

## KEY POINTS IN FERTILITY PRESERVATION TREATMENT STRATEGIES DURING COVID-19 PANDEMIC. AN UPDATE ON PHARMACOLOGICAL THERAPIES

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Manuscript received: February 2021

### Abstract

The fertility preservation (FP) field has developed in the two decades and offers women the possibility to have genetic children at some point in life. Fertility preservation is urgent by definition, performed for social reasons or medical indications, such as impending gonadotoxic therapy or radical gynaecological surgery. One year after the pandemic was declared, the COVID-19 infection imposed several restrictions and limited access to health care for the infertile couple. Ovarian stimulation is a pharmacological treatment used to induce the development of ovarian follicles; FP guidelines provide different options for ovarian stimulation. We performed a systematic search on fertility preservation (FP) procedures during the COVID-19 pandemic using the keywords: FP, ovarian stimulation, assisted reproduction techniques (ART), and COVID-19. In order to update the different treatment strategies in ovarian stimulation on fertility preservation studied in the last ten years, we searched for randomized clinical trials (RCTs) focused on therapeutic agents used in current protocols, gonadotropins, gonadotropin releasing hormone (GnRH), clomiphene citrate (CC), letrozole, androgens, metformin, tamoxifen, glucocorticoids, aspirin, coenzyme Q10, and sildenafil. Fertility may be influenced by SARS-CoV-2 infection - especially in men; until more evidence confirms the effects on fertility, patients with COVID-19 positive should delay FP procedures if possible. Access to fertility conservation services decreased during the analysed period due to the medical services restrictions and the reorientation of medical resources on patients with COVID-19, without major changes in the current therapeutic protocols. In terms of pharmacotherapy in ovarian stimulation (OS) procedures, letrozole is first line therapy, superior to CC for OS. Similar ovulation and pregnancy rate can be obtained in letrozole - induced ovulation compared to gonadotropin protocol. Adjuvant therapies may be used for OS but lack proven efficacy. Further studies on adjuvant therapies and complementary support are needed, to ensure optimal condition in assisted reproductive interventions for fertility preservation, especially in gonadotoxic therapies.

### Rezumat

Domeniul conservării fertilității (FP) s-a dezvoltat în cele două decenii și oferă femeilor posibilitatea de a avea copii genetici la un moment dat în viață. Conservarea fertilității este urgentă prin definiție, efectuată din motive sociale sau indicații medicale, cum ar fi terapia gonadotoxică iminentă sau chirurgia ginecologică radicală. La un an de la declararea pandemiei, infecția COVID-19 a impus mai multe restricții și a limitat accesul la îngrijirea sănătății pentru cuplul infertil. Stimularea ovariană este un tratament farmacologic utilizat pentru a induce dezvoltarea foliculilor ovarieni; ghidurile FP oferă diferite opțiuni pentru stimularea ovariană. Am efectuat o căutare sistematică a procedurilor de conservare a fertilității (FP) în timpul pandemiei COVID-19 folosind cuvintele cheie: FP, stimularea ovariană, tehnici de reproducere asistată (ART) și COVID-19. Pentru a actualiza diferitele strategii de tratament în stimularea ovariană privind conservarea fertilității studiate în ultimii zece ani, am căutat studii clinice randomizate (RCT) axate pe agenții terapeutici utilizați în protocoalele actuale, gonadotropine, hormonul eliberator al gonadotropinei (GnRH), citrat de clomifen (CC), letrozol, androgeni, metformină, tamoxifen, glucocorticoizi, aspirină, coenzima Q10 și sildenafil. Fertilitatea poate fi influențată de infecția cu SARS-CoV-2 - în special la bărbați; până când mai multe dovezi confirmă efectele asupra fertilității, pacienții cu COVID-19 pozitiv ar trebui să amâne procedurile FP dacă este posibil. Accesul la serviciile de conservare a fertilității a scăzut în perioada analizată din cauza restricțiilor serviciilor medicale și a reorientării resurselor medicale către pacienții cu COVID-19, fără modificări majore în protocoalele terapeutice actuale. În ceea ce privește farmacoterapia în procedurile de stimularea ovariană (OS), letrozolul este terapia de

primă linie, superior clomifenului (CC) în OS. O ovulație și o rată de sarcină similară pot fi obținute în ovulația indusă de letrozol în comparație cu protocolul gonadotropinei. Terapiile adjuvante pot fi utilizate pentru OS, dar nu au o eficacitate dovedită. Sunt necesare studii suplimentare privind terapiile adjuvante și sprijinul complementar, pentru a asigura o stare optimă în intervențiile de reproducere asistată pentru conservarea fertilității, în special în terapiile gonadotoxice.

**Keywords:** fertility preservation, ovarian stimulation, pharmacological agents, assisted reproductive techniques, COVID-19

## Introduction

The COVID-19 pandemic has brought a series of significant changes in all areas of activity and continues to weaken health systems around the world [1-3]. Fertility societies responded to the pandemic with the abrupt cessation of clinical interventions and the closure of fertility clinics, with some exceptions in the case of urgent conservation of fertility, a decision with a significant psychosocial impact on patients [4].

The global *in vitro* fertility (IVF) market was affected by the various restrictions of 2020, but it is still expected to recover and grow with a compound annual growth rate (CAGR) of 12% by 2023 [4], reflecting the increased number of people tuning into their reproductive health in recent years. Most of the time, infertility is a time-sensitive issue, if not from a medical but psychological perspective.

Cancer itself, gonadotoxic treatment, surgical procedures for benign or malignant gynaecological affections may determine gonadal damage and diminished ovarian reserve [5, 6]. Cytotoxic and immunomodulatory agents have a broad spectrum of undesired effects, on different organs and tissues, including the reproductive system [6-8], which may cause premature ovarian insufficiency (POI), infertility, and early menopause. Major factors determining the risk of induced POI are the type of agent, the dose, and the length of chemotherapy exposure. The patient's age at the moment of treatment is noticed to be a related factor for POI [9]. Less is known about the impact of the SARS-CoV-2 pandemic on fertility care.

Our study's objectives are to systematically evaluate the influence of the SARS-CoV-2 infection on fertility care from the beginning to the present moment, with an update of the scientific data on pharmacotherapy agents used for fertility preservation (FP's) ovarian stimulation protocols in the last ten years.

## Materials and Methods. Data Search

The first purpose was to perform a systematic search to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines on original published papers on topics (1) "fertility preservation", (2) "ovarian stimulation" and (3) "assisted reproductive techniques" – with a data filter on (AND) "COVID-19" – published in scholarly peer-reviewed journals (with no country restriction) during the pandemic period (the year 2020 - present) (Figure 1). The analysis on the last ten years refined to RCT/CT observed the constant interest at a low level on fertility

preservation topic, and an alarming decrease in assisted reproductive techniques (ART) in 2020 (Figure 2).

The present study's next purpose was to systematically review and evaluate the role of different therapeutic strategies on pregnancy achievement. Clinical trials (CT), meta-analyses (MA), and randomized controlled trials (RCTs) that evaluated eleven therapeutic agents (gonadotropins, GnRH, clomiphene citrate, letrozole, androgens, metformin, tamoxifen, glucocorticoids, aspirin, coenzyme Q10 and sildenafil) were included. Relevant studies published in the English language were comprehensively selected using PubMed/Medline and WoS until 2021. We included studies among ten years periods that investigated various agents during IVF protocol and reported pregnancy outcomes (Figures 1, 2, 3 and 4).

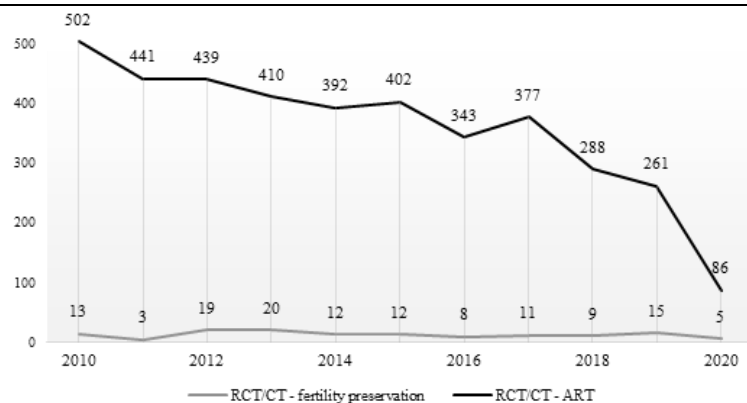
## Study selection

*PubMed*<sup>®</sup>/*MEDLINE* data search. Association "COVID-19" and "fertility preservation", revealed three results; the search refined to randomized controlled trials, clinical trials (RCT/CT) or reviews, systematic reviews or meta-analysis (R/SR/MA) retrieved no results; "COVID-19" and "assisted reproductive techniques" retrieved seven results, "COVID-19" and "ovarian stimulation" retrieved no results.

*Web of Science* data search. For the association "COVID-19" and "fertility preservation", the search retrieved three results; "COVID-19" and "assisted reproductive techniques" retrieved three results, "COVID-19" and "ovarian stimulation" retrieved four results. Bargraph of data retrieved on fertility preservation on period 2020 to present is described in Figure 1.

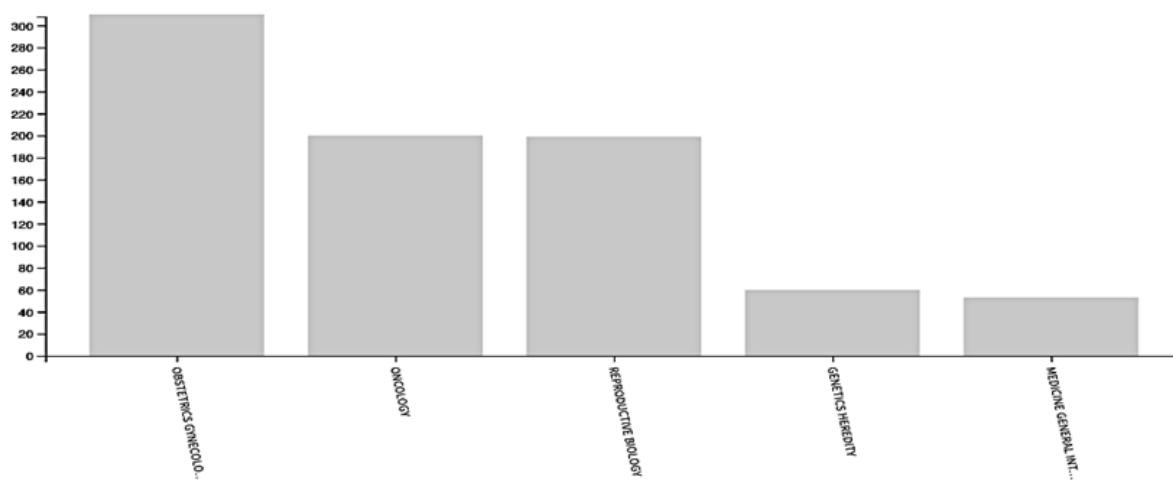
Over 88 studies were identified and screened for eligibility; according to the topic search, data extracted included demographic variables, participants in the study, treatment and safety profile. Thirty five papers were included in the present study section, centered on the main topics included in the search.

A total of 4071 studies were published on "ovarian stimulation" and "pharmaceutical agents" (letrozole, human chorionic gonadotrophin, gonadotropin-releasing hormone antagonist and agonist, recombinant FSH, human menopausal gonadotropin, glucocorticoids, androgens, aspirin, metformin, clomiphene citrate, coenzyme Q10, and sildenafil) on the PubMed<sup>®</sup>/Medline and Web of Science databases, from the past ten years, with 650 randomized controlled trials. In the last year, we observed and analysed thirty-nine RCT on ovarian stimulation (OS) therapies in ART.



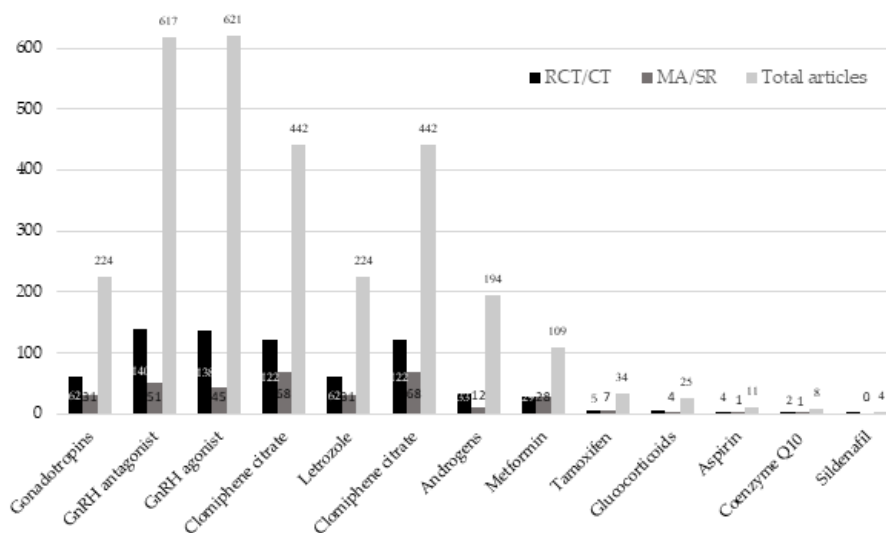
**Figure 1.**

Chart of a systematic search for the keywords “fertility preservation” and “ART” on the PubMed® database refined to RCT/CT (ten years topic: 2010 - 2020)



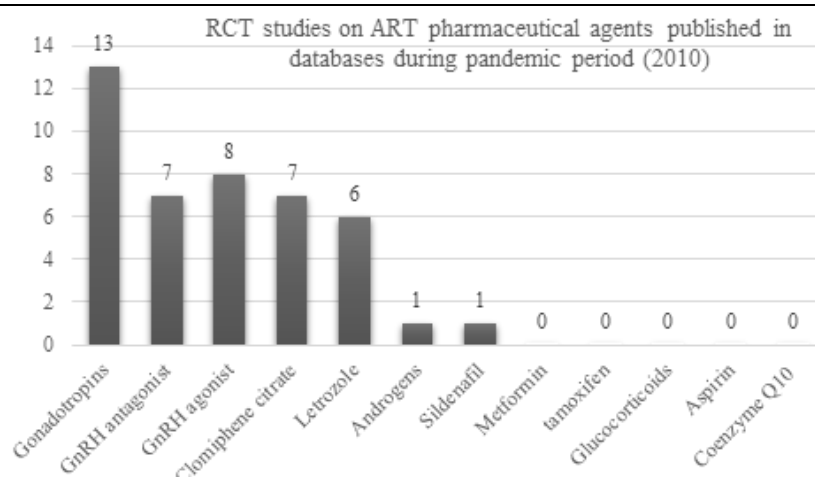
**Figure 2.**

Bargraph of data retrieved on Web of Science search on fertility preservation since 2020, on publication domain. The search retrieved 918 studies (Obstetrics and Gynaecology, Oncology, Reproductive Biology, Genetics Heredity, General Medicine)



**Figure 3.**

Distribution of research papers on pharmaceutical agents used in ovarian stimulation protocols - ten years topic (2010 - 2020) (total randomized controlled trials/controlled trials-black, meta-analyses/systematic reviews – grey, total papers on topic – light grey)



**Figure 4.**

The systematic search for the keywords “ovarian stimulation” AND “gonadotropins”, “GnRH”, “clomiphene citrate”, “letrozole”, “androgens”, “metformin”, “tamoxifen”, “glucocorticoids”, “aspirin”, “coenzyme Q10” and “sildenafil” on the PubMed® database refined to CT/MA/RCT (the pandemic COVID-19 period)

The statistical analysis was performed using Microsoft Excel® 2013 (Microsoft® Corporation, Redmond, WA, USA).

### The current state of knowledge on SARS-CoV-2 and human reproduction

Genomic analysis reveals that the new SARS-CoV-2 respiratory virus entry into cells mediated by the viral spike (S) protein *via* angiotensin-converting enzyme 2 (ACE2) receptors, enhanced by transmembrane serine protease 2 (TMPRSS2) [10]. Afterwards, the viral RNA is released, replication and transcription begin [11]. SARS-CoV-2 infection disrupts the renin-angiotensin system by downregulating ACE2 expression in the cells generating a pro-inflammatory response. Components of the renin-angiotensin system, Ang (1-7), Ang II, and ACE2, control essential reproductive system functions [12].

#### COVID-19 on male fertility

Studies show that ACE2 receptors are more expressed in the male reproductive system than in the female. ACE2 in the testis is highly expressed, with high levels in Leydig and Sertoli cells, and regulates the testicular and sperm function [12, 13].

SARS-CoV-2 can affect testicles through the genomic similarity with SARS-CoV. The virus's binding to ACE2-positive cells in testis could generate severe alteration of testicular tissue eventually provide sites for viral infection. The existing studies reveal only the male reproductive system and function injury regarding transmissibility so that the coronavirus outbreak may have a serious impact on fertility worldwide.

The SARS-CoV-2 infection affects male fertility by acting on testicular tissue (Sertoli cells); thus, the secretion of semen affects spermatogenesis; secretions from the prostate are harmful. Subsequent studies

in recovered patients will analyse the effect of the virus on orchitis determinism and the correlation with spermatogenesis and infertility [14, 15]. Another element is related to the associated diseases (cancer patients) and the possible impact on the overall outcome of SARS-CoV-2 infection, increasing the degree of infertility [16].

#### COVID-19 and female fertility

The evidence available suggests that ACE2 is expressed in the breasts, uterus, vagina, fallopian tube, placenta and most abundantly in the ovary, with high oocyte levels. The renin-angiotensin system's female reproductive system components control follicle development, steroidogenesis, oocyte maturation, ovulation, endometrial regeneration and embryo development. The broad expression of ACE2 in the female reproductive tract COVID-19 may favour the infection and disturb the female reproductive functions [12, 17].

### Fertility preservation and ART during the COVID-19 pandemic

Although recommendations from all relevant bodies supported the non-interrupted access to emergency fertility care even during lockdown periods [18, 19], there were raised many concerns and uncertainties for the oncofertility patients related to the full availability of treatments under the pandemic state.

Other pandemic-generated aspects impacting the fertility care sector are the following: the risk of viral transmission to patients, their gametes, embryos and reproductive tissues or the increased risk of assisted reproduction cycle cancellation due to superimposed infection with SARS-CoV-2. These issues are even more stringent for patients living in - remote areas - or developing countries [20].

COVID-19 and ART procedure have a coexisting issue of thrombotic risk [21, 22]. ART procedures have a

risk of thromboembolic complications in the case of OHSS. In COVID-19 positive women, any risk of OHSS should be avoided, and prophylactic measures are mandatory [23].

### Screening for SARS-CoV-2 in fertility preservation programs

There is a narrow fertility window in oncological patients to preserve their reproductive potential, so an active infection while proceeding with FP treatment could compromise the whole procedure and the patient's reproductive potential. Besides, during the entire routine of IVF procedure, the patient is exposed to a potentially COVID-19 interference. Although universal screening for COVID-19 is the ideal scenario [24], in real life, the availability of testing resources varies widely [25]. It is established that all patients resorting to ART must be subjected to triage, but there is no consensus yet on the optimal way of screening triage-negative asymptomatic patients attending the fertility clinic [26, 27].

Considering the disastrous consequences of an undetected SARS-CoV-2 infection in a fertility case, screening the patient (and partner) at least at the beginning of the FP treatment is mandatory [27]. The optimal screening algorithm remains unknown, but ideally, both serology and molecular tests should be used as the combined approach significantly increases detection rates [28].

It is necessary to periodically test healthcare workers from fertility clinics to avoid the nosocomial transmission and risk of iatrogenic infection in the laboratory samples.

### Cryopreservation technique and its safety

Cryopreservation of embryos, reproductive cells and tissues is a considerable part of any fertility program and a technique with an exponential rise in assisted reproduction usage for an expanding variety of indications. So the question arose regarding the safety of cryopreservation under the COVID-19 auspices.

Pomeroy *et al.*, in a study published in 2010, reveal the presence in the IVF laboratories of infectious organisms and the negligible risks of transmission to and between recipients. This information indicates an insignificant probability of SARS-CoV-2 presence in frozen reproductive specimens [29].

There is evidence that the risk of infectious cross-contamination during cryopreservation and storage is negligible [29] and the lack of cases of inflicting a transmissible/communicable disease *via* laboratory steps for IVF or cryopreservation is reassuring [30]. Data regarding the risk of virus transmission in gametes, human embryos, and reproductive tissue by infected people and the possibility of affecting early embryogenesis have many lacks [31]. Sperm, oocytes and

embryos are potential infectious disease sources, including the SARS-CoV-2 virus [32].

The first study published by Baragann *et al.* about viral RNA of SARS-CoV-2 detection in the oocytes of women who were infected found that the viral RNA was undetectable in all 16 oocytes studied, and there will not be the vertical transmission of the virus [33]. Until September 2020, no studies were evaluating a possible transmission of SARS-CoV-2 to oocytes in infected women [31].

Cryopreservation protocols have been developed individually for reproductive samples to minimize cross-contamination and transmission risk, to guarantee long-term safe storage and effective retrieval. When repeated washing and cryopreservation protocols have been respected, the samples' viral contamination risk was very low in the IVF laboratory [32]. All of the above and the fact that we are confronting a newly emerged virus led to good laboratory and tissue practice changes during the COVID-19.

### Ovarian stimulation (OS) protocols

The first element in OS protocols consists of stimulation with exogenous gonadotrophins to develop multiple follicles, followed secondarily by the association of gonadotropin-releasing hormone antagonist or agonist (GnRH) to prevent premature ovulation. The third element is represented by triggering the final maturation 36 - 38 hours before oocyte retrieval, commonly with human chorionic gonadotrophin (HCG) or with GnRH agonist in antagonist protocols.

In emergency fertility preservation, unconventional protocols to facilitate the start of ovarian stimulation have been proposed, such as immediate or random start ovarian stimulation, luteal phase stimulation and even double stimulation in the same menstrual cycle (Follicular *versus* luteal phase ovarian stimulation during the same menstrual cycle, DuoStim) [34]. These protocols are typically at a lower risk of developing the most feared iatrogenic complication of COS – the ovarian hyper-stimulation syndrome (OHSS), because of the combination between a short antagonist protocol and a GnRH agonist trigger for the final oocyte maturation. This approach has tremendously reduced the incidence of OHSS in patients at risk [35], but it does not eliminate the OHSS risk [36]. In conclusion, the optimal COS strategy should balance the maintenance of an optimal oocyte yield, with virtually zero risks of iatrogenic complications [37].

According to guidelines, the response after conventional ovarian stimulation (150 - 225 IU FSH) is classified as low ( $\leq 3$  follicles on day of oocyte maturation trigger and/or  $\leq 3$  oocytes retrieved), normal, and high ( $> 18$  follicles  $\geq 11$  mm on day of oocyte maturation trigger and/or 18 oocytes obtained) [38, 39].

FP guidelines provide different options for ovarian stimulation, taking into account the individualization

of protocols. Medications that stimulate the ovaries may be used to induce ovulation in patients with anovulatory infertility or to hyper-stimulate the ovaries in a controlled fashion in ovulatory patients as part of assisted reproductive treatments (ART).

The main therapeutic agents used to stimulate ovarian function include gonadotropins, pulsatile gonadotropin-releasing hormone (GnRH), clomiphene citrate, and letrozole. Adjuvant agents like glucocorticoids, aspirin, androgens, metformin, coenzyme Q10 and sildenafil are also discussed in terms of efficacy and safety.

#### *Gonadotropins*

Types of gonadotrophins available in ovarian stimulation (OS) protocols include recombinant FSH (rFSH), human menopausal gonadotropin (hMG), purified FSH (p-FSH) and highly purified FSH (hp-FSH), recombinant LH (rLH). Different associations of gonadotrophins are recommended for specific patient groups for an efficient and safe stimulation.

A total of 2108 studies were published in the last ten years on OS and gonadotropins on the PubMed® database, with 312 RCT and 125 SR/MA; 13 RCT on the topic in the last year.

For normal responders in GnRH antagonist, GnRH agonist and rHCG improve the oocyte maturity and embryo grading [40].

There may be little or no difference in a live birth, the incidence of multiple pregnancies, clinical pregnancy rate, or miscarriage rate between urinary-derived gonadotrophins and recombinant follicle-stimulating hormone in women with polycystic ovary syndrome. For human menopausal gonadotropin or highly purified human menopausal gonadotrophin *versus* urinary follicle-stimulating hormone, we are uncertain whether one or the other improves or lowers live birth, the incidence of multiple pregnancies, clinical pregnancy rate, or miscarriage rate [41].

For every birth achieved with gonadotropins, a similar increased risk of multiple gestations occurs. The randomized clinical trial data do not support the use of gonadotropin for OS-IUI in women with unexplained infertility [42]. We found no distinct evidence of a difference between rLH combined with rFSH and rFSH alone in live birth rates or OHSS [43] nor a difference between low doses of gonadotropins and gonadotropins combined with oral compounds in pregnancy outcomes compared with high doses of gonadotropins in ovarian stimulation regimens [44]. The use of rFSH and hMG is equally recommended for ovarian stimulation, with slightly higher efficiency, but not considered clinically significant, with hMG use in the live birth rate. No significant difference was reported in the OHSS rate [45]. The use of rFSH and pFSh or hpFSH in GnRH agonist protocol is equally recommended. No significant difference in live birth rate or OHSS rate is associated, but the use of rFSH is preferable to pFSH or hpFSH [46]. HpFSH is not preferable over hMG for ovarian stimulation in down-

regulation with GnRH agonist protocol, similar clinical pregnancy rate and number of oocytes retrieved being reported [47] rFSH + rLH use was associated with similar pregnancy rate compared to hMG, and with a higher risk of OHSS in GnRH agonist protocol [48].

#### *Gonadotropin-releasing hormone (GnRH)*

A total of 1015 studies were published in the last ten years on OS and metformin on the PubMed® database, with 172 RCT and 71 SR/MA; 8 RCT on the topic last year. GnRH antagonist protocols are preferred for ovarian stimulation in women undergoing FP for medical reasons because they reduce the duration of stimulation and enable triggering of oocyte maturation with GnRH agonist reducing the risk of ovarian hyper-stimulation syndrome (OHSS). GnRH antagonist protocol is preferred in normal responders, with similar pregnancy and live birth rates and decreased OHSS compared with GnRH agonist protocol [49, 50]. In low responders, the GnRH antagonist protocol is correlated with fewer oocytes retrieved, similar pregnancy and live birth rates, and a shorter length of treatment than GnRH agonist protocol [51]. Also, in low responders, a delayed start in antagonist GnRH protocol was a potentially efficient choice [52]. In high responders, the GnRH antagonist protocol is effective as GnRH agonist protocol in terms of pregnancy rate and the number of oocytes retrieved, and a significant decrease of OHSS [50]. During GnRH antagonist protocol, an increased progesterone level is independently associated with a reduced pregnancy rate in low and normal responders, but not in high responders' women [53].

#### *Clomiphene citrate (CC)*

Clomiphene Citrate (CC) is a selective oestrogen receptor modulator (SERM) with oestrogen receptor agonist and antagonist properties. A total of 442 studies were published in the last ten years on OS and clomiphene citrate on the PubMed® database, with 108 RCT and 70 SR/MA; 6 RCT on the topic last year. Current evidence does not recommend the use of CC instead of FSH in ovarian stimulation. No studies are available about the benefit of adding CC to gonadotropins, equal pregnancy outcome being obtained in COH protocol with CC or the conventional protocol in low responders [54]. In women with PCOS for ovulation induction, the late luteal phase administration of CC might be more effective than conventional administration [55]. CC is not an option in low responders because of high costs and low efficiency, short GnRH agonist protocol being the first option [56]. Clomiphene citrate is more successful than tamoxifen as first-line therapy for ovulation induction in women with PCOS [57].

#### *Letrozole*

A total of 225 studies were published in the last ten years on OS and letrozole on the PubMed® database, with 52 RCT and 31 SR/MA; 6 RCT on the topic in the last year. Letrozole, an aromatase inhibitor agent, increases the secretion of FSH and stimulates follicle development and maturation. Letrozole should be

considered the first option for ovulation induction in PCOS women with anovulatory infertility as pregnancy and live birth rates are improved, time to achieve a pregnancy is shorter, and multiple pregnancies are at risk lower compared to CC [58]. Similar ovulation and pregnancy rate can be obtained in letrozole-induced ovulation compared to gonadotropin protocol, with limited adverse effects. In PCOS women with CC resistance or failure, letrozole is an effective ovulation option, with higher pregnancy rates than CC administration combined with metformin [59, 60]. During the ovarian stimulation cycle, co-administration of aromatase inhibitors (e.g., letrozole) in oestrogen-sensitive diseases, such as breast cancer, endometrial cancer, or systemic lupus disease (SLE) reduce oestradiol levels and the proliferative effect of malignant cells, without affecting oocyte yield [61, 62].

#### *Adjuvant therapies on ovarian stimulation*

**Androgens.** A total of 194 studies were published in the last ten years on OS and androgens on the PubMed® database, with 21 RCT and 12 SR/MA; no RCT on the topic last year. Androgens increase antral follicles' response to stimulation, especially in older-reproductive age women, mediated by IGF-1. Inconsistent evidence is available regarding testosterone or dehydroepiandrosterone (DHEA) use before ovarian stimulation, ovarian response, clinical outcomes, dosage, duration and safety [63]. In poor responders, transdermal testosterone's addition seems to increase pregnancy and live birth rates [64]. In normal responders, DHEA administration did not modify the ovarian response to a standard low dose of gonadotrophin stimulation [65].

**Metformin.** A total of 114 studies were published in the last ten years on OS and metformin on the PubMed® database, with 28 RCT and 29 SR/MA. We found 13 RCTs on the topic in the last year. Adjuvant metformin use in women with PCOS undergoing ovulation induction with gonadotropins may increase the pregnancy and live birth rate [66]. Metformin is better than placebo for ovulation rate, pregnancy, and live birth rate, but with more gastrointestinal upsets. Metformin plus CC improves ovulation and pregnancy rate, with no difference in live birth rate or multiple pregnancies, but with the cost of a higher probability of gastrointestinal side effects than CC alone. Available studies about metformin *versus* CC use do not reveal statistically significant differences for live birth, pregnancy, or ovulation rate [67].

Metformin compared to placebo in GnRH agonist protocol reported no difference in a live birth, increase pregnancy rate and significantly fewer oocytes retrieved [68, 69]. In GnRH-antagonist protocol, metformin decrease live birth rate, without effect on pregnancy rate, with no impact on the number of oocytes retrieved or OHSS incidence [68, 70].

**Tamoxifen.** A total of 34 studies were published in the last ten years on OS and tamoxifen on the PubMed® database, with 5 RCT and 7 SR/MA; no RCT on the

topic in the last year. Selective oestrogen receptor modulator (e.g., tamoxifen) does not reduce estradiol concentrations, but has an inhibitory action on the oestrogen receptor in oestrogen-sensitive disease [63]. In inducing ovulation protocols, tamoxifen and clomiphene citrate are equally effective [71]. In terms of induction of ovulation cycles, a good effect will be from the combination of tamoxifen with letrozole [72]. In women with unexplained infertility, tamoxifen does not increase the clinical pregnancy rate [73].

**Glucocorticoids.** A total of 25 studies were published in the last ten years on OS and glucocorticoids on the PubMed® database, with 4 RCT and 4 SR/MA; no RCT on the topic in the last year. Glucocorticoids may improve folliculogenesis and pregnancy rates, but at the moment are insufficient data in the literature to confirm the hypothesis [63]. The glucocorticoid administration in women undergoing controlled ovarian hyper-stimulation is not established [74], with no support data of efficacy of methylprednisolone in the correlation between OHSS incidence and clinical outcomes [75]. Dexamethasone increased ovary response to gonadotropin stimulation, suppressed the progesterone secretion, and determined a higher cumulative live-birth rate [76].

**Aspirin.** A total of 11 studies were published on the last ten years on OS and aspirin on the PubMed® database, with 4 RCT and 1 SR/MA; no RCT on the topic in the last year. In anovulatory PCOS patients, the addition of low-dose aspirin (LDA) to tamoxifen improves ovarian stimulation response and pregnancy rates [77]. Adjuvant LDA increased the number of poor-quality embryos but not decreased the severity of OHSS [78]. In women undergoing IVF, LDA does not have a positive effect on the likelihood of pregnancy [79].

**Coenzyme Q10.** A total of 8 studies were published in the last ten years on OS and Coenzyme Q10 on the PubMed® database, with 2 RCT and 1 SR/MA; no RCT on the topic in the last year. Co-enzyme Q10 (CoQ10) – reverse oocyte quality and quantity in age-related infertility and improves ovarian response and embryo parameters in young women. In women with poor ovarian reserve, the addition of CoQ10 increased ovarian stimulation response in IVF-ICSI cycles [80]. In clomiphene-citrate-resistant PCOS patients, the adjuvant of CoQ10 improves ovulation and clinical pregnancy rates [81].

**Sildenafil.** A total of 4 studies were published in the last ten years on OS and metformin on the PubMed® database, with 2 RCT; no RCT on the topic in the last year. Adjuvant sildenafil citrate did enhance ovulation success rate and increased pregnancy rate [82] and does not enhance ovarian receptiveness in previous low ovarian response to controlled OHSS [83]. In the case of clomiphene citrate failure, the vaginal administration might enrich the potential of pregnancy [84]. Also, it may be used to increase ovarian

vascularization and live birth rates, but the RCT of Ataalla *et al.* reported no significant difference in the numbers of oocytes retrieved or pregnancy rates with adjuvant sildenafil [83].

## Conclusions

Unlike other medical conditions, fertility screening must be performed over a more extended period for the patients to improve the quality of life and reproduction. During the lockdown, counselling therapy was cancelled, or a follow-up appointment was replaced with telemedicine consultation to diminish the exposure to SARS-CoV-2. Real-data showed that fertility might be influenced by infection with SARS-COV-2 - more significantly in males. Patients COVID-19 positive should avoid becoming pregnant or participate in any fertility programs. Screening the patient (and partner) at least at the beginning of the FP treatment seems mandatory. It is necessary periodical testing of healthcare workers from fertility clinics to avoid nosocomial transmission. In Romania, FP practice is regulated by the Code of Practices, with no specific mentions regarding the ART register, indications for freezing or funding, and inconsistent data regarding the type of interventions, compared to other European countries.

The objective assessment of the impact of COVID-19 on fertility must be subject to further clinical studies assessing at least one year after the declaration of the SARS-CoV-2 pandemic. In the next period, COVID-19 has been, is, and will be an additional challenge for fertility.

The gonadotropins are used for OS as part of ART cycles. GnRH agonist and rHCG improve the oocyte maturity and embryo grading, rFSH and hMG is equally recommended for OS. In PCOS, Letrozole is superior to CC for OS and CC is more successful than tamoxifen. Similar ovulation and pregnancy rate can be obtained in letrozole - induced ovulation compared to gonadotropin protocol. Androgens, metformin, glucocorticoids, tamoxifen, aspirin, Coenzyme Q10, sildenafil, may be used as adjuvants for OS with a efficacy but lack proven efficacy. Further studies on adjuvant therapies and complementary support are welcomed, in order to ensure optimal condition in assisted reproductive interventions for fertility preservation, especially in gonadotoxic therapies.

## Conflict of interest

The authors declare no conflict of interest.

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