 3.5% *versus* a percentage of 0.01% for the seasonal flu [11].

The human-to-human transmission of this virus occurs through respiratory droplets from sneezing and coughing. *World Health Organization* (WHO) has also reported the possibility of transmission by air or through contaminated objects. SARS-CoV-2 was also found in blood and feces, but it is not clear whether or not the infection can also be transmitted through the various body fluids [3]. In addition, the presence of the RNA of this virus in the urine and the sperm of some infected patients has raised the suspicion of the possibility for the virus to be transmitted sexually [12], while the ocular pathway can also be a gate of entry [13].

Structurally, SARS-CoV-2 has four main structural proteins: the 'spike' (S) protein, the small membrane (SM) protein, the membrane (M) protein and the nucleocapsid (N) protein [14]. The main way by which SARS-CoV-2 penetrates and affects the host cell is by attaching the S protein to the angiotensin-converting enzyme 2 (ACE2), which is found in concentrations in alveolar cells, myocardial cells, spermatogonial stem cells, seminiferous duct cells, urothelial cells, proximal tubular cells, etc. [2, 12, 15].

At this moment, it is known that human cells that have ACE2 and transmembrane serine protease 2 (TMPRSS2) receptors may act as a portal of entry for the virus into the human body and its immune system [14–16]. The entry of the virus begins when the surface enzyme of the virus called S glycoprotein is linked to the ACE2 located on the membrane of the host cell. The S protein contains two different regions of the domain: S1 and S2, each having its own role in the virus penetration. This process involves a complex interaction between the viral cell and the host cells, which culminates in rapid virus replication inside the targeted cells. The current research is focused on the S1 domain of the 'spike' protein as a target for therapeutic antiviral therapy [3–5, 8].

Infection with SARS-CoV-2 alters the normal immune response by local and systemic damage to tissues and organs. After the virus enters the body, the first lesions are produced in the respiratory tract, with the secondary onset of pneumonia, while the patient might experience such symptoms as fever, cough with or without sputum, muscle pain and various other symptoms. Extrapulmonary lesions specific to COVID-19 include acute renal lesions/acute kidney damage, hepatocellular lesions, neurological diseases, myocardial dysfunction and arrhythmia, gastro-intestinal diseases, genital impairment [12].

The severity of this infection varies from completely asymptomatic cases to mild influenza-like cases (80% of the registered cases), yet it can turn into a critical illness sometimes associated with subsequent death (15–20% of the cases are severe, needing additional oxygen, while 5% are critical cases for which is mandatory mechanical ventilation). Patients in critical condition may have respiratory failure, shock, or multi-organ dysfunction. Risk factors for critical forms may include oldness, weight excess and a series of associated medical conditions like the cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension, and cancer. The death rate can reach up to 3% of the infected people [3].

COVID-19 and the male reproductive system

At this moment, it is acknowledged that men are much more predisposed to this infection than women are, with the positivity rate and death rate being higher among males [17].

Concerns about the possible impairment of male fertility arose in 2021 when a Hubei official website advised men who have experienced COVID-19 in the past to take fertility tests [5].

The impairment of the male reproductive system by the SARS-CoV-2 requires increased medical attention as not only this generation is affected, but also future generations will be because of the early impairment of the gametes [17, 18].

The possible impairment of the male reproductive system is because ACE2 receptors are in an increased number in the testes, seminiferous duct cells, spermatogonia, Leydig cells and Sertoli cells. This highest concentration may reduce the process of spermatogenesis, the division of male gametes and their transformations during fertilization [19, 20]. It has also been concluded in numerous published articles that the ACE2 expression is much stronger among young men aged 30–40 years [17].

Fever is an almost ubiquitous symptom in the case of COVID-19 infections, observed in more than 80% of the patients infected with COVID-19 and considering only this febrile state, it can be concluded that the SARS-CoV-2 can adversely affect the regulation of scrotal temperature as even a short-term febrile period may lead to decrease the number of spermatozoa, motility, and quality of the genetic material. In these cases, high temperatures can induce cell apoptosis [5]. Returning to normal sperm parameters can take a long time, sometimes almost three months [4].

In many cases, orchitis has been declared as a secondary complication of SARS-CoV-2 infection, but the mechanism is unclear. A possible explanation can be given by an autoimmune inflammatory reaction or the direct destruction of testicular cells by the cytopathic effect of the virus [16]. Likewise, the vascular thrombotic effect that could cause ischemic orchitis should not be neglected either [21].

Other authors have stressed that COVID-19 infections could affect male fertility by impairing the endocrine system. This deterioration is mirrored by a significant decrease in serum testosterone levels or luteinizing hormone levels reported, values which show the impairment of the male reproductive function [4, 18, 22].

The presence or absence of the virus in the genital organs remains a great controversy. Yang *et al.* [21] have conducted a study and identified pathological changes at the testicular level in the form of a reduction in the number of Leydig cells and an interstitial inflammatory infiltration among 12 patients out of a total of 19 patients who died of COVID-19 and were included in the study. Although they have discovered pathological changes at the testicular level, the authors have found no evidence of the presence of the virus in the testes in most cases [21]. Furthermore, in most studies, many authors have not noticed the presence of SARS-CoV-2 in semen [2, 21], except for that of Li *et al.*'s [19] who signal out its presence in few patients.

In a few articles, there have also been reported subjective claims about scrotal discomfort coming from patients. Such an example is given by Özveri *et al.* who have observed during the ultrasound (US) examination that in the case of these patients there is a slightly increased vascularization [23]. No other abnormalities have been discovered during the clinical examination of the scrotal region [23].

Regarding the impairment of the male reproductive system among patients infected with the SARS-CoV-2, the possible introduction of medication should not be neglected under no circumstances. Various medicines, such as Chloroquine phosphate or Interferon (IFN) alpha and Ribavirin (in combination with IFN or Lopinavir/Ritonavir), have been recommended for the COVID-19 treatment. Animal studies have shown that their administration decrease the level of testosterone and has inhibits spermatogenesis in rats, probably due to the oxidative stress it generates. The testicular dysfunction may also be caused by the glucocorticoids. In addition, it has been established that Chloroquine phosphate affects the spermatogenesis and epididymis function in male rats, which indicates that not only the disease itself, but also certain drugs may affect the testicular function in male patients with COVID-19 [24].

From another point of view, panic, stress, and negative conditions, such as depression and anxiety, often common among patients diagnosed with COVID-19 are associated with lower sex hormone-binding globulin (SHBG) and higher cortisol, as well as prolactin secretion [25]; while on the other side, there were cases in which cortisol level was low due to immune or direct injury of adrenal and pituitary glands [26]. This variability in hormones' levels may lead to changes in sperm count and motility as well as to an increase of the sperm deoxyribonucleic acid (DNA) fragmentation and of the sexual dysfunction. Therefore, in addition to its direct effects on the testes, SARS-CoV-2 may indirectly affect fertility *via* the central nervous system [2, 19, 21].

COVID-19 and the female reproductive system

Many published studies to date have pointed out that COVID-19 could affect female fertility and disrupt the functions of the female reproductive system [14].

From a genital point of view, the importance of ACE2 is given by the fact that it plays a role in the follicular and ovulation regulation and development, normalizes angiogenesis and luteal degeneration, and may induce changes in the endometrial tissue and the embryo, thus having a major impact on fertility and human reproduction [14, 27]. The impairment and the inhibition/down-regulation

of ACE2 by SARS-CoV-2 may cause changes in normal ovarian activity, such as follicular development and oocyte maturation, which may have consequences for the quality of the oocytes. The proinflammatory effects caused by the virus can increase oxidative stress, which can further affect the reproductive ability. Evidence is now suggesting that SARS-CoV-2 by binding to ACE2 receptors can interfere with female reproductive functions, resulting in menstrual disorders, infertility and/or fetal distress in pregnant patients [14]. The amount of mature oocytes may be reduced in patients with higher levels of anti-SARS-CoV-2 antibodies. Also, the number of blastocysts and euploid embryos is often affected [28].

Another SARS-CoV-2 receptor is basigin (BSG), which mediates its entry into host cells. BSG acts not only in the uterus, but also in the stroma and the ovary granular cells playing an important role in follicular development, yellow body formation and embryo implantation [29]. The effect of the functionality is potentiated by the reduction of zinc in the conditions of the cytokine storm and the appearance of reactive oxygen species [30]. Thus, a special attention should be given to fertile women to highlight potential ovarian damages [31, 32].

A possible explanation of spontaneous abortions reported at the patients diagnosed with COVID-19 infection is given by the fact that ACE2 receptors are also found at the endometrium, which could negatively interfere with embryo implantation [33]. Ding *et al.* in their article showed the possible effect that SARS-CoV-2 could have on ovarian function, namely the increase of testosterone and prolactin levels and the reduction of the ovarian reserve, therefore of the value of anti-Müllerian hormone (AMH) [31]. In other studies, such as those of Li *et al.*, no change in sex hormones and AMH levels was demonstrated [34]. These authors could not demonstrate whether the infection itself or the stress and panic associated with the COVID-19 pandemic caused these menstrual irregularities and the negative impact on oocyte quality [34].

We must also not neglect the way in which some drugs used to treat these conditions (the non-steroidal anti-inflammatory drug, etc.) may have a teratogenic effect or potentially have an influence on future fertility [35].

COVID-19 and the impact on fertility

In times of uncertainty about the economic future and the labor market stability, many families tend to avoid any long-term commitments, and the intention to have a child is one initially considered irreversible. The uncertainty about the present and the negative expectations about the future have led many families to postpone birth plans until "better" times. However, it should be noted that some of these "delayed" births may not materialize due to illness, family deaths or impact on the reproductive system [36–39].

Contrary to these facts, Anser *et al.*, in their study showed an increase in fertility rates and also in the incidence of sexually transmitted diseases (STDs), putting it all on the lockdown of the cities [37].

The theory that this virus can also be transmitted sexually and can cause infertility or testicular damage is supported by the fact that the virus can be isolated in the semen of COVID-19 patients but only during the disease. This has led some doctors to recommend sexual abstinence during infection even in asymptomatic patients [12].

However, to identify COVID-19 as a STD, viral infectivity must be documented by the certainty of transmission during a sexual act or a direct insemination and not only by the presence of its viral particles in the genital organs [18]. The identification of the ACE2 receptor in the genital organs suggested that SARS-CoV-2 could infect the gonads [40] and the evidence of orchitis induced by SARS-CoV-2 has suggested that the testicular infection could be a mirror of the fact that the disease can also be transmitted sexually [41].

COVID-19 and ART

An unprecedented situation in the global health care system was created during the COVID-19 pandemic. Many countries have introduced directives suggesting that non-essential medical activities should be resumed to focus system resources to combat the spread of SARS-CoV-2 [42]. Nevertheless, the definition of "non-essential care" has sparked much controversy and has automatically raised concerns. Given that the ART is considered a secondary medical branch, various opinions have been raised regarding the interruption or not of infertility procedures and treatments [43–45].

In the context of this pandemic, on 17 March 2020, the *European Society of Human Reproduction and Embryology* (ESHRE) and *American Society for Reproductive Medicine* (ASRM) issued several recommendations advising all patients diagnosed with infertility, regardless of whether or not they have symptoms specific to the SARS-CoV-2 infection or the diagnosis of COVID-19, to avoid pregnancy [7]. Thus, it was recommended to suspend the beginning of new treatment series. In the case of treatments that had already started, embryo preservation procedures were recommended. All other elective surgical interventions and consultations for the diagnosis and treatment of infertility have been suspended [7, 44–47].

It was not long before a petition was created by a provider of infertility treatment which gathered almost 14 000 supporters in a controversial response to the recommendations of *ASRM*. This document was entitled "The fight for women's rights to fertility treatment and evaluation" and contradicted the *ASRM* recommendations by mentioning that this type of treatment needs to be carried out at the right time, especially for older women, and also that the patient's rights and decisions must be respected, especially in the case of women, considered a vulnerable category. Moreover, the observation that there are differences between the degrees of COVID-19 impact to an area in a certain period triggered the idea of clinic shutdowns done in a timely manner according to specific strategy [47–49].

Infertility is a chronic, time-sensitive disease associated with physical and psychological distress. It has been demonstrated that, although short delays in the treatment of infertility do not seem to affect the chances of pregnancy, any interruption in the achievement of the intended purpose will lead to a significant psychological suffering [50]. A short time ago, *ASRM* was saying that the opportunity window for the infertile couples is narrow and that a too long delay in treatment could reduce the chances of pregnancy [51, 52].

Once the restrictions were relaxed, the reputable society in the treatment of infertility and ART issued recommendations for practice in this field and announced the resumption of the ART treatment [53].

Infertility diagnosis and treatment services involve a much closer and broader interaction with patients compared to other medical services. These services include counseling, blood analysis, clinical consultation, transvaginal US, and ART or/and procedures, such as genetic tests, hysteroscopy, laparoscopy, etc. [43, 52]. Numerous strategies for optimizing working conditions have also been suggested. *ESHRE* suggested a protocol dedicated to ART for triage regarding the possibility of infection with SARS-CoV-2 for both the patients and the medical staff. The purpose of following this protocol dedicated to ART is to identify in time any possible sources of infection for everyone involved in ART treatment [54].

With the evolution of the COVID-19 pandemic, *ASRM* has released several updates for "Patient management and clinical recommendations during the coronavirus pandemic (COVID-19)", a publication in which it was eventually recommended to carry out ART even if in a staged manner. Physical distancing, proper use of personal protective equipment, increased sanitation, and educating patients about known and unknown aspects of the COVID-19 infection are among the top recommendations. All members of the medical team should use appropriate personal protective equipment and receive appropriate training on safety procedures during this COVID-19 pandemic to reduce the spread of this virus. It is also recommended that every person should minimize contact with external personnel and, where appropriate, keep a distance of at least one meter from another person, while using appropriate facial protection [44, 54].

The risk of ovarian hyperstimulation syndrome (OHSS) must be considered during the COVID-19 epidemic, recommendations in this respect showing that doctors specialized in reproduction processes should follow the standard treatment for gonadotropin-releasing hormone (GnRH) antagonist agonist-triggered ovarian stimulation to minimize the risk of OHSS, hospital admissions and the occupation of the intensive care unit [43, 54].

In vitro fertilization (IVF) laboratories should offer male patients, whenever possible, the option to collect semen themselves at their own home and then bring them to the medical unit. Here, the collected sample should be considered a potential source of virus, and the handling of the semen should be prepared using a density gradient followed by the swimming technique. Although the presence of SARS-CoV-2 in male and female genital organs, in sperm or oocytes has not yet been clearly highlighted, an important aspect related to cryopreservation is the fact that it is possible to spread the virus during the preparation and cryopreservation procedures [51–55].

Depending on the capacity of the clinic staff, it is recommended that the staff should work in at least two or three alternating mini-teams in the workplace, thus limiting the spread of the virus. The medical staff must include at least one gynecologist, one medical assistant, one anesthesiologist and at least two embryologists. If someone in the group is exposed to the virus, enter quarantine only those with whom they have been in direct contact, thus ensuring that the rest of the staff can continue clinical activities [54–56].

Concerning the possible contamination of the embryology laboratory and of the embryology medical staff, it is recommended that all staff members should be trained in specific protocols for the treatment of persons with SARS-CoV-2 and should wear appropriate equipment [57]. When their physical presence is not required, the use of telemedicine for any fertility questions, including embryological results, may minimize the spread of the virus [38, 47, 53–56].

Sanitizing the environment, the equipment, and the devices in the laboratory with specific products or sterilization with ultraviolet (UV) radiation after each procedure or after each entry in a specific room must be part of the mandatory daily routine [54]. In addition, we have known for years that the risk of virus cross-contamination seems negligible if the harvested product is introduced into liquid nitrogen and that washing a harvested product with sterile liquid nitrogen can further reduce the risk of contamination. This is basically the technique used also for patients diagnosed with the human immunodeficiency virus (HIV) or viral hepatitis, in which case the products are frozen in separate containers/tanks [56]. The use of protective materials during the cryostorage process can protect the virus from the extreme temperatures to which the biological material is subjected, which can favor its subsequent spread. Since the possibility that viruses can cross the pellucid zone is of the utmost importance, repeated mechanical washing is necessary to minimize the risk [44, 51].

Taking all these details into account, ART procedures must be performed with great care because couples diagnosed with infertility are subject to a very strong emotional impact linked to the possible loss of the desired and imagined child, a loss which becomes a tangible one in the event of an implantation failure or an abortion.

SARS-CoV-2 will probably continue to remain a challenge for current medicine and that is why scientific knowledge about all the symptoms and complications that can appear in cases of COVID-19 is of great importance in the fight against this virus [58]. Given that time is an extremely valuable element in infertility, that his treatment requires some financial resources and psychological involvement, the closure of these clinics and the cessation of such treatment should be much better thought of [59, 60].

Fertility and the COVID-19 vaccine

At present, the data about the effect of COVID-19 during pregnancy are inconclusive, with some studies suggesting that there is no association between the two and other studies highlighting an increased risk of maternal and fetal complications [47, 61].

The need for the rapid appearance of these vaccines, initially licensed and promoted, raised many question marks and the appearance of numerous speculations in the media [62]. One of the main topics of debate in the online environment has been related to the fact that the vaccine could cause infertility [63].

Given the relatively short time since the first administrations of such vaccines, these vaccines have not passed the test of time and thus long-term data are missing [61, 64, 65].

Even if the first studies related to these vaccines did not discuss the issue of fertility, currently there is no

scientific basis regarding the fact that this vaccination would influence it. Even if there may be a decrease in sperm concentration and total motile count in the first three months after vaccination, they later return to the initial values, confirming the safety of vaccination despite some unwanted effects over a short period of time [66]. *ESHRE*, the *American College of Obstetricians and Gynecologists* (ACOG), ASRM and the *Society for Maternal–Fetal Medicine* (SMFM), the *Romanian Society of Obstetrics–Gynecology* (RSOG), the *Royal College of Physicians of Ireland* (RCPI), the *British Fertility Society* (BFS) and the *Association* of *Reproductive and Clinical Scientists* (ARCS) have issued numerous statements encouraging vaccination among young people and children stressing that "there is no evidence that any COVID-19 vaccine affects the fetus or fertility" and then *ASRM* have continued and reaffirmed their position that "everyone, including pregnant women and those who wish to remain pregnant, should get a COVID-19 vaccine" [8, 44, 61, 62].

Conclusions

Even though these are early discussions carried in the absence of serious scientific evidence, it can be concluded that the SARS-CoV2 can affect the reproductive health having potentially harmful consequences for couples seeking infertility treatment. Over the next few years, we may witness a much lower birth rate, a lower IVF birth rate with this virus present while performing delicate procedures. Of course, choosing the best method of treating infertility during COVID-19 pandemic or another pandemic is multifactorial. In addition to the psychological impact of an infertility diagnosis, the suspension of specific assisted human reproductive treatments brought with it additional unfavorable consequences among the couples involved in this problem.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Maria Sidonia Săndulescu and Anda Lorena Dijmărescu equally contributed to this article.

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Received: July 25, 2022

Accepted: December 28, 2022