Consensus Scientific Statement on Advisory Working Guidelines and Recommendations for the Female Population in COVID-19 Era by WINCARS

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Ind J Car Dis Wom 2020;5:175–194

Background

We are presently facing the rapid progression and uncontrolled spread of the COVID-19 pandemic, with uncertainties in its management. There are national and international guidelines in general for the diagnosis and management of COVID and precautions needed for non-COVID patients. There is an apparent gender disparity in mortality due to COVID 19, which is less in women than in men. However, many diseases are specific to (like pregnancy-related complications and ovarian carcinoma) or more frequent (many rheumatological diseases and mitral stenosis) in females, and have hardly been discussed in the context of the COVID pandemic. Moreover, recommendations are not available for our population. We, from the Women in Cardiology and Related Sciences (WINCARS) association, prepared a consensus scientific statement for the female population in this COVID-19 era.

Aim

Two aims of the studies are as follows:

1. To assemble the evidence for the management of different diseases pertinent to the female population in this COVID-19 era and formulate advisory guidelines and recommendations for medical fraternity and patients.
2. To highlight the issues, specific to female health care workers that require attention and formulate advisory recommendations.

published online
October 12, 2020

DOI https://doi.org/10.1055/s-0040-1718607.

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Methods

For the very first time, the present document aims to collect, analyze, and interpret the available data so far on severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in relevance to the female gender via an expert group of medical specialists. Besides the variability across the globe in preventing, reporting, diagnosing, and management strategies, the obstacles for a comprehensive assessment include the availability of only small, single centered, or retrospective data. Moreover, rapid evolution and frequent change of scientific information, as we learn more about the disease and its complexities, add to the limitations.

To circumvent these shortcomings, the Delphi technique was deployed for a consensus-based statement.[1,2] In this technique, a cluster of experts or individuals conversant on the subject are included. A task force committee constituted by 23 expert doctors (►**Appendix 1**; available online only) from the different departments were included. As this technique is applicable for the present article, it finds maximal utility in areas of limited or conflicting evidence where committee members may be geologically dispersed (from all over India), and anonymity is maintained to control for dominant individuals. The present document utilized the Delphi technique, and data collection was done from expert group members widespread across the nation.

Twenty-three members of the task force committee are from different places in India and also from different departments who took care of women patients from the onset of this pandemic. These expert doctors were requested to write the review articles with the latest literature, their personal experiences and recommendations, available in this COVID-19 era for both COVID-19 positive and negative female patients. The task force committee included gynecologists, obstetricians, rheumatologists, neurologists, internists, cardiologists, pulmonologists, preventive medicine specialists, endocrinologists, oncologists, microbiologists, and basic scientists.

Web-based brainstorming discussions were conducted with all experts, taking each disease separately. After scientific statements are prepared with a thorough literature search, views of another set of experts (names are mentioned in acknowledgments, ►**Appendix 2** [available online only]) were taken in the questionnaire form. We mentioned the questionnaire and concordance rate of the expert's opinion as a percentage to the particular statement (mentioned as the table in ►**Appendix 3**; available online only). The scientific statements have been enlisted among various medical disciplines affecting women the most via the SARS-CoV-2 virus. Authors have suggested the pertinent class of recommendation in the text subject to change via an ever-growing and evolving data on COVID-19. Audio of consensus scientific statement is available online (►**Audio 1**).

Audio 1

Audio of consensus scientific statement. Online content including audio sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0040-1718607.

Purpose and Clinical Application of the Scientific Statements

These scientific statements are prepared with sufficient knowledge of the subspecialties to ensure that women patients will be managed appropriately, in time, and effectively. The expertise of these sub-specialized medical branches domains is covered elsewhere and not included in this document.

Cardiology

Cardiovascular Disease and COVID-19: Issues in Women

Though American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) medical bodies released recommendations and statements on acute coronary syndromes (ACS) presentation in COVID-19 patients, we discussed specific problems related to women with COVID in India (►**Table 1**).

According to Wu et al,[3] in their large study of 18,465 laboratory-confirmed cases, the predictors of mortality were comorbidities like hypertension, diabetes, and chronic kidney diseases. Furthermore, the association between diabetes and the risk of death from COVID-19 was prominent in women (hazard ratio [HR] = 1.69, 95% confidence interval [CI]: 1.27–2.25) than in men (HR = 1.16, 95% CI: 0.91–1.46;P for interaction = 0.036).

All the recent studies[4-7] of hospitalized patients with COVID-19 infection found that apart from comorbidities, an additional determinant of mortality was myocardial injury diagnosed by an elevated troponin, incidence of which was no different in men and women.

Atypical clinical symptoms, along with late presentation, cause delays in diagnosis and management in women, which have been more pronounced during this pandemic according to published literature.[8-13]

Rapid antigen testing should be done before primary angioplasty following an ST elevation myocardial infarction (STEMI), according to CSI (Cardiological Society of India)

Table 1 COVID-19 in women with CVD

Scientific statements for CVD in females with COVID-19	References
The association between diabetes and risk of death from COVID-19 is more in women than men	3
Incidence of myocardial injury is not different between men and women, but is associated with increased mortality upon COVID	4–7
Diagnosis of acute coronary syndromes in the setting of COVID-19 is further confounded in women and is fraught with delays in presentation resulting in dilemmas in management (more so in women)	8–13
Point of care antigen testing should be done before primary PCI in STEMI patients	14
A strategy of fibrinolysis in STEMI and COVID-19 in India is an acceptable alternative, especially in women as nonobstructive coronary artery disease incidence is high	8,14–16

Abbreviations: COVID-19, novel coronavirus disease 2019; CVD, cardiovascular disease; PCI, percutaneous coronary intervention.

document on acute myocardial infraction (AMI) care during COVID-19. The document also insists that proper protection to the operator and staff in the form of appropriate personal protection equipment (PPE) should be available whenever primary percutaneous coronary intervention (PCI) is planned for STEMI.[14] In India, fibrinolysis is the dominant strategy used in patients with STEMI in view of logistic considerations.[15] European guidelines recommend primary PCI even in patients with COVID-19 infection.[16] With the available literature, fibrinolysis for STEMI can be graded as class-IIB, level-C recommendation.

Venous Thromboembolic Events in COVID-19—Are Women Different?

As International Society on Thrombosis and Haemostasis (ISTH)[17]/NATF/ European Society for Vascular Medicine (ESVM)/Intrauterine Adhesions (IUA) consensus paper and multiple medical bodies published on the prothrombotic state of COVID-19, predisposing these patients' to venous thromboembolic events (VTE). In this study, we mentioned the prophylaxis and management specifically for all ages of females with COVID-19 (►**Table 2**).

Barring one study by Cui et al[18] in which a female predilection for VTE was found to the tune of 64% in women versus 46% men, almost all the other studies have shown higher predilection of VTE events in the male population. Spiezia et al[19] and Ranucci et al[20] reported 91 and 94% of patients having VTE in males, respectively, whereas most of the other studies reported 60 to 80% of their patients with COVID-19 having VTE in men.[21] A recent study from Italy[22] published in mid-July, persistent gender gap in the occurrence of VTE events was further emphasized. In answer to our questionnaire, there was discordance with only 34.8% of experts opining less VTE predilection in COVID positive women. However, there is enough evidence to suggest otherwise. This also explains the imperative need to publish the assimilated data and put forth the differences in VTE predilection in COVID positive women.

Table 2 VTE in females with COVID-19

Scientific statements for VTE in females with COVID-19	References
Less female predilection of VTE in COVID-19 pandemic is observed	18–22
Combined oral contraceptives and estrogen replacement therapy should be discouraged in COVID-19-positive women to prevent VTE	23–26
Thromboprophylaxis in standard doses is must in all COVID-19-positive hospitalized women (with low bleeding risk, to continue in menstrual period)	17,27,28
Thromboprophylaxis in intensified doses is recommended in COVID-19-positive hospitalized women with deranged hematological and clinical parameters of disease severity (with low bleeding risk, to continue in menstrual period)	29–34
COVID-19-positive women on home quarantine should receive thromboprophylaxis only when at high risk for VTE (with low bleeding risk)	1,28
Extended thromboprophylaxis post-discharge is recommended in COVID-19-positive women with high VTE risk and low bleeding risk	1,27,29,36–38

Abbreviations: COVID-19, novel coronavirus disease 2019; VTE, venous thromboembolism.

With ongoing research on the effects of SARS-CoV-2 on coagulation systems, the issues of aggravated risk of VTEs associated with combined oral contraceptives (COC's) and other estrogen therapies as well as pregnancy-associated risks needs to be resolved. COC use is associated with a 2- to 6-fold increase in risk for VTEs.[23] Similar data exist for oral hormone replacement therapy (HRT) in menopausal women[24] and oral estrogen therapy in male-to-female transgender patients. In pregnancy, the risk of VTEs increases four to five folds.[25] The hypercoagulable state in the pathophysiology, and the duration for which thrombogenic milieu might persist after discontinuing therapy remains to be understood. However, on the basis of usual preexistent recommendations to discontinue estrogen-containing preparations 2 weeks before planned activities that may increase thrombogenesis, such as surgery or long flights, it might be considered to discourage initiation and hold these drugs in women who develop SARS-CoV-2 infection.[26] With the available literature information, the avoidance of combination therapy of COC and estrogen can be graded as class-II, level-B recommendation.

Thromboprophylaxis for VTE in COVID-19-positive hospitalized women remains essentially similar to males. Issues may arise in women with menorrhagia;secondary to dysfunctional uterine bleeding (DUB), fibroids, adnexal malignancies, and masses, hypothyroidism, women on anticoagulation, etc., where bleeding risks are to be considered. The guidelines can be similar in either sex, with attention to bleeding risk scenarios and menstrual physiology specific to women. Given COVID-19's thrombogenic potential, it is suggested that thromboprophylaxis should be continued in standard doses in a normal menstrual period with monitoring for menorrhagia. One of the first published guidelines Chinese Medical Doctor Association (CMDA),[27] the ISTH,[28] and thrombosis-UK[17] recommendations advocated a standard approach to in-hospital thromboprophylaxis of COVID-19 patients, with a standard dose following a validated clinical score.[17,27] With the available literature information, the thromboprophylaxis in COVID-19 patients can be graded as class-I, level-C recommendation.

Intensified/therapeutic doses of thromboprophylaxis may be considered in sicker COVID-19-positive women with clinically severe disease and raised markers of disease severity (e.g., D-dimer, ferritin, and fibrinogen). Bleeding risks due to menorrhagia need to be considered, and it is suggested to continue intensified thromboprophylaxis during a normal menstrual cycle. Chinese Consensus Statement (CCS),[29] the joint guidelines of the French Working Group on Perioperative Hemostasis (GIHP) and the French Study Group on Thrombosis and Haemostasis (GFHT),[30] the NIPHN,[31] the Society of Thrombosis and Haemostasis (GTH),[32] the Spanish Society of Cardiology (SSC),[33] and the Swiss Society of Haematology[34] recommended intensified doses of heparin for thromboprophylaxis based on the severity of the clinical or biological disease. Four guidelines suggested using

full-dose anticoagulation according to inflammation-related biological parameters in all patients on oxygen[30,33] therapy or in patients with an increase of D-dimers while on prophylaxis.[32,34] With the available literature information, the intensified doses of thromboprophylaxis in COVID-19 patients as can be graded as class-I, level-C recommendation.

In women with mild COVID-19 who have been quarantined, the role of pharmacological prophylaxis is yet uncertain (just as in men);hence these patients can be advised to remain mobile at home. The pharmacological prophylaxis in these patients could be reserved for women at high risk of developing VTE (and low bleeding risk). For instance, in those who have reduced mobility, a previous history of thromboembolic event, or in those who have active ongoing malignancy. Standard-dose thromboprophylaxis is recommended in outpatient COVID-19 patients with multiple VTE risk factors by the Society for Thrombosis and Haemostasis (SISET) and the GTH guidelines. The ISTH[17]/NATF/ESVM/IUA consensus paper also recommends considering thromboprophylaxis on an individual case basis for patients with an elevated risk of VTE without high bleeding risk (►**Table 1**). Based on available literature information, the thromboprophylaxis in home-quarantined female COVID-19 patients can be graded as class-II, level-C recommendation.

Investigation, management including type of heparin during acute stage, and novel oral anticoagulant (NOAC) subsequently and method of follow-up are similar to both men and women.

A daily dosing regime of low molecular weight heparin (LMWH) has an advantage over unfractionated heparin with twice-daily doses in COVID-19 by reducing the use of PPE and exposing the COVID-19 health care workers. For in hospital prophylaxis, the World Health Organization recommends daily LMWH or twice daily subcutaneous unfractionated heparin. Hence just as in males, LMWH may be preferred over unfractionated heparin (UFH) in COVID-19-positive females.[35] This is graded as class-II, level-C recommendation with available information.

COVID-19-positive women with persistent high VTE risk and low bleeding risk are suggested to continue an extended thromboprophylaxis regime up to 45 days. ASH guidelines,[36] the CMDA,[27] the CCS[29] recommendations, the GTH,[37] the Italian (SISET),[38] and the ISTH/NATF/ESVM/IUA[1] position paper recommend extended prophylaxis post-discharge up to 45 days in case of a high risk of VTE with low bleeding risk.[38] This is considered as class-II, level-C recommendation with available information.

Catheter-based therapies should be reserved only when systemic fibrinolysis may not be feasible in the settings where infection control is well equipped, appropriate, and equivalent. Bedside extra corporeal membrane oxygenator (ECMO) might be considered in COVID-19-positive patients rather than the utilization of interventional modalities needing cardiac catheterization laboratories or operating rooms.[35] This is graded as class-II, level-C recommendation with available information.

An elevated D-dimer level, a marker of severity of COVID-19, might not routinely indicate an underlying venous thromboembolic process.[39] A VTE event should be suspected in a woman of COVID-19 when she developed typical deep vein thrombosis (DVT) symptoms, hypoxemia was out of proportion to the underlying respiratory pathology or development of acute unexplained right ventricle (RV) dysfunction. The diagnostic challenges in a patient with COVID-19 for VTE are the risk of transmitting the infection to other patients or health care workers due to an unstable patient and prone position of the patient with severe acute respiratory distress syndrome (ARDS) limiting the imaging studies. Echocardiography might be considered in these patients with COVID-19 for evaluation of worsening RV dysfunction and diagnosis of right ventricular clots/clots in transit.[40] Computed tomography (CT) pulmonary angiography may be omitted in very sick COVID-19 patients due to minimal anticipated therapeutic benefits and increased exposure of health care worker. Routine imaging modalities for VTE evaluation are not advisable; this is graded as class II, level-C recommendation and available information.

In patients without COVID-19 and acute VTE, outpatient management, or an early discharge should be considered.[41] This is graded as Class I, level-C recommendation with available information. Telemedicine could be the preferred methodology of follow-up (class I, level C). Regarding pharmacotherapy, these patients could be maintained on NOACs or LMWH to avoid recurrent contact with the health care workers for maintenance of international normalized ratio's (INR's) inpatient receiving vitamin-K antagonists. This is graded as class-I, level-C recommendation with available information. In patients already receiving vitamin-K antagonists, extending INR testing in intervals could be suggested if prior INR's have been stable. Home-based INR's check or drive through INR testing should be encouraged, though switching to NOACs or LMWH would be the clinically appropriate strategy wherever feasible. The NOACS used are dabigatran or rivaroxaban. There are a few studies with oral antithrombolytic enzyme (nattokinase) as anticoagulant.

COVID-19 and Cardioobstetric Risk Indicators

Recently preventive medicine is paying much importance to the cardioobstetrics risk stratification for the future onset of cardiovascular disease (CVD) in pregnant females. As there is limited information about the effect of COVID-19 on pregnancy, which may influence the mother's long-term cardiac health, through these scientific statements, we are trying to fill the knowledge gaps (►**Table 3**).

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, have been found to cause pulmonary disease progression in COVID-19 infection in a few anecdotal reports by French authorities. Indian Council of Medical Research (ICMR), in an official statement on 27 March 2020, issued an advisory for avoiding NSAIDs for patients with diabetes, hypertension, and heart diseases due to increased risk of SARS-CoV-2 progression and advised paracetamol as a safer alternative. However, later on, World Health Organization (WHO) and Spanish Ministry of Health and European Medicines Agency in their reports, stated that there is no scientific evidence that ibuprofen (or other NSAIDs) could worsen SARS-CoV-2 infection.[42] Given this uncertainty,

Table 3 Cardio-obstetric risk indicators in females with COVID-19

Scientific statements for cardioobstetric risk indicators in females with COVID-19	References
Low dose aspirin as prophylaxis for placental complications including pre-eclampsia and fetal growth restriction should not be withdrawn in high-risk COVID-19 pregnant women in fear of the increased risk of SRAS-CoV-2 progression	42
COVID-19 infection in pregnant women does not lead to a greater incidence of obstetric complications like preterm birth, pre-eclampsia	43
Near term pregnant or postpartum women with COVID-19 pneumonia, developing high respiratory rate or dyspnea should be evaluated for new-onset cardiomyopathy with the help of handheld point-of-care echocardiograms	44,45
Pregnant women with severe COVID-19 infection can develop a PE like syndrome that might be distinguished from actual PE by additional estimation of biomarkers	46
All pregnant women admitted with COVID-19 infection should be considered for antenatal VTE prophylaxis while those with mild COVID-19 infection and on home isolation should undergo VTE risk assessment to decide about VTE prophylaxis	47,48

Abbreviations: COVID-19, novel coronavirus disease 2019; SRAS-CoV-2, severe acute respiratory syndrome-coronavirus-2; VTE, venous thromboembolism.

aspirin, because of greater beneficial effects than low-level data of potential harm, should not be withheld as a prophylactic measure for preeclampsia in high-risk pregnant females, especially in the initial few months. Near-term, patients should be assessed on a case-by-case basis for the risk-benefit ratio. The statement on continuation of aspirin prophylaxis in preeclampsia is graded as Class II, level C recommendation with available information.

Limited case series and small cohort studies report increased incidence of preterm births and preeclampsia in COVID-19 infected pregnant females with no effects on miscarriage rate, stillbirths, and teratogenicity (class II, level C-LE [cutaneous lupus erythematous]). Most preterm births are reported to be iatrogenic either due to the severity of illness or maternal/fetal safety.[43] Diagnosis of preeclampsia in severe SARS-CoV-2 infection is challenging due to overlapping clinical and laboratory profile. Thus in the absence of definitive diagnostic testing like placental histopathology, the Doppler assessment that is an actual incidence of preeclampsia in severe infection needs reconsideration.

New-onset cardiomyopathy has been demonstrated in 33% of nonpregnant COVID-19 patients who required intensive care.[44] An increased incidence of stress/takotsubo cardiomyopathy (TCM) was found in a cohort study of 1,914 patients who presented with acute coronary syndrome during the COVID-19 pandemic compared with the prepandemic period.[45] However, the effects of SARS-CoV-2 on myocardial function or incidence of peripartum cardiomyopathy (PPCM) in pregnant females remain mostly unknown to date due to diagnostic challenges. Pregnant women with confirmed or suspected COVID-19 infection, presenting with respiratory distress, should be evaluated for new onset of systolic dysfunction by cardiac enzymes and echocardiogram (class I, level C-LD).

Overlapping clinical and laboratory parameters of preeclampsia/HELLP and COVID-19 infection like liver injury, thrombocytopenia, and coagulopathy may confer diagnostic challenges to clinicians. Presenting fever symptoms in COVID-19 infection or predominant finding of high blood pressure (BP) in pulmonary embolism (PE) may help differentiate between both to some extent on clinical grounds. The Doppler assessment (uterine artery pulsatility index) and estimation of angiogenic factors (soluble FMS-like tyrosine kinase-1/placental growth factor and lactate dehydrogenase) are few of the diagnostic measures to distinguish severe COVID-19 infection from true PE. Therefore, diagnosis of preeclampsia[46] in COVID-19 needs a careful approach and should interpreted in all aspects.

American College of Obstetricians and Gynecologists (ACOG) advises antenatal thromboprophylaxis in all suspected/confirmed COVID-19 pregnant patients, particularly in severe/critical disease.[47] Royal College of Obstetricians and Gynecologists (RCOG) recommends that pregnant women with mild infection and home isolation undergo clinical VTE risk assessment via telehealth or office visits, and thromboprophylaxis should be considered based on their risk score.[48] There is no such scientific statement by Indian academic bodies for the mildly symptomatic pregnant subgroup (class II, level B). As pregnancy and COVID-19 together may pose a distinctive increased thrombotic risk, whether patients with mild infections should be risk assessed or empirically started on prophylaxis remains questionable.

Drug-Drug and Drug–Disease Interactions in Females with COVID-19

Treatment protocols of COVID-19 are still evolving. Here, we mentioned the interactions between COVID-19 drugs and drugs taken by female patients for their gender-specific diseases (►**Table 4**).

Though the revised protocols of ICMR allow hydroxychloroquine (HCQ) to be prescribed to patients in the early course of the disease, it has also advised against the use of severe disease.[49] HCQ administered to nursing women is excreted in human milk.[50] It is known that infants are susceptible to the toxic effects of 4-aminoquinolines. No need to discontinue this drug during pregnancy.[51] If Systemic lupus erythematosus (SLE) women on this drug become pregnant; it has not shown any adverse effects on the fetus even though the cord blood sample has the same concentration of the drug of the mother serum concentration.

Anticoagulants are indicated in moderate and severe degrees of COVID disease, as this is a procoagulant status. Any patient who is admitted to the hospital during the COVID-19 pandemic and is taking warfarin (or any other coumarin anticoagulant, e.g., phenindione and acenocoumarol) should be considered for switching to a direct oral anticoagulant (DOAC) to avoid the need for ongoing monitoring in hospital and community-based clinics. But this conversion should

not be done in a few clinical condition like situations when patients should not be switched from warfarin.[52,53]

According to ICMR revised treatment protocol, tocilizumab (off label) may be considered in patients with moderate disease with progressively increasing oxygen requirements and mechanically ventilated patients were not improving despite steroids.[54] Tocilizumab is a novel monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to its receptor (IL-6R). Hoeltzenbein et al[54] and Saito et al demonstrated that no indication for a substantially increased malformation risk was observed with tocilizumab usage during pregnancy.[55,56] Monoclonal antibodies are actively transported across the placenta during the third trimester. They may affect immune response in the in utero exposed infant as the immunoglobulin (Ig)-G isotype's endogenous immunoglobulins are excreted into human milk. It is advisable to discontinue the drug during lactation.

According to ICMR's latest guideline for COVID-19 treatment, remdesivir (under Emergency Use Authorization) may be considered in patients with moderate disease (those on oxygen). Remdesvir is considered an investigational drug.[57] In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. Inhibitors of MRP4 include nonsteroidal inflammatory drugs, phosphodiesterase inhibitors, cardiovascular drugs, and flavonoids, among others.[57] Phosphodiesterase inhibitors, Which are used in primary pulmonary hypertension, common in females have drug-drug interaction (DDI) with remdesivir (level II, evidence C).

According to ICMR's latest guideline for COVID-19 treatment, favipiravir is considered an investigational drug.[58] The favipiravir drug undergoes metabolism in the liver mainly by aldehyde oxidase (AO), and partially by xanthine oxidase, producing an inactive oxidative metabolite T-705M1 excreted by the kidneys.[59] Selective estrogen receptor modulators (raloxifene, tamoxifen, and estradiol), which are used in treatment of breast cancer, osteoporosis, and postmenopausal symptoms are potent AO inhibitors (in vitro). However, the clinically relevant DDI based on AO inhibition has yet to be established,[60] precaution is to be taken when favipiravir given along with selective estrogen receptor modulators (level II, evidence C).

Table 4 Drug and drug-disease interactions in females with COVID-19

Scientific statements for drug-drug and drug disease interactions in females with COVID-19	References
Caution be exercised when administering hydroxychloroquine to breastfeeding women	49–51
To avoid strict monitoring in COVID-19 patients already on warfarin, conversion of warfarin to direct oral anticoagulant is advised except in pregnant or breastfeeding women or mechanical heart valves or severe mitral stenosis or triple positive anti-phospholipid syndrome	52,53
Tocilizumab may be given to COVID-19 pregnant women if risk versus benefit favors drug usage, but not lactating women. If it is essential for lactating women, then better discontinue breastfeeding	54–56
Remdesvir and phosphodiesterase inhibitors, both affect each other as both are MRP4 inhibitors	57,58
Monitoring for side effects of favipiravir is required as the drug levels are increased in patients when given along with estrogen receptor modulators	58–60

Abbreviation: COVID-19, novel coronavirus disease 2019.

Internal Medicine

Scientific Statement on Clinical Spectrum in COVID-19

There are extensive reviews based on the experience of several practitioners describing the typical clinical presentation of COVID 19 in the form of influenza-like illness in the literature. We therefore aim to concentrate on few of the other important clinical components which require special attention, and have not yet received much recognition, like the new onset of lung fibrosis as a consequence, predominant gastrointestinal involvement and role of androgen hormone in clinical symptomatology (►**Table 5**).

Data from previous coronavirus infections, such as SARS and the Middle East respiratory syndrome (MARS), and emerging data from the COVID-19 pandemic suggest that there could be substantial fibrotic consequences following SARS-CoV-2 infection. Antifibrotic therapies[61] that are available or in development could have value in preventing severe COVID-19 in patients with idiopathic pulmonary fibrosis (IPF). These drugs may be useful even in severe COVID-19 in patients without IPF[62] and might have a role in preventing fibrosis after SARS-CoV-2 infection (class II, level C). As there are increasing reports of lung fibrosis secondary to SARS-CoV-2 infection, there is an urgent need for preventive therapies that alleviate the severity of COVID-19.

A systematic review and meta-analysis of data from 29 studies, including 6,064 patients with COVID-19, showed a pooled prevalence of 15% (95% CI: 10–21) for digestive symptoms[63] most common being nausea or vomiting, diarrhea, and anorexia. Around 10% of patients presented with

Table 5 Clinical spectrum in COVID-19

Scientific statements on clinical manifestations of COVID-19	References
All COVID-19 patients with moderate to severe lung involvement shall be closely followed and evaluated for post COVID-19 pulmonary complications with follow-up pulmonary function tests and CT chest to assess for new-onset pulmonary fibrosis to target for timely antifibrotic therapies	61,62
Patients presenting with only GIT symptoms like nausea, vomiting, diarrhea shall be evaluated for COVID-19 infection even in the absence of respiratory symptoms during the ongoing COVID-19 pandemic	63,64
Males with an androgenic pattern are more susceptible to COVID-19 infection and that too with higher severity	65

Abbreviations: COVID-19, CT, computed tomography; novel coronavirus disease 2019; GIT, gastrointestinal tract.

gastrointestinal symptoms[64] without respiratory features when infected with SARS-CoV-2. These patients' sunset is more likely to have a delayed diagnosis, owning to predominant gastrointestinal involvement only, which can lead to potential problems of mismanagement and can pose transmission to health care workers (class II, level A).

Recently scientists discovered that an enzyme called transmembrane protease serine 2 (TMPRSS2) helps virus entry inside the cells as it cleaves the SARS-CoV-2's spike protein, enabling it to bind to the angiotensin converting enzyme 2 (ACE2) receptor. The gene that encodes TMPRSS2 is activated when male hormones, particularly dihydrotestosterone, bind to the androgen receptor (a protein on the cells' surface, including hair cells and lung cells). The more male hormone, the more androgen receptor binding, and the more TMPRSS2 is present, and the easier it is for the virus to get in. This has been supported in a preliminary, non–peer-reviewed study that correlated the androgen levels of hundreds of people in the United Kingdom with COVID-19 severity. Higher androgen level (exemplified by baldness) was associated with susceptibility to and severity of COVID-19 in men[65] (but not women, who have much lower androgen levels in their blood; level II, evidence C).

Management of COVID-19: Evidence and Experience

ICMR and hospital-based management guidelines are available for all the grades of the COVID-19. Here, we mention the scientific statements pertaining to the controversial areas of treatment with steroids, Remdesvir, and Tocilizumab along with laboratory investigations (►**Table 6**).

Infection-mediated endothelial cell damage (expression of ACE2 in arterial and venous endothelium) leads to excessive thrombin production, inhibition of fibrinolysis, and activation of complement pathways, leading to thromboinflammation and deposition of microthrombi and microvascular dysfunction.[66] Elevated/rising D-dimer levels associated with hypoxia is due to VTE or in situ thrombosis (level of evidence moderate for prophylactic and low for therapeutic).

The hyperinflammatory state in COVID-19 due to a dysregulated systemic inflammation leads to a cytokine release syndrome with an increase in inflammatory markers (C-reactive protein [CRP], ferritin, IL-6, and lactate dehydrogenase [LDH]). Steroids are used as anti-inflammatory agents[67] (level of evidence, moderate).

Remdesivir demonstrates the best results early in the disease in COVID-19 patients requiring only supplemental oxygen rather than those on mechanical ventilation.[68] (level of evidence moderate).

Proinflammatory cytokines (IL-6) are released during the COVID-19 illness. Tocilizumab, an IL-6 blocker, was shown to reduce mortality in only one study in which there is no control arm[68] (level of evidence, knowledge gap).

Table 6 Management of COVID-19—controversies

Scientific statements for management of COVID-19	References
Elevated/rising D-dimer levels, along with worsening hypoxemia, may indicate ongoing thrombosis and need to be treated with prophylactic or therapeutic doses of anticoagulants	66
In patients hospitalized for COVID-19, with hypoxemia, glucocorticoids are to be used (dexamethasone 6-mg IV or oral for 10 days/till discharge)	67
Consider the use of remdesivir for 5 days in patients with moderate COVID-19 disease, not on mechanical ventilation	68
Consider tocilizumab in the context of a clinical trial	68

Abbreviations: COVID-19, novel coronavirus disease 2019; IV, intravenous.

Gynecology—Obstetrics

Scientific Statements on the Gynecology Practice during COVID-19 Pandemic

AGOS (American Gynecological and Obstetrical Society) and the Federation of Obstetric and Gynecological Societies of India laid down the guidelines for gynecological practices in this COVID-19 era. This scientific statement's main aim is an odoption of the standard gynecological practices for pre and postmenopausal bleedings to our local geographical area (►**Table 7**).

Patients who present with abnormal uterine bleeding should be assessed initially regarding the severity of bleeding. If the bleeding is extremely severe, needing a blood transfusion, a temporary measure, like curettage, can be performed to arrest bleeding, and further management can be planned[69] (class IIa, level C-LD). Medical management with progesterone should be offered to patients with mild to moderate bleeding as a measure to delay surgery.

In women with postmenopausal bleeding, the risk of malignancy should be given utmost priority. However, patients can be triaged based on their risk factors and the thickness of endometrium on ultrasound. Women with a low risk of malignancy and a normal ultrasound endometrial thickness can be managed conservatively and need to be counseled to maintain follow-up[70] (class IIa, level C-EO).

Scientific Statements on Gynecological Endoscopic Surgery during COVID-19 Pandemic

International societies, like British Society of Gynecological Endoscopy (BSGE), published guidelines for gynecological endoscopic surgery during COVID-19 pandemic. The following statements (►**Table 8**) are for preoperative screening

Table 7 COVID-19 infections and gynecology practice

Scientific statements on COVID-19 infections and gynecology practice	References
Patients with heavy menstrual bleeding should be managed medically when feasible unless the patient presents with acute or intractable bleeding causing anemia, and requiring blood transfusion	69
Patients with postmenopausal bleeding and low risk of malignancy with normal ultrasound can be offered reassurance and advised to report persistent or recurrent symptoms as the risk of malignancy in these patients is relatively low	70

Abbreviation: COVID-19, novel coronavirus disease 2019.

strategy before gynecologic endoscopic surgery for the safety of the operating team, surgical smoke generation during gynecologic endoscopy, and risk of transmission of infection and alternative treatments.

In addition to screening patients clinically for symptoms or contact with COVID-19, most studies have recommended using reverse transcriptase polymerase chain reaction (RT-PCR) for diagnosing COVID-19 infection, as it has a sensitivity between 70 and 85%.[71] The likelihood of a false negative RT-PCR, which has been reported up to 15%, should be borne in mind, and a CT of chest can be considered besides for efficient diagnosis as this has a direct impact on the operating team, anesthetic team, and entire theater staff (class IIA, level C-LD).

The presence of COVID-19 in the aerosol particles of evacuated smoke during laparoscopy has not been identified. However, it is surmised from the existing limited evidence of demonstrating viruses in the aerosol generated during endoscopic surgery.[72]

To minimize the leakage of aerosolized viral particles into the theater environment, measures need to be taken for closed-circuit smoke evacuation with commercial smoke evacuators or a wall suction.[73] The main aim is to avoid concentration of the viral particles in the patient's abdomen by using a lower abdominal pressure during surgery, lesser usage of electrocautery, minimizing the duration of surgery, and by avoiding the contamination of sterile operation theater air by using ultra-low particulate air filter with smoke evacuation, so that the safety of the health care professionals can be ensured (class IIA, level C-EO).

Prioritizing the health care professional's safety, delaying elective surgery has been recommended (class IIa, level C-LD), where it can be balanced with the risk of impending harm to the patient by delaying treatment.[74,75] The choice of route of surgery should be individualized to the patient depending on the indication for surgery, associated comorbidity, the likelihood of COVID-19 infection based on preoperative screening, the urgency of surgery, and most importantly, the availability of resources to the operating team.

Table 8 Gynecological endoscopic surgery during COVID-19 era

Scientific statements on gynecological endoscopic surgery during COVID-19 pandemic	References
Preoperative clinical screening for symptoms of COVID-19 and nasopharyngeal swab for reverse transcriptase polymerase chain reaction are recommended. However, computed tomography of the chest along with the above investigations can be performed to increase further the sensitivity of diagnosing COVID-19 infection	71
The theoretical risk of dispersion of COVID-19 by the carbon dioxide used to create pneumoperitoneum from the patient's abdomen to the outside environmental air has to be considered. Effective systems should be in place for proper smoke evacuation and filtration	72,73
Gynecologic endoscopic surgery can be considered to be safe when performed cautiously with the usage of personal protective equipment. However, alternative routes of surgery like laparotomy and vaginal surgery can be considered in appropriate situations, especially when resources are limited	74,75

Abbreviation: COVID-19, novel coronavirus disease 2019.

COVID-19 Infections in Pregnancy

In this study, scientific statements are made on the vertical transmission of COVID-19 to fetus in utero, the need for universal testing for COVID-19 before entering the labor room, and the preferred mode of delivery in COVID-19-positive pregnant ladies (►**Table 9**).

Clinical manifestations of COVID-19 in pregnant females seem to be similar to females who are not pregnant. However, since pregnancy itself alters the body's immune system and response to viral infections in general, COVID-19 infection during pregnancy can be related to more severe symptoms.[76,77]

Not all pregnant women are more susceptible to complications due to COVID-19. Pregnant women over the age of 35 years, overweight or obese women, and those who have preexisting medical problems, such as high blood pressure, diabetes, respiratory problems, and heart disease, are at a higher risk of developing severe illness.[78]

All patients should be screened for signs and symptoms of COVID-19, as well as whether they have had close contact with a confirmed case, or persons under investigation, before entering the hospital for admission to the labor and delivery unit. Where testing capacity allows, universal testing of all pregnant women presenting for labor admissions should be performed due to the likely high rate of asymptomatic COVID-19-positive patients.[79,80]

Vertical transmission of the disease from the mother to the baby in utero or during childbirth is possible. However, the proportion of pregnancies affected and the significance to the neonate is yet to be determined.[81,82]

Mode of birth should not be influenced by the presence of COVID-19 unless the woman's respiratory condition demands urgent delivery.[83]

All patients should be screened for signs and symptoms of COVID-19 and whether they have had close contact with a

Table 9 COVID-19 infections in pregnancy

Scientific statements on COVID-19 infections in pregnancy	References
COVID-19 infection during pregnancy may produce more severe symptoms	76,77
Pregnant women with high-risk category (described in the text) require more attention as these women are at a higher risk of developing severe illness	78
All pregnant women should be screened for signs and symptoms of COVID-19	79,80
There is a possibility of vertical transmission from mother to fetus in utero or during childbirth	81,82
Mode of birth should not be influenced by the presence of COVID-19 unless the woman's respiratory condition demands urgent delivery	83
Universal testing of pregnant women for COVID-19 at admission to labor suite is required	79,80

Abbreviation: COVID-19, novel coronavirus disease 2019.

confirmed case or persons under investigation, before entering the hospital for admission to the labor and delivery unit.

Where testing capacity allows, universal testing of all pregnant women presenting for labor admissions should be performed due to the likely high rate of asymptomatic COVID-19-positive patients.[79,80]

Infertility Treatment in COVID-19 Pandemic

There is a controversy that infertility treatment is not an urgent modality of treatment, and whether it should be encouraged during this pandemic or not. A review on this topic was discussed in this special issue. Here are the scientific statements on this (►**Table 10**).

Due to the current situation in the COVID-19 pandemic and the relaxation permitted by the government gradually permitting nonessential services, infertility services are being resumed according to the guidelines set by the Ministry of Health and Family Welfare. Patient selection and prioritization for fertility services should be based on the impact of delay on patient prognosis due to medical factors such as age, ovarian reserve, or endometriosis, and patients' mental and emotional wellbeing. Assisted reproductive treatment (ART) cycles for fertility preservation in cancer survivors to be started at the earliest (level IIB, evidence C). High-risk patients (those with hypertension, diabetes, on immunosuppressants, or transplant patients, with renal, liver, lung disease, or medical conditions) should be deferred for treatment during this period.[84]

Diagnostic evaluation for COVID-19 testing is done using RT-PCR, and the testing should be done at the commencement of treatment, that is, on day 2 of the in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycle (level IIB, evidence C), in the center where the COVID-19 test takes more than 24 hours, the test can be done 1 to 2 days prior. A repeat test is done before the human chorionic gonadotropin (hCG) trigger. If a patient comes out to be positive, the cycle should be canceled.[85]

Table 10 COVID-19 infections and infertility treatment

Scientific statements on COVID-19 infections and infertility treatment	References
Infertility IVF services should be reopened, especially for patients with a decreased ovarian reserve and those requiring fertility preservation such as cancer survivors, after proper counseling and individualizing a case	84
The COVID-19 testing should be done on day 2 of the cycle before ovarian stimulation and should be repeated 24 hours prior to the ovarian trigger	85
The husband also needs testing at least once during the cycle	85
COVID-19 testing should be done for all patients undergoing infertility-related procedures such as semen analysis, hysterosalpingography, hysteroscopy, laparoscopy, ovulation-induction, intrauterine insemination	86

Abbreviations: COVID-19, novel coronavirus disease 2019; IVF, in vitro fertilization.

The husband also needs testing at least once during the cycle (level IIB, evidence C), preferably at the start of the cycle. Before embryo transfer, COVID-19 testing is done approximately 1 to 2 days before the procedure. In case either partner turns positive on tests, they should help in contact tracing in keeping with the national policy.[85]

Currently, very little is known about the impact of COVID-19 on reproduction and pregnancy. There are reports of women who have tested positive for COVID-19, they have delivered babies free of disease. Ideally, pregnancy should not be allowed in COVID-19-positive patients, and infertility procedures in these patients are futile.[86] So, COVID-19 testing should be done for all patients undergoing infertility-related procedures (level IIa, evidence B).

Endocrinology

Endocrine Diseases in Women and COVID-19 Infection

Here, we discuss the management modalities and follow-up of nonpregnant and pregnant women with diabetes, including gestational diabetes (►**Table 11**).

Diabetes has been associated with greater morbidity and mortality from COVID-19 infection with increased

Table 11 COVID-19 infections and endocrine diseases

Scientific statements on COVID-19 infections and endocrine diseases	References
Insulin should be the mainstay for hyperglycemia treatment in women who develop moderate to severe COVID-19 infection. Persons infected with COVID-19 infection are at increased risk of worsening of hyperglycemia in pre-existing diabetes or ocurrence of stress hyperglycemia as well as de novo diabetes mellitus. Therefore, capillary blood glucose monitoring should be intensified during COVID-19 to guide and titrate insulin therapy. Continued glucose monitoring is required after recovery to determine long-term glycemic status and guide treatment	87–90
Pregnant women should continue to receive optimal diabetes care during the pandemic with advice on nutrition, self-monitoring of blood glucose, and insulin therapy, where required. To minimize the chances of inadvertent exposure to infection during clinic visits, telemedicine services should be considered for all pregnant women with diabetes for remote monitoring of glycemic control and insulin dose titration	91–94
For routine screening of pregnant women for gestational diabetes mellitus, alternative screening strategies such as fasting plasma glucose (≥100 mg/dL) and glycosylated hemoglobin (≥5.7%) should be considered in place of oral glucose tolerance test (OGTT) to minimize chances of exposure of pregnant women to COVID-19 infection	95–99
Women with adrenal insufficiency who develop COVID-19 infection need to increase the dose of glucocorticoids (hydrocortisone 20 mg every 6 hours) to reduce the adrenal crisis risk. In case of severe infection or clinical deterioration, intravenous glucocorticoid 50 mg every 6 hours or as continuous infusion should be administered	100–102

Abbreviation: COVID-19, novel coronavirus disease 2019.

risk for hospitalization and intensive care unit admissions, respiratory distress and need for mechanical ventilation, cardiovascular involvement, acute kidney injury, and thrombotic events.[87,88] COVID-19 infection may itself lead to worsening of hyperglycemia due to increased secretion of counter-regulatory hormones and cytokines and the use of medications, such as glucocorticoids, may impact glycemic control.[87] Patients with mild infection who maintain adequate oral intake can continue previous antidiabetic medications with close self-monitoring of blood glucose (SMBG) and follow sick-day guidelines.[88] However, insulin is the most effective and safe treatment for hyperglycemia management in persons with diabetes who develop moderate-to-severe COVID-19 infection.[87-90] For critically ill patients, insulin is administered as an intravenous insulin infusion with hourly blood glucose monitoring. However, in resource-limited settings where hourly blood glucose monitoring is not feasible, frequent bolus doses of rapid-acting insulin analogs given subcutaneously in every 4 to 6 hours can be considered. Insulin protocols can be tailored to the SMBG profile, dietary intake, and general well-being of the patient.

It is important to empower all pregnant women with diabetes regarding medical nutrition therapy, SMBG, insulin technique and administration, self-titration of insulin doses, and hypoglycemia recognition and management in the first clinical visit itself. Since physical visits to the clinic increase infection transmission risk, subsequent follow-up can be done via tele/video consultation. Physical visits to the diabetes care team can be timed along with visits to the obstetrician and ultrasounds.[91-94]

Oral glucose tolerance test (OGTT) at 24 to 28 weeks remains the gold standard for detecting gestational diabetes mellitus (GDM). However, as this would require repeated phlebotomy and more time spent at the specimen collection center, many experts have argued that this would increase the women's risk of acquiring COVID-19 infection. Therefore, many alternative screening strategies have been suggested by various countries. These include fasting plasma glucose and glycosylated hemoglobin (HbA1c) in place of OGTT as a temporary alternative measure to screen women for GDM. An HbA1c cut-off of 5.9% and above, when measured by the National Glycohemoglobin Standardization Program (NGSP), certified method has been recommended to diagnose GDM during the pandemic.[95-99]

Any acute medical or surgical illness can precipitate an adrenal crisis episode in patients who have long-standing adrenal insufficiency. This is true for the COVID-19 infection as well. Therefore, patients who have primary or secondary adrenal insufficiency or those on long-term glucocorticoid therapy should be advised to use stress doses of glucocorticoids if they develop COVID-19 infection and contact their endocrine care provider.[100-102] It is important for health care providers caring for COVID-19 infected patients to elicit any history or prior adrenal disease or glucocorticoid use and administer stress doses of steroids until the clinical condition improves. Glucocorticoids are also used in moderate to severe infection for their proposed benefits in improving outcomes by their immunomodulatory effects.

Rheumatology

Scientific Statements in Rheumatological Diseases with COVID-19

Here, scientific statements on the risk of COVID-19 in patients with rheumatic diseases, treatment of COVID-19 in patients with rheumatological diseases (RD) like drug dosage adjustments, and continuation of essential drugs are made (►**Table 12**).

The risk of COVID-19 in RD similar or only slightly higher than that of the general population. There is a small increased risk in non-SLE systemic autoimmune disease. A higher steroid dose is a risk factor for severity. The risk with biologic disease modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs are not clear. One study found patients on tumor necrosis factor (TNF) inhibitors to have lesser severity. The risk factors for COVID-19 are similar to the general population, including age, diabetes, cardiovascular comorbidity, and chronic lung disease. The effect of gender has not been specifically explored in rheumatic diseases compared with the general population.[103-106]

The clinical features of COVID-19 are similar in patients with RD. There is a higher risk of intensive care unit (ICU) admission and respiratory failure in patients with RD who develop COVID-19 compared with controls. Mortality is similar to non-RD patients.[107,108]

Testing for COVID-19 should be as per local guidelines. COVID-19 treatment should be the same in patients with RD as with non-RD. Biologic DMARDs and tsDMARDs except Tocilizumab may be interrupted. Steroids should not be stopped suddenly in patients on long term steroids.[109,110]

Treatment of stable RD should continue unchanged. It is unclear if there is an increased risk of COVID-19 in patients on biologics/tsDMARDs or any immunosuppression. Since

Table 12 COVID-19 infections and rheumatological diseases

Scientific statements on COVID-19 infections and rheumatological diseases (RD)	References
The risk of COVID-19 in RD is similar or slightly higher than that of the general population, especially in non-SLE systemic autoimmune disease	103–10[6]
Even though there is a higher risk of ICU admission and respiratory failure in patients with RD who develop COVID-19 than controls, the mortality is similar to non-RD patients	107,108
Steroids should not be interrupted in a patient on long term steroids. Biologic DMARDs (disease modifying antirheumatic drugs) and tsDMARDs (targeted synthetic) except tocilizumab may be interrupted if required	108,109
Higher doses of steroids are a risk factor for COVID -19. There is no clear evidence that there is an increased risk of COVID in patients on biologics/ tsDMARDs or any immunosuppression	108,109

Abbreviations: COVID-19, novel coronavirus disease 2019; DMARDs, disease modifying antirheumatic drugs ICU, intensive care unit;

higher doses of steroids are a risk factor for severity, the dose should be kept as low as necessary for disease control. Treatment of new/disease flare should be individualized. In stable patients with RD, teleconsultations may be done instead of in-person consultations.[109,110]

Oncology

Care of Women with Gynecological Cancers during the COVID-19 Pandemic

Here, scientific statements on cervical cancer, endometrial cancer, and epithelial ovarian cancer managements during COVID-19 are mentioned (►**Table 13**).

Outcomes in gynecological cancers are heavily stage dependent, ranging from 5-year survival 95% in early stage to less than 15% in advanced stages. Early diagnosis and timely treatment are, therefore, of the utmost importance. Women in developing countries are an especially vulnerable group whose health care needs are often neglected. While it is prudent to suspend all screening services and evaluation of low grade lesions, all cases of invasive cervical cancers should preferably undergo diagnostic workup and treatment without delay.[111,112] Depending on local pandemic factors and availability of expertise, radiotherapy and concomitant radiochemotherapy should replace surgery as first-line treatment whenever possible. Cervical cancer being a rapidly dividing tumor with a high potential for cure, there is no clinical situation where the treatment can be safely delayed. Hypofractionation schedules should be considered whenever feasible, and brachytherapy should not be delayed.[113] All treatment should be preferably completed within 8 weeks, and delays should be avoided since they impact local control and survival.

All patients with abnormal uterine bleeding and suspected endometrial cancer should undergo endometrial biopsy without delay. Surgery should not be delayed in high risk patients with active bleeding. A short delay of less than 8 weeks can be considered in patients with clinically early disease without active bleeding. Patients with low risk grade-1 disease may be offered hormonal therapy strategies like oral progestins or IUDs. Patients with higher risk disease (grade 2 or 3 or high-risk histology) should be considered for simple hysterectomy and bilateral salpingo-oophorectomy alone, with or without sentinel node sampling. The decision for adjuvant therapy should be based on risk factors. Patients with advanced disease should be considered for tissue biopsy to confirm diagnosis followed by systemic therapy.[111,112] Hormonal therapy may be used in patients with endometrioid histology if adjuvant radiation needs to be delayed.[113] Adjuvant radiation therapy may be delayed between 6 and 8 weeks following surgery in most cases.[113] Adjuvant therapy might be deferred during the crisis in stage-I or -II disease with low-risk features, where as in cases with intermediate to high-risk features, Brachytherapy is preferred considering fewer hospital visits and lesser risk of complication.[112] External beam radiotherapy with or without chemotherapy should be considered without any delay after surgery in high-risk patients and also for patients with symptomatic unresectable primary tumor not suitable for surgery. It may be prudent to increase the interval between chemotherapy cycles whenever deemed feasible.

Table 13 COVID-19 infections and gynecological cancers

Scientific statements on COVID-19 infections and gynecological cancers	References
Cervical cancer is an aggressive malignancy with a good potential for cure in localized stages, and should be treated without delay even during the pandemic	111–113
Management of women with endometrial cancer during the COVID-19 pandemic should be based on risk stratification	111–113
Management of patients with epithelial ovarian cancers should be individualized during the COVID-19 pandemic based on risk versus benefit	111,112,114

Abbreviation: COVID-19, novel coronavirus disease 2019.

Multiple factors, such as performance status, comorbidities, and family history, should be considered in patients with suspected ovarian cancer. Physical examination and a thorough diagnostic evaluation with pelvic ultrasound, CT/magnetic resonance imaging (MRI), and/or serum markers, such as CA125 and HE4, to assess malignancy risk should be performed as early as feasible.[112] In fit patients, surgery is considered mandatory if the disease is localized and limited to the pelvis and includes hysterectomy, bilateral salpingo-oophorectomy, and peritoneal staging. Lymphadenectomy may be avoided in low grade endometrial cancer due to its uncertain benefit. It can be considered in cases where the nodal status would help make decisions regarding adjuvant chemotherapy for ovarian cancers are best avoided during the COVID-19 pandemic.[114]

A tissue biopsy should be performed for confirmation in patients with clinically advanced-stage disease. In such cases, three to six cycles of neoadjuvant chemotherapy and delayed surgery are the recommended approaches since extensive surgical procedures can be risky for patients and health care workers during the pandemic. In patients receiving neoadjuvant chemotherapy, the treatment plan can be extended to six cycles, instead of three, before interval cytoreduction. This decision should be balanced against the additional risk of chemotherapy induced immunosuppression.[111,112,114]

Maintenance therapies following completion of adjuvant chemotherapy may be withheld, considering the additional risk of infection on the patient, families, and health care teams due to the need for repeated visits.[112] In patients, active COVID-19 infection, surgery, and chemotherapy should be postponed till recovery. In general, extensive surgical procedures and highly immunosuppressive chemotherapy should be avoided during the outbreak whenever feasible.[114]

Follow-up

Surveillance can be deferred based on the level of risk of recurrence. In case of cervical cancer, patients treated with radical radiation therapy for early stage disease can be advised follow-up after 6 months. Follow-up visit after

palliative treatment for advanced/recurrent disease can be postponed up to 2 months.

In case of endometrial cancer, follow-up can be converted to tele consultations, in intermediate-to-low risk patients. Follow-up visits (clinical and pelvic exam) in patients after palliative treatment for advanced/recurrent disease can be postponed up to 6 months in the absence of symptoms.

Follow-up visits can be converted to tele consultations, wherever feasible. Investigations like blood tests and imaging studies can be done in laboratories close to home and tele consultations provided.

Care of Women with Breast Cancer during the COVID-19 Pandemic

These are the scientific statements on diagnostic and staging procedures, surgical decisions, adjuvant postoperative radiation, and systemic therapies in breast cancer patients (►**Table 14**).

Current estimates suggest that the age-standardized incidence rate of breast cancer in India has increased significantly by 40·7% from 1996 to 2016.[115] It is currently the most common cancer in females, constituting about a fourth of cancers in them.[116] Women in India often delay seeking medical care; therefore, a greater proportion present in advanced stages. Stigma, fear, denial, family responsibilities, embarrassment, and lack of affordability and access to care are significant reasons for the delay in diagnosis and treatment.[117] Mandatory lockdowns can significantly limit access to care.[118] Cancer treatment is time sensitive, and outcomes depend on the stage at presentation. Therefore, every effort should be made to ensure timely referral, workup, and treatment for patients suspected to have breast cancer while at the same time minimizing the risk of infection, reducing patient visits, and shifting to a quality system of telemedicine when appropriate.[119] The Government of India has issued guidelines for telemedicine in March 2020. Economic obstacles can also prove a major deterrent in accessing care for India.[117,118] Therefore, all stakeholders should work together to recognize women with cancer as a vulnerable population and put mechanisms in place to ensure affordability, accessibility, and continuity of care.[118]

Table 14 COVID-19 infections and breast cancers

Scientific statements on COVID-19 infections and breast cancers	References
Diagnostic and staging procedures for suspected cases of breast cancer should be prioritized, and any delay should be avoided	115–119,160
Surgical decisions in patients with breast cancer should be based on disease biology and risk stratification	119–121
Adjuvant post-operative radiation should not be delayed for breast cancer patients with high-risk features (described in the text)	122–126
Decisions regarding systemic therapies in breast cancer during the COVID-19 pandemic should weigh the risk versus benefit	119,120,127,161

Abbreviation: COVID-19, novel coronavirus disease 2019.

The surgery decision should be based on the status of the pandemic, availability of surgical expertise, and clinical condition of the patient.[119,120] Many centers in India have canceled or postponed nonessential surgeries during the pandemic. Surgery during the pandemic carries a higher risk of postoperative morbidity. In many cases, neoadjuvant chemotherapy can be used to defer surgery while balancing the risks of immunosuppression due to chemotherapy. Neoadjuvant endocrine therapy can be used judiciously in hormone-receptor positive patients to delay surgery.[121] Curative surgical procedures should be prioritized in patients who have completed neoadjuvant chemotherapy (NACT) and those who show the progression of NACT. All procedures for benign breast lesions or preinvasive low-grade cancers can be postponed. All prophylactic or reconstructive surgeries should be avoided during the pandemic.[119,120]

High-risk patients include those with T3/T4 tumors, high-grade tumors, node-positive disease, perinodal deposits, inflammatory breast cancer, triple-negative, or HER2-positive disease, residual disease at surgery postneoadjuvant therapy, and young age (<40 years) at diagnosis.[122] These patients should receive radiation therapy on schedule as delays can result in inferior survival outcomes. In patients with intermediate risk, radiation may be deferred for 3 to 6 months, depending on local circumstances.[122,123] In such situations, the patients should receive oral endocrine therapy when eligible.

The use of hypofractionated regimens is strongly recommended, and the 40 Gy in 15 fractions schedule is suitable for most cases. In suitable patients, accelerated partial breast irradiation (APBI)[124] or the five-fraction protocol of the FAST or FAST forward trials is strongly recommended.[125,126] The omission of tumor bed boost is reasonable except in high-risk cases (young age, high-grade DCIS, etc.). Finally, radiation therapy can be omitted in low-risk disease patients who are elderly (age >70 years) or have significant comorbidities.[123]

During the pandemic, every effort must be made to limit infection risk for patients and health care personnel without compromising oncological outcomes. Several international oncological societies have issued recommendations for the prioritization of care of breast cancer patients. These guidelines need to be adapted to the local resources, health care delivery models, and local pandemic status.[127] Chemotherapy decisions should consider the magnitude of benefit from the intervention versus the risk of immunosuppression and the disruption of life quality. In low-risk endocrine receptor positive patients, chemotherapy can be avoided because of uncertain benefits, and oral endocrine therapy must be started. Ongoing therapy should be continued in patients who are already on NACT or adjuvant chemotherapy. Two or three weekly schedules should be preferred over weekly schedules. Ongoing maintenance trastuzumab can be deferred for 6 to 8 weeks if necessary, and reducing the total duration of trastuzumab from 12 months to 6 months should be strongly considered.[125] Strong consideration should be given to avoid highly immunosuppressive regimens when outcomes are not likely to be affected. Whenever possible oral agents should

be preferred. Decisions should be made on a case-by-case basis keeping in mind the effects on quality of life and likely benefit versus harm.[119,120,127] In general, administering mTOR inhibitors and immune checkpoint inhibitors should be avoided during the pandemic, given the higher risk of adverse outcomes with these agents. Bone-modifying agents like bisphosphonates or denosumab can be deferred in most cases.[119,120]

Finally, the decentralization of outpatient chemotherapy and remote monitoring services should be considered when travel to cancer centers is difficult, or the risk of infection is high. Stakeholders must work together to ensure an ongoing supply of essential oncology drugs during the pandemics as disruption of supply chains can lead to shortages/ nonavailability.

Neurology

Scientific Statements on COVID-19 Infections and Neurological Disorders in Women

In this, scientific statements on thrombolytic therapy in pregnant and nonpregnant women with stroke and the risk of developing cerebral venous sinus thrombosis in women with COVID-19 are mentioned (►**Table 15**).

It is well recognized that the quality of care for women with acute ischemic stroke is lower than that for their male counterparts. It is reasonable to treat otherwise eligible pregnant/ menstruating women with thrombolytic therapy as per the available guidelines for the early management of acute ischemic stroke[128] (class IIa, level C-EO). Various international and Indian guidelines have advocated thrombolytic therapy in COVID-19 suspect/positive patients with acute ischemic stroke.[129-131] There have been concerns surrounding disseminated intravascular coagulation in COVID-19 and the risks of excessive bleeding in these patients. However, COVID-19-induced coagulopathy (CIC) appears to be more prothrombotic than hemorrhagic.[132] Though specific thrombolytic therapy data on COVID-19-positive pregnant stroke patients is not available, it seems reasonable that the eligible pregnant stroke patients should benefit from thrombolytic therapy. Risks of additional bleeding should be assessed in menstruating women with stroke before offering thrombolytic therapy (class IIb, level C-LD).

COVID-19 associated coagulopathy increases the risks of the development of thrombotic phenomena. Cerebral venous sinus thrombosis due to SARS-CoV-2 infection has been reported repeatedly during this pandemic.[131-133] Oral contraceptive pills (OCP) consumption is a well-recognized risk factor for development of CVT.[134] Increased thrombosis is expected if both the risk factors are combined (class IIa, level C).

Table 15 COVID-19 infections and neurological disorders in women

Scientific statements on COVID-19 infections and neurological disorders in women	References
Thrombolytic therapy is probably indicated in otherwise eligible COVID-19 suspect/positive women with acute ischemic stroke who are menstruating and do not have a history of menorrhagia after ruling out any additional contraindications like coagulopathy	128,162
Thrombolytic therapy for moderate and severe stroke may be considered in pregnant COVID-19 suspect/ positive women when the likely benefits of stroke treatment outweigh the anticipated bleeding risks (uterine bleeding)	128–130,162
SARS-CoV-2 infection may further increase the risk of developing cerebral venous sinus thrombosis in women consuming oral contraceptive pills (OCP)	131–134

Abbreviations: COVID-19, novel coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

Preventive Medicine

Key Considerations for the Safety of Health Care Workers

Nearly 70% of health care workers are females in this COVID-19 pandemic and special attention is to be paid to them. Here, scientific statements on menstrual health and hygiene (MHH) while using PPE kits and HCQ prophylaxes for female health care workers are mentioned (►**Table 16**).

Table 16 COVID-19 infections and the safety of health care workers

Scientific statements on COVID-19 infections and the safety of health care workers	References
The wearing of PPE kits for long durations (8 hours or more) in female healthcare workers leads to problems in menstrual health and hygiene (MHH). Hence, duty hours should be reduced to 4 hours while simultaneously ensuring MHH and wash facilities	135–137
HCQ prophylaxis should be recommended to all healthcare workers working in COVID-19 and non-COVID-19 healthcare settings for 8 weeks and more	138,139
HCQ prophylaxis in female healthcare workers, during pregnancy, should be continued	140
Relative infant dose (RID) must be the critical parameter and should be calculated if HCQ prophylaxis needs to be given in lactating health care worker, for postexposure prophylaxis	141,142
Menstrual hygiene materials and painkillers should be provided to female patients quarantined in health care facilities or COVID-19 designated centers and training of caretakers and support for water sanitation and hygiene (wash)	
Materials for maintaining menstrual health and hygiene should be available in sufficient quantities for female healthcare workers during menstruation. This should be provided by the health department or facility to avoid women bleeding into PPE suits during menstruation or to avoid unwilling suppression of menstruation with oral contraceptive pills	141

Abbreviations: COVID-19, novel coronavirus disease 2019; HCQ, hydroxychloroquine; PPE, personal protective equipment.

The wearing of PPE kits for long durations (8 hours or more) in female health care workers leads to problems in MHH. Hence, duty hours for them should be reduced to 4 hours, while simultaneously also ensuring MHH and wash facilities. (class I, level EO). The COVID-19 response, depending on the intensity of the disease, and subsequent measures taken by each country, can result in mild to severe disruption of necessary facilities like water sanitization and hygiene (WASH), and can also lead to a reduction in the capacity of individuals to have free access to such services.[135] This poses a special challenge to female health care workers, since globally, women make up 70% of the health workforce.[136] In addition to those mentioned above, COVID-19 also imposes additional challenges to women, in terms of managing their menstrual hygiene, which, often compromises their health, dignity, and the ability of the health care system to function optimally.[137] Therefore, it is strongly recommended that a stable supply of MHH and WASH facilities is ensured to female workers, and that their working hours are reduced.

The absence of a vaccine makes the medical and scientific community look carefully, closely, and intensely at a drug that can potentially be used for pre- and postexposure prophylaxis in the COVID-19 pandemic. The systemic review of 41 interventional studies registered in governmental clinical trials was undertaken to analyze the positioning of HCQ for COVID-19 prophylaxis in exposed health care workers.[138] The National Task Force issued guidelines regarding the extended use of HCQ prophylaxis beyond 8 weeks,[139] making it a well-recommended drug (class I, level A).

There appears no need to discontinue HCQ during pregnancy as the former has no adverse effects on fetal outcomes. It is recommended that HCQ should be given with caution in breastfeeding and lactating health care workers (class IIa, level A). In addition to that, it is recommended to calculate relative infant dose (RID) in postexposure prophylaxis in female healthcare workers, who are breastfeeding. (RID, dose offered to the infant via breast milk divided by the mother's weight; class I, level A).[140]

According to the policies of the Ministry of Health and Family Welfare regarding COVID-19, all suspects and contacts of COVID-19 cases are being quarantined in health care facilities or COVID-19 designated areas. This is especially challenging in the case of female patients who require access to WASH and MHH supplies. A joint report published in 2019 by WHO and UNICEF outlines that WASH services in many health care facilities across the world are missing or substandard. Menstrual hygiene materials and painkillers for symptomatic relief should be part of essential items provided at health care facilities and quarantine centers for female patients. Caretakers appointed in theses facilities should be provided with training to assist and educate girls and women with personal and menstrual hygiene.[141,142]

Women constitute the majority of the health workforce, and they are more likely to be at the front line in this COVID-19 pandemic. They have to face additional challenges compared with their male counterparts in the form of managing their menstruation. It compromises their ability to deliver effective health care services and their health and dignity. Menstrual hygiene materials should be considered as essential supplies for female health care providers. It should be procured in sufficient quantity and of good quality by the concerned health department or facility. Since donning and doffing PPE prevents frequent changing of menstrual hygiene materials, access to an adequate PPE quantity would allow them to take breaks at least every 4 hours to change tampons or high absorbency pads. Ensure health facilities are women employee friendly and they have access to water sanitation and hygiene in health care facilities[141]

Research

COVID-19 Infections and Research

Here, scientific statements on recent advances in understanding genome sequences of SARS-CoV-2, and causes for female gender protection and male gender predilection are mentioned (►**Table 17**).

Genome sequences of SARS-CoV-2 from across the world show that they originate from two ancestral lineages A and B. Clade A2a, which arose from lineage A, is now the most prevalent clade of SARS-CoV-2 throughout the world. The disparity in COVID-19 manifestation in the severity of the disease or mortality does not seem to be because of the difference in the virus.[143-147]

SARS-CoV-2 enters host cells through binding ACE-2 receptors expressed on the cell surfaces. Men have shown to express higher levels of ACE2 on lung epithelial cells and in soluble form. ACE-2 has also been shown to be downregulated by estrogen. TMPRSS, a protease, facilitates SARS-CoV-2 binding with ACE2. *TMPRSS* gene has an androgen-regulated element. These are the most established reasons men get higher SARS-CoV-2 infections than women.[148-155]

Estrogen and testosterone have differential effects on immunity. The former strengthens immunity, and the latter diminishes it. Many other proteins involved in immune reactions are expressed on X-chromosome. With two allelic options for X-chromosome genes and X-chromosome inactivation in their cells, women are believed to be at an immune advantage. The role of these in protecting women from

Table 17 Research in COVID-19

Scientific statements on COVID-19 infections and research	References
The disparity in COVID-19 manifestation in the severity of the disease or mortality does not seem to be because of differences in the virus (different clades)	140–147
Men get higher SARS-CoV-2 infections than women due to higher levels of ACE-2 on lung epithelial cells and *TMPRSS* gene (androgen-dependent) which facilitates SARS-CoV-2 binding with ACE-2	145–155
Women may be protected from SARS-CoV-2 infections, which may be due to immune advantage (details are given in the text)	153–159

Abbreviations: ACE2, angiotensin converting enzyme 2; COVID-19, novel coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

SARS-CoV-2 infection or severity of COVID-19 is yet to be studied and understood.[156-159]

Concordance with the Expert's Opinion

The formulation of scientific statements by the panel was followed by the circulation of the given statements to an expert group in respective branches in the form of a questionnaire. The questionnaire was given in yes or no format. The concordance rate was then calculated for every scientific statement and tabulated. The concordance rate was defined as the percent of cases in which both member pairs share a particular attribute. All questions asked, and the average responses are mentioned in concordance tables, in ►**Appendix 3** (available online only). The average concordance rate for each subject was calculated by averaging all concordant responses to questions.

The number of experts contacted was 22 in cardiology, 22 in preventive medicine, 45 in endocrinology, 13 in rheumatology, 20 in gynobs (gynecology and obstetrics), 32 in internal medicine, and 17 in neurology. The average accordance was maximum with rheumatology scientific statements (95.20%), followed by endocrinology (92.29%), preventive medicine (92%), internal medicine (81.90%), cardiology (64.95%), neurology (68%), and gynobs (57%), respectively.

This methodology of data collection via questionnaire from experts is fraught with certain limitations. First, the experts were not informed beforehand about the details of this study. All of them were requested to respond within 5 days. So, this may be the doctors; opinion with their existing knowledge that is based on complete review of the literature. Moreover, a short duration of 5 days was permitted for responding to the questionnaire, which would herby be a mere opinion of physicians and not reflect a complete review of the literature. Second, few questions were left unanswered and blank by the experts. This could reflect a physician's unawareness of that particular topic or a drawback of the binominal yes or no format of the questionnaire, not allowing them to submit their opinion. Third, in ►**Appendix 4** (available online only), explanations for discordance are given. Despite of these gross limitations, the opinion poll was utilized to the direct for the strength of each scientific statement. In ►**Appendix 5** (available online only), definition of class of recommendation and level of evidence is mentioned.

Conclusion

Variant gender-specific and gender-frequent manifestations of diseases in the female population, especially in the COVID-19 pandemic era make it imperative to lay down a management strategy and approach for targeting this population. Besides describing, managing and prognosticating these diseases in women in COVID-19 pandemic, these scientific statements also draw attention to the female health workers requirement which has usually been an area of neglect. This paper attempts to tide over the existing knowledge gap in the arena of women health in COVID-19 era which has so far been untouched and not discussed.

Conflict of Interest
None declared.

Acknowledgment
We want to acknowledge all the following doctors for valuable advises in preparation of the scientific statements, reviewing the article and excellent guidance at each step.

Prof. Krishnam Raju (Chief Cardiologist—Previous President of IAE), Prof. M.K. Das (Chief Cardiologist—CSI President), Prof. Gurpreet Singh Wander (Chief Cardiologist—BC Roy National Awardee, CSI Executive Committee Member), Prof. Alpesh Gandhi (Chief Gynecologist—FOGSI President Elect), Prof. Padmaja (Chief Gynecologist), Prof. Manjeesh Tiwasker (Chief Internist—API General Secretary), Prof. Satyanarayana Raju (Chief Internist—API Vice President), Prof. Vitul K. Gupta (Senior Internist—CSI Executive Committee Member), Prof. Sanjay Kalara (Chief Endocrinologist—ESI President), Prof. Rakesh Sahay (Chief Endocrinologist—ESI Vice President), Prof. PV Rao (Chief Endocrinologist—ESI Previous President), Prof. Pramod Pal (Chief Neurologist—IAN President), Prof. J.M.K. Murthy (Chief Neurologist—IAN President Elect), Prof. Sapan Pandya (Chief Rheumatologist—IRA Secretary), Prof. Alakendughosh (Chief Rheumatologist—IRA President), Prof. Urk Rao (Chief Rheumatologist—IRA Former President), Prof. Kaushik Bhattacharya (Chief Oncologist—General Secretary AROI-TS) And Prof. Sanjeeva Kumari (Chief Radiation Oncologist).

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