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Covid-19 and its implications for the provision of gynecological services globally

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ABSTRACT

Covid-19 took the world by surprise and has completely changed the way humans live and work. There is hardly an aspect of life that has not been affected. Whether social, economic, physical, psychological, cultural or religious, this pandemic has revolutionized every aspect of our lives and some of these changes are here to stay for the unforeseeable time. Although much has been written about the negative effects of Covid-19 on our social lives, some technological advances on COVID-19 have profoundly affected various aspects of our lives. These are mostly to do with how we communicate, deliver health services, innovate and investigate new preventative measures and treatments, travel and indeed influenced the carbon footprint of the planet. Although most of gynaecology is elective and was therefore not considered a priority in the early phases of COVI-19, there are considerable consequences of delaying treatment for some of these elective conditions. Of particular importance are infertility, pre-malignant conditions, chronic pelvic pain, sexual disorders and those affecting the psychological and social aspects of women and families. The pandemic forced a rethink of how healthcare is delivered with wide adoption of remote/virtual consultation and triaging of clinical presentations. The rapid development of immunization and drugs against the virus was met with doubts by a large proportion of the population with reluctance to accept these. Consequently, there remains unvaccinated portions of both low and high-risk populations, some of whom may be denied access to gynaecological care. On the other hand, some pregnant women who are frightened of the impact of vaccination on pregnancy put their own lives at risk. While significant progress has been made to combat the pandemic, lessons about healthcare delivery (face-to-face versus virtual), education of the end users and introduction of new technologies into the development of drugs and vaccines must be evaluated and improved moving forward not only during the ongoing epidemic but with future outbreaks.

Introduction

Corona viruses have generally been the cause of various infections in mammals, birds and humans, where they specifically target the respiratory system. Over the past 20 years, there have been three new corona virus related lethal outbreaks of zoonotic origin. The 1st was the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) in 2002–2003 followed by the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and lately, the most severe of them, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the 2020 March Covid-19 pandemic [1,2]

SARS-CoV-2 spread very rapidly after the first reported case of pneumonia like disease of unknown origin at the time, from a seafood and live animal market in Wuhan city, China, in late December 2019 [3]. Human respiratory epithelial cells were subsequently used to isolate a new virus subsequently known to the world as SARS-CoV-2. The World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern (PHEIC) on January 30th 2020 and subsequently as a pandemic on March 11th 2020 [4]. More than 5.7 million deaths have been reported worldwide (as of February 4, 2022) [5]. Three major factors are thought to be responsible for this (a) increased transmissibility (b) characteristic pathogenicity and (c) globalization [6,7].

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Virology of SARS- CoV-2

SARS CoV-2 is characterized by a comparatively higher basic reproductive number (Ro) which further explains its rapid spread worldwide [8]. It belongs to the *ortho*-coronavirinae subfamily and is the seventh member of the family of Corona viruses that infects humans. The virus is spherical with a core shell and surface with protein projections like the spikes of a crown, hence named Corona (Crown in Latin). The most important of the three main proteins is the spike (S) protein which is responsible for attachment to the host cell membrane receptor followed by fusion and finally entry into the host cell. The remaining two are the membrane (M) protein which is the most abundant and the envelope (E) protein and together they make the viral membrane. Another, the N protein is part of the helical nucleocapsid that includes the genome RNA [9].

The virus has a single-stranded positive-sense RNA of around 30 kb and is non-segmented [10]. Phylogenetic analysis of the virus shows that SARS CoV-2 shares more than 80% genetic sequences with SARS-CoV-1 and more than 50% with MERS [11]. The WHO has classified the virus as β CoV of the group 2B [12,13].

Epidemiology

Epidemiological evidence suggests that SARS-CoV-2 is zoonotic in origin with bats being the primary host and spreading to humans via an intermediary host, probably pangolin, which is eaten in China as an exotic food [14]. The widespread nature of the disease worldwide suggests rapid person-to-person transmission, probably through different routes but mainly via direct contact and droplet spread through coughing and sneezing by infected individuals [15].

Clinical features

SARS-CoV-2 causes the disease that has been named COVID-19 by the WHO. With an incubation period of approximately 5.2 days (2–14 days), the clinical manifestations are widespread ranging from no symptoms to acute severe respiratory distress syndrome (ARDS) and multiple organ failures. Covid-19 also shares some clinical features with other beta corona viruses such as dry cough, high grade fever and pneumonia with bilateral ground glass opacities on Chest CT [16]. Just like MERS- CoV and SARS-CoV-1 infections, a comparatively greater proportion of Covid-19 patients may also develop gastro-intestinal symptoms such as diarrhoea. SARS-CoV-2 uniquely targets the lower airways [17] where it causes destruction of pneumocytes with infiltrating inflammation [17]. Other clinical features include loss of smell and taste. The development of acute respiratory distress syndrome (ARDS), cardiac and lung injury are poor prognostic features that could ultimately lead to death [18].

Diagnosis and treatment options

The gold standard for detecting SARS CoV-2 is reverse transcription polymerase chain reaction (RT-PCR) from the respiratory tract or salivary secretions. Other methods for the detection of SARS-CoV-2 include viral identification and immunological tests [20a]**.** Laboratory findings supporting the diagnosis include a combination of lymphopenia, high levels of hs-CRP (high sensitivity C- reactive protein) and eosinopenia; all of which are useful in triaging patients highly suspicious of SARS-CoV-2 infection and requiring radiological/CT evaluation of the chest for evidence of pneumonia. Other tests like blood gases, troponin levels, liver function tests, lactate dehydrogenase (LDH) and D-dimers are used to assess the risk and extent of multi-system involvement and prognosis. Procalcitonin levels are used to detect possible bacterial coinfection [20a].

The mainstay of treatment is supportive as there is as yet no definitive treatment for Covid-19. Symptomatic treatment focuses mainly on rest, hydration, temperature control and nutritional support. Oxygen therapy is needed if the patient fails to maintain adequate oxygen levels which may necessitate mechanical ventilation. The use of corticosteroids such as dexamethasone and anticoagulation with low molecular weight heparin have been shown to reduce mortality in those that are severely ill [19,20].

Impact on the global health resources

SARS-CoV-2, due to its extreme infectivity and virulence, has had a major impact on healthcare systems across the globe regardless of the socio-economic status of the countries. This has seriously challenged the integrity and resilience of these systems [21,22]. Its impact on global socioeconomic dynamics has been so severe that many of the world's otherwise stable economies and indeed all the other economies are still struggling to sustain their health services [23,24]. However, Covid-19 has demonstrated how collectively the world can willingly collaborate in research and share knowledge and technical know-how to address such health challenges. The case of vaccine development over such a short time is a classical example of this global co-ordination. The speed with which some of these developments have moved, however, has attracted severe criticism for not following the basic principles of research methodology and thus possibly compromising the quality of research with the potential of misleading results [25]. Indeed, various studies published data of efficacy of drugs such as hydroxychloroquine on the virus that were later shown to be unsubstantiated [26].

Covid-19 and the Women's health

The available evidence suggests that, although individuals of all ages are affected, the case fatality is age dependent with elderly men suffering the most especially those with comorbidities [27]. Interestingly, there is now compelling evidence that females are less severely affected by Covid-19 disease compared to males who suffer higher morbidity and mortality [28]. These differences were also observed with other viral epidemics including SARS-CoV-1 and MERS [29]. Whether this is because of the risk prone life style of males with comparatively more co-morbidities or some other perhaps biological factors, which make females less vulnerable to these infections remains uncertain.

SARS- CoV-2 uses its spike protein (S) to attach to the ACE 2 receptor on the alveolar epithelial membrane. It needs the Transmembrane protease serine 2 (TMPRSS2) to act as a vital factor priming the S protein which it cleaves thus facilitating activation and entry into the host cell. [30,31].

Interestingly, it has been suggested that the two X chromosomes in females as opposed to one in males are associated with the highest number of immune regulated genes in the whole human genome [32]. Normally one of the two X chromosomes in females is transcriptionally silenced as per the Lyon theory [33]. Interestingly, about 15–30% of the genes, mostly located on the short arm of the X-chromosome escape the silencing process [34]. Since ACE2 maps at the same location on the short arm of X-chromosome which escapes inactivation, the observed difference and more ACE2 expression in females could be due to this phenomenon [35]. More ACE2 availability in females means more availability for converting angiotensin-I into Angiotensin 1–7 (Ang 1–7) which promotes tissue protection via the Mas receptor (MasR) [28]. Theoretically, more ACE2 in females would mean more viral entry into cells but the rate limiting crucial factor TMPRSS2 expression is thought to be lower in females due to low androgens and high estrogens thus providing another level of protection [28].

Additionally, difference in hormone profiles with females being estrogenic and males androgenic, has been suggested to lead to a better immune-modulation (driven by estrogens) in females, making them less vulnerable to viral attacks [36]. In fact, there is evidence supporting the anti-viral role of estrogens against a group of viruses including human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Ebola virus

(EBV), Influenza-A and human cytomegalovirus (CMV) [37-40].

Covid-19 and gynecological care

Social distancing 2 metres (2 M) between individuals) was imposed by most authorities as a preventive measure and widely accepted to reduce the spread of SARS-CoV-2. This was based on old data [41] which did not take into consideration, other factors such as hand hygiene and cleaning, air management, use of personal protective equipment (PPEs) including face masks involved in respiratory transmissions of these viruses [42,43].

Virtual consultation revolution

The pandemic drove the need for innovative/alternate approaches to delivery of healthcare. Amongst these initiatives was virtual consultation. Face-to-face consultations in hospitals have therefore decreased significantly especially for minor complaints, in favor of virtual consultations since the onset of the pandemic. In Scotland for example all new and review appointments were quickly re-categorized to assess their suitability for virtual consultation for initial assessment and treatment advice. More than 50% patients can and are being managed through this arrangement. The Royal College of Obstetricians & Gynaecologists (RCOG) guidance about the initial management of patients in these circumstances has been implemented within the UK NHS system [44].

Unpublished data from Scotland has also shown a significant fall in the number of women requesting termination of pregnancy. Covid-19 related changes in health service modelling has also led to greater than 80% of women being managed at home using medical regimens as recommended by the RCOG [44].

Gynecological emergency services in some French hospitals witnessed a 41% drop in face-to-face consultations and comparatively a smaller (20%) drop in emergency admissions with a significant increase in the hospitalization to consultation ratio (3.9 % to 5.4%; $P < 0.0001$), during the Covid-19 peaks [45]. It is not clear if the drop was due to patients' reluctance to attend for fear of acquiring the virus especially if their condition was not judged to be severe or due to diversion of available resources when the whole focus was on controlling the spread and providing critical care to those affected by Covid-19. In another study conducted in a tertiary academic center in New York, a significant increase ($P < 0.001$) in the proportion of gynecological emergency surgical procedures (for ectopic pregnancy, miscarriage and concern for cancer) was noticed during the Covid −19 time [46].

With respect to the emergency care of ectopic pregnancies, it seems Covid −19 was associated with a higher rate of rupture with higher morbidity reported in a tertiary medical facility in Tel Aviv [47]. Whether similar trends were noticed for other gynecological emergencies is yet to be reported.

Covid-19 and reproductive health

Reproductive health includes a harmonized state of social, psychological, mental and physical health that is so necessary for procreation in a healthy environment. Reproductive health has been affected not only by SARS-CoV-2 itself but by the pharmacological /chemical interventions given to those exposed to the virus and the impact of the pandemic on provision of services (often not considered as emergency).

On entering the body SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE-2) receptor through its spike (S) protein [40]. This interaction is mediated, by the transmembrane protease serine 2 (TMPRSS2) or cathepsins B and L (encoded by the genes CTSB and CTSL respectively), when TMRSS2 is absent [48]. Evidence remains inconclusive on whether the female genital tract is one of the prime targets of SARS-CoV-2 due to the sparse presence of ACE-2 and TMRSS2 receptors [49]. Human ovaries, on the other hand, have been shown to express ACE-2 receptor activity in relation to folliculogenesis and maturation, steroid synthesis and ovulation, hence are a potential target for SARS-CoV-2 which may potentially cause damage via the ACE2 /TMPRSS pathway [50,51].

In males, there is robust evidence of ACE-2 receptors and TMPRSS2 expression on testicular tissue suggesting a potential damage by SARS-CoV-2 to this organ and potentially an adverse effect on its function [52,53]. Additionally, testosterone seems to facilitate SARS-CoV-2 spread via activation of TMPRSS2 [54] thus increasing the attractiveness of the virus onto the testicular tissue. Although orchitis is a recognized complication of the SARS-CoV group [55], it is believed that SARS-CoV-2 through binding to ACE2 receptor, may potentially cause orchitis and possible testicular atrophy and sub-fertility [56]. Furthermore, there have been reports of isolation of SARS-CoV-2 in semen of infected males [57] raising the possibility of sexual transmission.

For pregnant women affected with Covid-19, emerging data do not show any robust evidence of vertical transmission, however, SARS-Cov-2 may increase the risk of miscarriage and is associated with a significantly higher risk of preterm birth but not stillbirths [50,51].

Professional guidance on Women's health practice in the Covid-19 era

Obstetrics and Gynecology professional bodies across the globe including the WHO, FIGO and the RCOG responded to the covid-19 pandemic by issuing guidance that meet local needs. Unfortunately, the rapidly changing situation and uncertainty about the future course made it very difficult to put a time line on the recommendations and keep up to date with the changing Covid-19 pandemic. Patients were advised to follow Covid-19 related updates and general guidance on covid-19 issued by their respective public health ministries [58].

Generic recommendations

The initial recommendations by the various bodies/societies/organizations were to follow infection control standard operating procedures (SOPs) including use of personal protective equipment (PPE), social distancing, face masks, hand hygiene etc. [42]. Additionally,

1. All non-urgent and routine gynecological surgeries were advised to be postponed pending improvement in the Covid-19 pandemic situation and
2. Virtual online consultations for non-urgent cases and triaging were advocated in favor of face-to-face consultations.

Critical to these recommendations was the expectation that medical services should be catering for patient's individual needs and those needing urgent attention would still receive appropriate management within the available resources [59]. However, there was acknowledgement that this strategy might not be easy and practicable in less resourced countries [60]. Because of the very dynamic nature of the pandemic, various bodies maintained open-source information/communication with clinicians. The American College of Obstetricians and Gynecologists (ACOG) communicated with its members via a dedicated web page with comprehensive Q & As based on expert opinion and guidance from the Centers for Disease Control and Prevention (CDC) [61].

Similarly, the Royal College of Obstetricians and gynecologists (RCOG) UK, in collaboration with the specialist societies such as British Society of Gynecological Endoscopy (BSGE), British Gynecological Cancer Society (BGCS), British Society for Colposcopy and Cervical Pathology (BSCCP), British Society of Uro-gynecology (BSUG) and British Fertility Society (BFS), established a web link for members guidance on gynecological services and practice during the Covid-19 pandemic [44].

The Federations of International Societies of Gynecology and

Obstetrics (FIGO), in a statement, provided very useful links from the FIGO's national member societies, guiding the practice on issues related to the women's health and covid-19 [62].

Professional guidance on reproductive medicine and Covid-19

Sub-fertility or infertility affects 8–12% of couples trying to conceive and has significant adverse physical, mental and social consequences if not treated timely. However, during the Covid-19 pandemic, it was not considered requiring urgent care. However, it is a time sensitive condition whose prognosis gets worse with time. Provision of services for this condition were therefore suspended at the start of the pandemic as recommended by the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), but subsequently, cautious resumption was encouraged in a joint statement along with the International Federation of Fertility Societies (IFFS) [63]. Of particular interest was the learning from the Italian experience mentioned below and recommendations from the Italian Society of Fertility and Sterility and Reproductive Medicine (ISFSRM) [64], one of the worse Covid-19 affected countries in the West.

The ISFSRM advocated suspension of all *in-vitro* fertilization (IVF) and intra-uterine insemination (IUI) related activities including embryo transfers and non-urgent gamete cryo-storage for those who had not yet started stimulation unless there was urgency. The exceptions included cancer related fertility preservation treatments or advanced age of the female partner who could not delay for longer or for patients already in active cycles. Also mandatory was the necessity to ensure that there was no possibility of active SARS-CoV-2 infection or definite exposure at the time of treatment. The patients were offered preliminary screening via telephone to ensure that there were no active respiratory symptoms suggestive of Covid-19 or exposure to high risk factors including recent travel. Those for face-to-face consultation underwent secondary screening and covid-19 testing. Extra care was advised to avoid ovarian hyperstimulation syndrome (OHSS) as a combination of Covid-19 and OHSS induced intra-vascular dehydration could be lethal. Despite lack of evidence about the presence of the virus in gametes and embryos, couples including donors were interviewed to exclude possible exposure. A donor returning from an at risk area was suspended for 14 days from return or 14 days from the end of any Covid-19 like symptoms if there were any. A separate closed cryo-storage system was used for anyone who was symptomatic and potentially infected. Cycle cancellation was advised for couples developing Covid-19 infection during the treatment and so too were egg or embryo cryo-storage if the symptoms developed after egg collection.

With regard to staffing, it was recommended that shifts and duties be scheduled for critical staff members so as to avoid exposure to SARs-CoV-2 of all of them together. This was supported by adequate contingency plans to combat acute staff shortage. On the whole, these recommendations seem to endorse those from other international societies including ESHRE, ASRM and the IFFS as mentioned above [63].

With regards to the requirement for covid-19 testing, ESHRE endorsed selective testing unlike the British fertility society (BFS) and the association of reproductive and clinical scientists (ARCS) who recommended testing at the start of treatment and prior to any procedure [65]. The later more cautious approach also catered for the almost 18–30% asymptomatic carriers who could be contagious despite being asymptomatic [66].

Vaccination against SARS-CoV-2

Vaccination is seen as the best way to reduce the spread of the pandemic as well as its consequences. The available vaccines are either inactivated SARS-CoV-2 vaccine, RNA Vaccines or non-replicating vector vaccine [67]. The WHO maintains a working document that includes the various vaccines that are in different phases of development [68]. Results of phases I, II and III trials on most of these support their clinical efficacy [69]. While phase III trials were on various populations, none were on women in early pregnancy or indeed undergoing fertility treatment. The impact/effect of the vaccines on gametes and early embryos is therefore unknown. In a joint statement [70], the International Federation of Fertility Societies (IFFS) and the European Society of Human Reproduction and Embryology (ESHRE) advised that women who are planning to conceive in an environment with ineffective control of the pandemic and with limited resources for vaccination should adopt measures to mitigate risk of exposure (social distancing, hand hygiene, face mask) and defer pregnancy until the situation is much improved with regards to SARS-CoV-2 infection or until vaccination is available. Those with access to vaccination should consider this as soon as possible and at the same time adopting the mitigation measures while trying to conceive.

In the context of reproduction, a recent study of men who had been vaccinated did not show any adverse effects of the mRNA vaccine on sperm parameters. There seems to be an improvement on parameters in oligozoospermic men [71]. In women, the vaccine was shown to have no effect on response to ovulation stimulation as well as parameters of successful stimulation [72,73]. In animals, the vaccine has been shown to have no adverse effects on reproduction [74].

These data are reassuring and support the recommendations of the various reproductive medicine societies. The mRNA vaccines being non-live, are unable to replicate and should not pose a risk of infection to pregnant women or their fetus. Despite the lack of safety concerns, there is still insufficient evidence to offer routine Covid-19 vaccination during pregnancy [75]. More recently, data from the follow-up of over 1800 out of 30,000 women who were pregnant at the time of vaccination (V-safe) did not show any adverse effects of the mRNA vaccine either on the fetus or the pregnancy woman [76]. Indeed on the basis of these data the consensus from the WHO, FIGO, CDC, SMFM, ACOG, RCOG and NICE is that vaccination should be offered to pregnant women and the joint committee on vaccination and immunization (JCVI) recommends vaccination only to high risk pregnant women (high risk of exposure/ with co-morbidities) after full counselling and explaining the confirmed benefits of vaccination [77]. The European Board & College of Obstetrics and Gynecology (EBCOG) recommend that vaccination against Covid-19 should be offered to all high-risk pregnant women and should be available to all other pregnant and un-vaccinated breastfeeding women willing to take the vaccine after adequate counselling provided there are no contra-indications [78]. Equally, the Royal College of Obstetricians and Gynaecologists advocates vaccination especially with the mMRA vaccine in pregnancy, during breastfeeding and in those seeking fertility treatment [61].

The decision to have vaccination finally rests with the woman and the role of her physician is to guide her through the decision making by answering queries and providing facts.

One of the serious emerging phenomena in the post Covid-19 era is the risk of re-infection and even more seriously, infection after vaccination rarely leading to serious morbidity or death. Various factors have been suggested for these phenomena namely inefficiency of natural immunity, variants of major epitopes in cases of re-infections [79-81] and possibly high viral load, co-morbidities, mutant strains, casual attitudes with lack of Covid-appropriate behavior before and after vaccination in cases of infection after vaccination [82].

Lessons learnt during pandemic which would shape the future service delivery models

While Covid-19 has caused severe morbidity and mortality worldwide, including having a major impact on cancer surgery with considerable delays that inevitably will affect survival data, it has allowed for the introduction of innovative/new ways to current and future healthcare as well as potential avenues for training and research in medicine. Some of these innovations/new approaches to healthcare include

1- increased use of telemedicine not only in triaging but management of non-emergency cases,
2- Increased role of medical methods of managing gynaecological problems in preference to surgical interventions (for example heavy menstrual bleeding (HMB) with more reliance on the levonorgestrel intra-uterine system, oral progestogens, gonadotropin releasing hormone-agonist (GnRHa,) endometrial ablations under local block) etc.
3- Greater investment on simulation training for undergraduate and postgraduate training as advocated by the EBCOG in its position statement [83]
4- Increased utilization of alternatives to care as in the case of termination of pregnancy which has been revised so as to allow women to take mifepristone (RU 486) at home. Unpublished data after 12 months in Scotland showed that only 5% of admissions with bleeding following this approach required emergency evacuation.

Conclusion

Covid-19 has had devastating effects not only on the physical, mental and social aspects of human health but also on the economy which indirectly affects health across the globe. Women's health in general and reproductive health in particular suffered significantly from the pandemic. This pandemic brought together international societies and the WHO to address the health challenges – resulting in guidance on care, prevention and treatment - a collaboration which if replicated could have a major impact on other health challenges. Postponing elective work, minimizing face-to-face consultations in favor of virtual consultations, prioritizing and individualizing care based on needs and the available resources without compromising safety. At the outset most of gynaecology apart from emergency and oncology were not considered priority. As understanding of the epidemiology of the epidemic improved, aspects that could be managed virtually were defined and with time, reproductive medicine resumed albeit with clear guidance. With a gradual return to near normal, the backlog of patients (such as on the NHS Waiting list) will continue to negatively affect those seeking gynaecological care (including reproductive medical services). There is a need to continue to undertake efficacy and safety trials of treatment and prevention options while at the same time gathering data on vaccination and reproductive and pregnancy outcomes and on the innovative approaches to healthcare which are likely to persist.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus disease 2019–COVID-19. Clin Microbiol Rev 2020 Jun 24;33(4):e00028–120.
[2] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2020 Oct;6:1–4.
[3] Taylor DB. A timeline of the coronavirus. The New York Times. https://www.nytimes.com/article/coronavirus-timeline.html. Published February 13, 2020. Accessed December 29, 2020.
[4] WHO. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19-11 March2020 https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020.
[5] World Health Organization. WHO Corona virus (Covid-19) Dashboard. https://covid19.who.int/ February 4, 2022. Accessed February 6; 2022.
[6] Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect 2020 Jun 1;26(6):729–34.
[7] Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020 Jun 1;49(3):717–26.
[8] World Health Organization, World Health Organization. WHO MERS global summary and assessment of risk. Middle East respiratory syndrome coronavirus (MERS-CoV) (2018) Available: https://www. who. Int/csr/disease/coronavirus_infections/riskassessment-august-2018. pdf. 2018.
[9] Masters PS. The molecular biology of coronaviruses. Adv Virus Res 2006 Jan;1(66):193–292.
[10] Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020 Mar 11;27(3):325–8.
[11] Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging Microbes Infect 2020 Jan 1;9(1):221–36.
[12] Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Diseas 2020 Feb;1(91):264–6.
[13] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020 Jan;24(382):727–33.
[14] Sun J, He WT, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. In: Trends in Molecular Medicine 2020 Mar 21; 2020. https://doi.org/10.1016/j.molmed.2020.02.008.
[15] Wu P, Hao X, Lau EH, Wong JY, Leung KS, Wu JT, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Eurosurveillance. 2020 Jan 23;25(3):2000044.
[16] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020 Feb 15;395(10223):497–506.
[17] Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003 May 15;348(20):1986–94.
[18] Fernández-Sarmiento J, Acevedo L, Mulett H, Bastidas S, Sarta M, Durán N, et al. Severe SARS-CoV-2 infection in critical care. Trend Crit Care 2020 Jul;11(34):28–37.
[19] RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021 Feb 25;384(8):693–704.
[20] Falcone, M., Tiseo, G., Barbieri, G., Galfo, V., Russo, A., Virdis, et al. 2020, December. Role of Low-Molecular-Weight Heparin in Hospitalized Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia: A Prospective Observational Study. In Open forum infectious diseases (Vol. 7, No. 12, p. ofaa563). US: Oxford University Press.
[21] Sorbello M, Greif R. COVID-19 pandemic: A multifaceted challenge for science and healthcare. Available from Trend Anaesth Crit Care 2020 Oct;34:1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7502251/.
[22] Kavaliunas A, Ocaya P, Mumper J, Lindfeldt I, Kyhlstedt M. Swedish policy analysis for Covid-19. Health Pol Technol 2020 Dec 1;9(4):598–612.
[23] Straka W, Kondragunta S, Wei Z, Zhang H, Miller SD, Watts A. Examining the Economic and Environmental Impacts of COVID-19 Using Earth Observation Data. Remote Sensing. 2021 Jan;13(1):5.
[24] crsreports congress gov. Global Economic Effects of COVID-19. 2020 [cited 2021 Jan 7]; Available from: https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-.
[25] Bramstedt KA. The carnage of substandard research during the COVID-19 pandemic: a call for quality. J Med Ethics 2020 Dec 1;46(12):803–7.
[26] Kashour Z, Riaz M, Garbati MA, AlDosary O, Tlayjeh H, Gerberi D, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chemother 2021 Jan;76(1):30–42.
[27] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020 Mar 28;395(10229):1054–62.
[28] Foresta C, Rocca MS, Di Nisio A. Gender susceptibility to COVID-19: a review of the putative role of sex hormones and X chromosome. J Endocrinol Invest 2020 Sep;16:1–6.
[29] Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis 2018 Aug 1;18(8):e217–27.
[30] Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. Science 2020;367(6485):1412–3.
[31] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020 Apr 16;181(2):271–80.
[32] Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. J Autoimmun 2012 May 1;38(2–3):J187–92.
[33] Lyon MF. Gene action in the X-chromosome of the mouse (Mus musculus L.). Nature 1961 Apr;190(4773):372–3.
[34] Posynick BJ, Brown CJ. Escape from X-chromosome inactivation: an evolutionary perspective. Front Cell Dev Biol 2019 Oct;22(7):241.
[35] Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, et al. Landscape of X chromosome inactivation across human tissues. Nature 2017 Oct;550(7675):244–8.
[36] Pirhadi R, Talaulikar VS, Onwude J, Manyonda I. Could Estrogen Protect Women From COVID-19? J Clin Med Res 2020 Oct;12(10):634.
[37] Smith SM, Baskin GB, Marx PA. Estrogen protects against vaginal transmission of simian immunodeficiency virus. J Infect Dis 2000 Sep 1;182(3):708–15.
[38] Robinson DP, Hall OJ, Nilles TL, Bream JH, Klein SL. 17β-estradiol protects females against influenza by recruiting neutrophils and increasing virus-specific CD8 T cell responses in the lungs. J Virol 2014 May 1;88(9):4711–20.

[39] Hayashida K, Shoji I, Deng L, Jiang DP, Ide YH, Hotta H. 17beta-estradiol inhibits the production of infectious particles of hepatitis C virus. Microbiol Immunol 2010; 54(11):684–90.
[40] Rodriguez-Garcia M, Biswas N, Patel MV, Barr FD, Crist SG, Ochsenbauer C, et al. Estradiol reduces susceptibility of CD4+ T cells and macrophages to HIV-infection. PLoS ONE 2013 Apr 17;8(4):e62069.
[41] Flugge C. Uber luftinfection. Z Hyg Infektionskr 1897;25:179–224.
[42] Jones NR, Qureshi ZU, Temple RJ, Larwood JP, Greenhalgh T, Bourouiba L. Two metres or one: what is the evidence for physical distancing in covid-19?. bmj. 2020 Aug 25;370.
[43] When You Are Sick, to prevent the spread of COVID-19 Stay home except to get medical care. When You Are Sick, do not share personal. 2019; Accessible version: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html.
[44] Athiel Y, Civadier MS, Luton D, Ceccaldi PF, Bourret A, Sroussi J, et al. Impact of the outbreak of SARS-CoV-2 infection on urgent gynecological care. J Gynecol Obstet Human Reproduct 2020 Jun 23;49(8):101841.
[45] Spurlin, E.E., Han, E.S., Silver, E.R., May, B.L., Tatonetti, N.P., Ingram, M.A., et al., Where Have All the Emergencies Gone? The impact of the COVID-19 pandemic on obstetric and gynecologic procedures and consults at a New York City hospital. J Minim Invas Gynecol; 2020.
[46] Anteby M, Van Mil L, Michaan N, Laskov I, Grisaru D. Effects of the COVID-19 pandemic on timely care for extrauterine pregnancies: A retrospective analysis. Lancet Regl Health-Europe 2021. Jan 100026.
[47] Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, et al. SARS-CoV-2 receptor ACE 2 and TMPRSS 2 are primarily expressed in bronchial transient secretory cells. EMBO J 2020;39(10). May 18 e105114.
[48] Goad J, Rudolph J, Rajkovic A. Female reproductive tract has low concentration of SARS-CoV2 receptors. PLoS ONE 2020;15(12). Dec 14 e0243959.
[49] Singh B, Gornet M, Sims H, Kisanga E, Knight Z, Segars J. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its effect on gametogenesis and early pregnancy. Am J Reprod Immunol 2020;84(5):1–9.
[50] Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020;222(6):521–31.
[51] Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, Leydig and Sertoli cells. Cells. 2020 Apr;9(4):920.
[52] Paoli D, Pallotti F, Turriziani O, Mazzuti L, Antonelli G, Lenzi A, et al. SARS-CoV-2 presence in seminal fluid: Myth or reality. Andrology. 2020 May 26.
[53] Pozzilli P, Lenzi A. Testosterone, a key hormone in the context of COVID-19 pandemic [Commentary]. Metabolism 2020;108:154252.
[54] Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 2006 Feb 1;74(2):410–6.
[55] Batiha O, Al-Deeb T, Al-zoubi EA, Alsharu E. Impact of COVID-19 and other viruses on reproductive health. Andrologia 2020 Oct;52(9):e13791.
[56] Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA network open. 2020 May 1; 3(5):e208292-.
[57] A guide to WHO's guidance on COVID-19 [Internet]. Available from: https://www.who.int/news-room/feature-stories/detail/a-guide-to-who-s-guidance (Accessed on Apr 27, 2021).
[58] COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics | ACOG [Internet]. [cited 2021 Jan 6]. Available from: https://www.acog.org/clinical-information/physician-faqs/covid19-faqs-for-ob-gyns-gynecology.
[59] Cash R, Patel V. Has COVID-19 subverted global health? Lancet [Internet]. 2020; 395 (10238):1687–8. Available from: https://doi.org/10.1016/S0140-6736(20)31089-8 (Accessed on Apr 27, 2021).
[60] American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician–gynecologists, Gynecology. COVID-19 FAQs. Washington, DC: ACOG. 2020 May 30. https://www.acog.org/clinical-information/physician-faqs/covid19-faqs-for-ob-gyns-gynecology (Accessed on Apr 27, 2021).
[61] Royal College of Obstetricians and Gynecologists. Corona virus (Covid-19) and gynaecological services. RCOG. 2020. https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/coronavirus-covid-19-and-gynaecological-services/ (Accessed on Apr 27, 2021).
[62] International Federation of Gynecology and Obstetrics. Covid-19 (Corona virus) statement. FIGO.2020. https://www.figo.org/covid-19-coronavirus-statement (Accessed on Apr 27, 2021).
[63] Veiga A, Gianaroli L, Ory S, Horton M, Feinberg E, Penzias A. Assisted reproduction and COVID-19: a joint statement of ASRM, ESHRE and IFFS. Hum Reprod Open. 2020 Mar 1; 2020(3).
[64] Vaiarelli A, Bulletti C, Cimadomo D, Borini A, Alviggi C, Ajossa S, et al. COVID-19 and ART: the view of the Italian Society of Fertility and Sterility and Reproductive Medicine. Reprod Biomed Online 2020 Jun;40(6):755–9.
[65] Papathanasiou A. COVID-19 screening during fertility treatment: how do guidelines compare against each other? J Assist Reprod Genet 2020 Aug;37(8): 1831–5.
[66] Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020 Mar 12;25 (10):2000180.
[67] Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F. A systematic review of SARS-CoV-2 vaccine candidates. Signal transduction and targeted therapy; 2020 Oct 13; 5(1):1-4. . Available from: https://doi.org/10.1038/s41392-020-00352-y.
[68] WHO. Draft landscape of COVID-19 candidate vaccines. World Health Organisation; 2020 Jun 17. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
[69] Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, et al. Efficacy and Safety of COVID-19 Vaccines: a Systematic Review and Meta-Analysis of Randomized Clinical Trials. Vaccines 2021 May;9(5):467.
[70] Ory S, Veiga A, Horton M, Gianaroli L. Joint IFFS/ESHRE statement on COVID-19 vaccination for pregnant women and those considering pregnancy. Human Reproduction Open. 2021;2021(2):hoab016..
[71] Daniel C. Gonzalez, BS Daniel E. Nassau, MD, Kajal Khodamoradi, PhD Emad Ibrahim, MD, Ruben Blachman-Braun, MD Jesse Ory, MD Ranjith Ramasamy, MD. Sperm Parameters Before and After COVID-19 mRNA Vaccination. JAMA July 20, 2021 Volume 326, Number 3.
[72] Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J. Ravit Nahum and Adva Aizer Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reproduct Biol Endocrinol 2021;19:69. https://doi.org/10.1186/s12958-021-00757-6.
[73] Bentov, Y. Beharier, O. Moav-Zafrir, A. Kabessa, M. Godin, M. Greenfield, C.S. et al., Ovarian follicular function is not altered by SARS–CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination Human Reproduction, Vol.36, No.9, pp. 2506–2513, 2021 Advance Access Publication on August 7, 2021 doi:10.1093/humrep/deab182.
[74] Bowman CJ, Bouressam M, Campion SN, Cappon GD, Catlin NR, Cutler MW, et al. Claudia Lindemann Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine. Reprod Toxicol 2021;103:28–35.
[75] Adhikari EH, Spong CY. COVID-19 vaccination in pregnant and lactating women. JAMA 2021 Mar 16;325(11):1039–40.
[76] Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. for the CDC v-safe COVID-19 Pregnancy Registry Team Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. April 21, 2021. DOI: 10.1056/NEJM.
[77] Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020 - GOV.UK [Internet]. [cited 2021 Jun 12]. Available from: https://www.gov.uk/government/publications/prioritygroups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020.
[78] Martins I, Louwen F, Ayres-de-Campos D, Mahmood T. EBCOG position statement on COVID-19 vaccination for pregnant and breastfeeding women. Europ J Obstet Gynecol Reproduct Biol 2021 May 14.
[79] dos Santos WG. Co-infection, re-infection and genetic evolution of SARS-CoV-2: Implications for the COVID-19 pandemic control. J Cancer 2021;2(3):56–61.
[80] Jain VK, Iyengar K, Garg R, Vaishya R. Elucidating reasons of COVID-19 re-infection and its management strategies. Diabet Metabol Synd Clin Res Rev 2021 May;7.
[81] Brouqui P, Colson P, Melenotte C, Houhamdi L, Bedotto M, Devaux C, Gautret P, Million M, Parola P, Stoupan D, La Scola B. COVID-19 re-infection. Europ J Clin Investigat; 2021 May;51(5).
[82] Jain VK, Iyengar KP, Ish P. Elucidating causes of COVID-19 infection and related deaths after vaccination. Diabet Metabol Syndr Clin Res Rev 2021 Jul;15:102212.
[83] EBCOG position statement – Simulation-based training for obstetrics and gynaecology during the COVID-19 pandemic.