Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action

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Inclusion of pregnant women in COVID-19 clinical trials would allow evaluation of effective therapies that might improve maternal health, pregnancy, and birth outcomes, and avoid the delay of developing treatment recommendations for pregnant women. We explored the inclusion of pregnant women in treatment trials of COVID-19 by reviewing ten international clinical trial registries at two timepoints in 2020. We identified 155 COVID-19 treatment studies of non-biological drugs for the April 7–10, 2020 timepoint, of which 124 (80%) specifically excluded pregnant women. The same registry search for the July 10–15, 2020 timepoint, yielded 722 treatment studies, of which 538 (75%) specifically excluded pregnant women. We then focused on studies that included at least one of six drugs (remdesivir, lopinavir–ritonavir, interferon beta, corticosteroids, chloroquine and hydroxychloroquine, and ivermectin) under evaluation for COVID-19. Of 176 such studies, 130 (74%) listed pregnancy as an exclusion criterion. Of 35 studies that evaluated high-dose vitamin treatment for COVID-19, 27 (77%) excluded pregnant women. Despite the surge in treatment studies for COVID-19, the proportion excluding pregnant women remains consistent. Exclusion was not well justified as many of the treatments being evaluated have no or low safety concerns during pregnancy. Inclusion of pregnant women in clinical treatment trials is urgently needed to identify effective COVID-19 treatment for this population.

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Introduction

Evidence on the effects of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, during pregnancy is scarce. According to a report[1] of 8207 pregnant women with COVID-19, done by the US Centers for Disease Control and Prevention between Jan 22 and June 7, 2020, after adjusting for age, presence of underlying conditions, and race and ethnicity, the risks of intensive care unit admissions and mechanical ventilation were significantly higher among pregnant women than women who are not pregnant. Findings from Sweden[2] indicate that pregnant women with COVID-19 were five-times more likely to be admitted to the intensive care unit and four-times more likely to receive mechanical ventilation compared with those who are not pregnant. Cohort data on the natural history are still missing, leading to challenges in formulating clinical guidance based on solid evidence for the management of pregnant women with COVID-19.[3,4]

Calls for inclusion of pregnant women in clinical trials and surveillance studies[5–7] have recently been published supporting consensus views of numerous medical societies and organisations, including the American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and the Elizabeth Glaser Pediatric AIDS Foundation. A review of the US clinical trial registry (ClinicalTrials.gov) in April, 2020, identified that most trials excluded pregnant women from COVID-19 trials in this single registry.[6,7] To quantify the focus, inclusion, and exclusion of pregnant women in COVID-19 trials worldwide, we did a comprehensive search of WHO-approved clinical trial registries at two time-points during the pandemic outbreaks. We describe the method of the search, provide an overview of the findings, and reflect on the implications regarding exclusion of pregnant women in COVID-19 treatment trials.

Search and review of clinical trial registries

To quantify the number of registered COVID-19 trials, we searched within the 21 online International Committee of Medical Journal Editors (ICMJE) registries and WHO-accepted clinical trial registries at two timepoints: April 7–10, 2020, and July 10–15, 2020, using the search terms "COVID" and "SARS-CoV-2". In addition to clinical trials, these registries include observational and registry studies. To identify COVID-19 studies focused on pregnant women, a similar search was done using the search terms "COVID", "SARS-CoV-2", "pregnant", and "pregnancy". To assess the specific exclusion of pregnant women in clinical studies (ie, the explicit exclusion of pregnant women in the exclusion criteria, or inclusion requirements for women to use contraception before and during treatment for COVID-19), we selected a subset of ten clinical trial registries that were accessible and had more than one registered study on COVID-19 at the April 7–10, 2020 timepoint. We searched titles using the terms "COVID" and "treatment"; the registries' search engines also automatically included trials with SARS CoV-2 in the title. The ten registries included the following country or region-based registries: the USA, the UK, the EU, Iran, India, China, Australia and New Zealand, the Netherlands, Brazil, and Switzerland. The title was reviewed for all studies. We included studies on non-biological drugs and high-dose treatment with vitamins A, B-complex, C, D, E, and zinc. We excluded studies on biological therapies (eg, convalescent serum samples, plasma infusions, monoclonal antibody inhibitors, plasma exchange, plasmapheresis, vaccines, and stem-cell infusions), ventilator and oxygen delivery,

Panel: Pregnancy safety profiles of drugs under evaluation for COVID-19

Lopinavir–ritonavir

Lopinavir–ritonavir is a US Food and Drug Administration (FDA) pregnancy category C medication[8] used for the treatment of HIV. Category C means that animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans; therefore, whether treatment with category C medication will harm a baby is unknown. Since 2005, lopinavir–ritonavir has been used extensively worldwide for pregnant women with HIV infection to prevent mother-to-child transmission of HIV. Birth defects are not higher in women taking this medication.[9]

Chloroquine and hydroxychloroquine

Chloroquine has not been assigned a pregnancy category by the US FDA. There are no controlled studies in human pregnancies. However, chloroquine is the drug of choice for the prophylaxis and treatment of non-chloroquine-resistant malaria during pregnancy and has not shown fetal harm.[10,11]

Remdesivir

Remdesivir is a potential treatment for Ebola virus disease, with no assigned US FDA pregnancy category. However, in a trial[12] in which 17 (6·1%) of 277 pregnant women had Ebola virus disease, 6 (35%) of 17 were randomly assigned to remdesivir. There were no significant maternal, pregnancy, or neonatal adverse effects noted in the remdesivir group.

Interferon beta

Interferon beta has been used to treat multiple sclerosis in pregnant women. In 2019, the European Medicines Agency released a recommendation that women with relapsing multiple sclerosis can continue interferon beta treatment while pregnant and breastfeeding. Exposure to interferon beta in early pregnancy had no influence on birthweight, risk of preterm birth, or other adverse pregnancy outcomes, according to a German prospective cohort study,[13] and further studies showed no effect on the rates of congenital anomalies or spontaneous abortions (from cumulative exposure data and prevalence of pregnancy and infant outcomes in pregnant women with multiple sclerosis).[14] Although interferon beta drugs are classified as pregnancy category C, the potential benefits could outweigh risks, as noted from published evidence of use in pregnant women.

Corticosteroids (prednisone, dexamethasone, hydrocortisone)

Corticosteroids are potent anti-inflammatory drugs. They are considered safe in second and third trimesters of pregnancy when used in low doses and are classed as US FDA category B drugs.[15]

Ivermectin

Ivermectin is an FDA pregnancy category C medication used for the treatment of parasitic infections. Pregnant women (397 women, 399 pregnancy outcomes) received ivermectin as part of an open-label randomised controlled trial[17] and no neonatal deaths, maternal morbidity, preterm births, or low birthweight were recorded. A non-significant risk of spontaneous abortions, stillbirths, and congenital anomalies has been reported but data remain inconclusive.[16]

See Online for appendix

extracorporeal membrane oxygenation, other device-related interventions, prone positioning, and radiation exposure owing to known or possible pregnancy safety issues. We excluded prevention and medical prophylaxis interventions; pre-exposure prophylaxis; trials of herbal remedies, Chinese traditional medicines, and Ayurveda treatments due to unknown effects in pregnancy; and studies among health-care workers.

As a subgroup review, treatment studies were identified from the ten high-volume registries that included studies of at least one drug with known safety or vitamins for which safety data show no or low risk of adverse birth outcomes. The medications included in our search were lopinavir–ritonavir, remdesivir, interferon beta, corticosteroids (prednisone, dexamethasone, hydrocortisone), chloroquine and hydroxychloroquine, and ivermectin. A detailed description of the indicated use and pregnancy safety data are shown in the panel.[8–17] Studies evaluating the use of vitamins for treatment of COVID-19 were analysed as an additional subgroup.

The data extraction from clinical trial registries was conducted by MMT, LK, CK, and NBB using a Microsoft Excel data sheet. Second review was performed by MMT. For trials with questionable criteria for inclusion, MMT made the final determination of whether a trial was included or excluded based on a repeat review of the trial registry. To assess the possible entry of clinical trials of treatment for COVID-19 in more than one clinical trial registry, we reviewed 108 clinical trial entries in the clinical trial registry with the largest number of registered clinical trials (ClinicalTrials.gov) and cross-matched key title words in national registries (appendix pp 1–2).

Among the 21 clinical trial registries accepted by WHO and the ICMJE, we identified 1121 studies with COVID-19 in the title for the April, 2020 search period, and 5492 cumulative studies for the July, 2020 search period, representing a 390% increase in trial registrations between the two time periods (appendix pp 3–4). In April, 2020, six studies that specifically focused on COVID-19 in pregnant women were identified (appendix p 5), whereas 40 studies were identified during the July, 2020 search period. Of those 40, 25 studies are being done in the USA, five in Australia, and four in Italy. 16 of these 40 studies are observational, ten are prospective cohort studies, five are case-control studies, and five are randomised controlled trials designed to specifically evaluate treatments in pregnant women with COVID-19 (appendix pp 6–12).

Our April, 2020 search, of the ten high-volume clinical trial registries yielded 155 COVID-19 treatment studies of non-biological drugs. Most studies (124 [80%] of 155) specifically excluded pregnant women. The same registry search during the July, 2020 time period, identified 722 cumulative COVID-19 treatment studies (including those identified during April, 2020), of which 538 (75%) specifically excluded pregnant women (table 1). A subsample cross registry search (n=108) found less than 5% duplicate registration of studies (appendix pp 1–2).

For the subgroup analyses, 176 (24%) of 722 clinical treatment trials evaluated at least one of the six treatments under review. Of these, 130 (74%) listed pregnancy as an exclusion criterion (table 2). Of 35 trials that evaluated high-dose vitamin treatment for COVID-19, 27 (77%) excluded pregnant women (appendix p 13).

	Number of COVID-19 treatment studies (April 7–10, 2020)	Number of treatment studies excluding pregnant women (April 7–10, 2020)	Cumulative COVID-19 treatment studies* (July 10–15, 2020)	Cumulative number of treatment studies excluding pregnant women (July 10–15, 2020)
UK ISRCTN registry	4	3 (75%)	6	3 (50%)
Brazilian Clinical Trials Registry (ReBec)	2	2 (100%)	2	2 (100%)
US ClinicalTrials.gov	84	64 (76%)	429	328 (77%)
Clinical Trials Registry - India (CTRI)	2	1 (50%)	5	5 (100%)
Australia and New Zealand Clinical Trial Registry (ANZCTR)	3	3 (100%)	6	3 (50%)
Chinese Clinical Trial Registry (ChiCTR)	33	30 (91%)	92	68 (74%)
EU Clinical Trials Register (EU-CTR)	19	18 (95%)	34	28 (82%)
Iranian Registry of Clinical Trials (IRCT)	5	3 (60%)	143	101 (71%)
The Netherlands Trial Register	1	0	1	0
Swiss FOPH Human Research Projects	2	0	2	1 (50%)
Total	155	124 (80%)	722	538 (75%)

Studies are included irrespective of design. *Cumulative search in July, 2020, is inclusive of the studies originally identified during April, 2020.

Table 1: **Registered COVID-19 treatment studies that exclude pregnant women**

	Remdesivir	Chloroquine and hydroxychloroquine	Corticosteroids*	Ivermectin	Interferon beta	Lopinavir–ritonavir	Unique studies of any one of the six medications†
UK ISRCTN registry	0/0	0/0	0/1	0/1	0/0	0/1	0/2
Brazilian Clinical Trials Registry (ReBec)	0/0	0/0	0/0	0/0	0/0	0/0	0/0
US ClinicalTrials.gov	5/9	75/98	9/11	6/8	6/6	17/22	87/117
Clinical Trials Registry - India (CTRI)	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Australia and New Zealand Clinical Trial Registry (ANZCTR)	0/0	1/2	0/0	0/0	0/0	0/0	1/2
Chinese Clinical Trial Registry (ChiCTR)	0/0	1/2	0/0	1/1	2/3	7/8	11/13
EU Clinical Trials Register (EU-CTR)	0/0	6/7	2/2	1/1	0/0	1/1	8/9
Iranian Registry of Clinical Trials (IRCT)	1/1	9/14	3/3	1/3	9/10	3/6	23/33
The Netherlands Trial Register	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Swiss FOPH Human Research Projects	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Total	6/10	92/123	14/17	9/13	17/19	28/38	130/176

Showing the number of trials that specifically excluded pregnant women out of the total number of trials for each drug. *Prednisone, dexamethasone, hydrocortisone. †Unique studies refer to those evaluating only a single medication, not in combination with other treatments.

Table 2: **Registered COVID-19 treatment studies that exclude pregnant women**

Implications and call to action

Our search of clinical trial registries during two timepoints identified a substantial increase in the overall number of registered COVID-19 studies, including an increase in the number of COVID-19 studies in pregnant women. However, a large proportion of COVID-19 treatment studies identified from high-volume clinical trial registries specifically excluded pregnant women. Most studies that specifically mentioned pregnant women in the title were observational studies (cross-sectional, prospective cohort studies, and registries), designed to evaluate pregnant women with COVID-19 by focusing on maternal outcomes as a primary endpoint. Studies that included at least one of the six medications with known safety, or vitamins for which safety data show no or low risk of adverse birth outcomes, routinely excluded pregnant women. Reasons for these exclusions are not delineated on clinical trial registration sites but might be due to the perceived risks of use in pregnant women, exposure of the fetus or neonate to medication, and the historical exclusion of pregnant women from clinical trials. Combining the challenges of research with provision of medically complex or advanced patient care has led to automatic exclusion of pregnant women from treatment trials for other infectious conditions such as influenza and HIV.[18,19] The ongoing exclusion of pregnant women from therapeutic trials for COVID-19 will result in missed opportunities to identify efficacious and safe treatments to prevent adverse maternal, pregnancy, and birth outcomes. Consideration of the risks and benefits of inclusion should not preclude participation of pregnant women in clinical treatment trials.

The six commonly proposed drug regimens in registered treatment studies for COVID-19 have been previously used as treatments in pregnant women.[9–23] Low or non-significant safety concerns are associated with lopinavir–ritonavir, chloroquine, interferon beta, corticosteroids, and ivermectin, when administered to pregnant women.[9–11,13–17] The available data on the use of remdesivir in pregnant women remain scarce.[12] We found that a high proportion of treatment studies evaluating these medications and those evaluating vitamins excluded pregnant women.

The Council for International Organizations of Medical Sciences (CIOMS) states: "It is imperative to design clinical research for pregnant and breastfeeding women to learn about the currently unknown risks and potential individual benefits to them, as well as to the fetus or nursing infant".[20] Perhaps the most relevant to COVID-19, CIOMS prioritises "interventions for conditions that affect the general population and are reasonably expected to be used without adequate evidence during pregnancy (for example off-label use of medications)".[20] The CIOMS guidelines emphasise that pregnant women should not be universally considered as vulnerable for all clinical trials, despite the limited data on potential harms and benefits posed by treatments on infants and pregnant women. This point should be emphasised in order to limit the impact of processes exerted by other stakeholders such as research ethics committees. This advice aligns with other guidelines used worldwide such as the US Common Rule.[21] The Task Force on Research Specific to Pregnant Women and Lactating Women,[22] set up by the 21st Century Cures Act to provide guidance on the knowledge and research gaps pertaining to safe and effective therapies, provides clear recommendations on the need to include pregnant women in clinical research to increase the quantity, quality, and timeliness of research. Categorising women as members of a vulnerable group on the basis of pregnancy status alone, rather than as individuals who are pregnant at the time of the trial, limits their individual choice and access to potentially life-saving treatment.[23] Clinical trials could provide pregnant women with clear messages in lay language on the potential benefits and risks of exposure to candidate drugs for the treatment of COVID-19 and women could be given the right to make their own informed decision regarding participation.

The 2016 international ethical guidelines from CIOMS[20] provide a detailed description on how to include pregnant women in therapeutic research trials and maintain ethical principles and safe conditions. Based on these principles, COVID-19 treatment trials should clearly specify the reasons for exclusion of pregnant women beyond being considered a vulnerable population. WHO has called for the inclusion of pregnant women in research to evaluate the prevention and therapeutics for infection.[23,24] In a unified statement to the US Food and Drug Administration dated March 18, 2020,[11] the American Academy of Obstetrics and Gynecologists, the Society of Maternal Fetal Medicine, and 17 US medical societies called for the inclusion of pregnant women in clinical trials to evaluate treatment of COVID-19. Our findings confirm recent reports from clinical trials of COVID-19 from a single trial registry[6,7] and extend these findings by providing evidence of systematic exclusion of this population based on ten international trial registry sites with focus on therapeutics for pregnancy safety profiles.

Active intentional inclusion of pregnant women in clinical trials requires addressing the institutional, socioeconomic, and cultural barriers to women's participation in clinical trials. These and other barriers might be compounded for pregnant women who are from ethnic minority groups, who are young, less literate, do not have stable housing, and are migrants or living in humanitarian crisis.[25,26] Without an explicit and proactive effort to recruit and retain pregnant women in clinical trials, the understanding of treatment effects, dosing, side-effects, and potential benefits of COVID-19 treatment for pregnant women (who might be at increased risk of severe COVID-19 illness) will be limited. Inclusion of pregnant women is a matter of equity as much as efficacy and safety, and thus the numerous barriers to participation also need to be addressed.[25,26]

As the COVID-19 epidemic has progressed, the implications of issues related to biology, socioeconomic factors, and factors associated with sex-based differences are becoming clearer. Epidemiological trends vary across settings and depend on the access to testing. In some settings, more women are infected and in others, more men are infected and have a higher chance of dying.[27] Gender-based immune and hormone-related factors, presence of comorbidities, and differential behavioural factors (eg, handwashing, health-seeking, smoking) are intertwined with socioeconomic inequities influencing exposure risks and these factors contribute to worse COVID-19 outcomes among populations at higher risk.[28–31] Pregnant women intersect these gender-based risk strata and seem to face increased risk of severe disease and adverse outcomes.[1,2] Evidence is scarce and needs cautious interpretation with considerations of lower thresholds for providing intensive care to pregnant women. The interplay between risk factors such as obesity, diabetes, gestational diabetes, and socioeconomic determinants is unknown. Large evidence gaps further highlight the need for inclusion of pregnant women in trials, from a perspective of their need for efficacious treatment and also given the need to document the clinical course among these women, with and without treatment.

As knowledge of COVID-19 expands, so does the use of clinical algorithms to correctly triage and provide care for patients. To provide evidence-based care, which is inclusive of special health needs of pregnant women, collective knowledge generated from treatment and

natural history trials is urgently needed. In this context, inclusion of pregnant women in sufficient numbers is essential to stratify findings by disease prognosis, pregnancy outcomes, and safety concerns. Specific trials among only pregnant women might also be warranted. Agencies and other research entities such as universities and pharmaceutical companies, responsible for trials or sponsoring trials that exclude pregnant women without appropriate considerations related to safety concerns, need to carefully consider international ethical guidelines.[20] Inclusion of women in trials has been on the medical research agenda for more than 70 years, and the default exclusion of pregnant women during a pandemic is problematic in terms of global unity, general inclusiveness, and rights to participate and access research.

There are limitations to our study that should be considered. Given the increase in the number of registered clinical COVID-19 trials, a time lapse to publication could affect the cumulative numbers. Trials that are not registered in the 21 ICMJE and WHO-accepted clinical trial registries would have been missed in this analysis. We did not carry out cross-referencing to ensure exclusion of trials published in more than one registry. However, these limitations would most likely not result in substantial overcounting or undercounting.

Inclusion of pregnant women is crucial at the initial stage of research design for all clinical trials to provide access to research, equity, and transparent allocation processes for diagnostics, therapeutics, and vaccines. The non-inclusion of pregnant women should be justified. The same holds true for post-trial research on access and socioeconomic effects for all population subgroups. Most therapeutic clinical trials for COVID-19 in this analysis excluded pregnant women. Given the scarce data that are available, inclusion of pregnant women in therapeutic trials would help to understand the efficacy and potential side-effects of candidate treatments and contribute to the development of a research framework for improved understanding of pregnancy and perinatal-associated transmission of the SARS-CoV-2 virus. Considering the scale of this global epidemic and future epidemics, a public health obligation exists to include pregnant women in treatment and vaccine trials to adequately identify and implement appropriate prevention and care.

Contributors

MMT, LK, CK, AA, and AET wrote the initial draft of the manuscript. MMT, LK, CK, and NBB searched the clinical trials registry. All authors critically reviewed the manuscript, provided edits, and approved the final version.

Declaration of interests

We declare no competing interests.

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