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# Inclusion of pregnant women in clinical trials of COVID-19 therapies: what have we learned?

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Editor—The Intensive Care National Audit and Research Centre (ICNARC) report from more than 200 ICUs in England, Wales, and Northern Ireland showed that 2.8% of critically ill coronavirus disease 2019 (COVID-19) patients were currently pregnant or had been pregnant recently.[1] A systematic review of COVID-19 occurring during pregnancy ($n$=108) also reported 'severe maternal morbidity as a result of COVID-19'.[2] Observational studies describing infected pregnant women noted worsening hypoxaemia of clinical concern. Pulmonary infiltrates were described in 79% of the pregnant women with COVID-19 in the Wuhan cohort. The Italian cohort described pneumonia in 45% and ICU admission for 9% of pregnant women.[3] There have been also case reports of severe COVID-19 related cardiomyopathy, multiorgan failure, and deaths in pregnant women.[4,5]

As the *COVID-19* pandemic spreads globally, an increasing number of patients are receiving experimental treatments, some within the framework of RCTs and others as off-label or compassionate use. Off-label or compassionate drug treatment is provided in the face of a life-threatening disease with no proven treatment, that is clinical equipoise exists regarding treatment. The justifications for compassionate use of investigational drugs include both the contribution of data (efficacy, safety) for the benefit of future patients and possible benefits to the patient enrolled. The European Medical Agency (EMA) Guideline on Compassionate Use of Medicinal Products clearly states that compassionate use is performed primarily for therapeutic purposes. Thus off-label or compassionate use of medication is theoretically justified also in pregnant women.

Inclusion of pregnant women in clinical trials is more challenging. Until the 1990s, women were almost categorically excluded from participating in clinical trials solely for being pregnant or even of childbearing age. The disastrous experiences with diethylstilboestrol and thalidomide entrenched concerns regarding potential fetal harm. However, since the 1993 Council for International Organizations of Medical Sciences declared that exclusion of women from participation in clinical trials is unjust, this approach is no longer acceptable. The EMA and the US Institute of Medicine both endorse fair enrolment of any woman eligible for participation in clinical research. The US Food and Drug Administration states that 'investigational drugs may be used in pregnant women if adequate non-clinical studies (including studies on pregnant animals) have been completed and there is a prospect of direct benefit to the pregnant woman and/or fetus',[6] and the US National Institute of Health 'strongly encourages including pregnant women in clinical research in all circumstances in which their inclusion is scientifically valid and ethically permissible'.[7]

A recent editorial on drug use during pandemics stated that the 'tragedy of not discovering new therapies during an outbreak cannot be repeated'.[8] It also elaborated that 'By participating in an RCT, both patients and clinicians can benefit from the unique opportunity to directly contribute to the discovery of new therapies'. However, there is ongoing tension between the bioethical and research consensus that pregnant women should be included in clinical trials and actual implementation of such inclusion in a reality where one in four medical lawsuits may be an obstetric case. We studied the approach towards recruitment of pregnant women to interventional clinical trials for COVID-19. To this end, we searched the US National Library of Medicine registry (Clinicaltrial.gov) for studies including the terms '*COVID* OR *coronavirus* OR *SARS-COV-2*' up to April 15, 2020. Overall, 630 registered trials were identified. After applying a filter for study type ('interventional' trials), we identified 401 trials which were retrieved and screened. Duplicate trials, withdrawn or suspended trials, and trials unrelated to the COVID-19 pandemic were excluded. The data on the final 371 included trials are presented in Table 1. Among the 371 interventional trials registered, most declare pregnancy an exclusion criterion (251/371, 68%). This is most striking in trials investigating the use of drugs (235/310, 75.8%). Many trials altogether avoid mention of pregnant women in their inclusion/exclusion criteria (117/371, 31%). Several trials (including those on the use of chloroquine) suggest referring to 'known'

Table 1 Inclusion/exclusion of pregnant women in clinical trials on COVID-19. See text of paper for trial identification methods. *In 1/146 of the trials, investigators declared the intention to revise the protocol if more than three pregnant women are excluded according to exclusion criteria. †In 6/36 of the trials, exclusion criteria related to pregnancy were not applicable, because of populations composed by children, older adults or post-menopausal women. ECMO, extra-corporeal membrane oxygenation; $ECCO_2R$: extra-corporeal $CO_2$ removal; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

| Intervention | Trials, N | Purpose, N (%) | Participants, N | Pregnancy as exclusion criterion, N (%) | Specific gestational age as exclusion criterion, N (%) | Pregnant participants clearly defined as includable, N (%) | No specific information provided on pregnancy, N (%) |
|---|---|---|---|---|---|---|---|
| ***Drugs*** | | | | | | | |
| Chloroquine or hydroxychloroquine | 39 | 18/39 (46%) Prophylaxis 18/39 (46%) Treatment 3/38 (8%) Treatment and prophylaxis | 147 105 | 25/39 (64) | 0/38 (0) | 1/39 (3) | 13/39 (33) |
| Anti-SARS-CoV-2 plasma or human immunoglobulin | 19 | 1/19 (5%) Prophylaxis 18/19 (95%) Treatment | 1958 | 7/19 (37) | 0/19 (0) | 0/19 (0) | 12/19 (63) |
| Antimalarials and azithromycin | 18 | 1/18 (6%) Prophylaxis 17/18 (94%) Treatment | 8581 | 14/18 (78) | 0/18 (0) | 0/18 (0) | 4/18 (22) |
| Stem cells or derivatives | 18 | 18/18 (100%) Treatment | 607 | 16/18 (89) | 0/18 (0) | 0/18 (0) | 2/18 (11) |
| Corticosteroids | 10 | 10/10 (100%) Treatment | 1476 | 10/10 (100) | 0/11 (0) | 0/11 (0) | 0/11 (0) |
| Tocilizumab | 7 | 7/7 (100%) Treatment | 1556 | 5/7 (71) | 0/7 (0) | 0/7 (0) | 2/7 (29) |
| Lopinavir/ritonavir | 3 | 2/3 (67%) Prophylaxis 1/3 (33%) Treatment | 2260 | 1/3 (33) | 0/3 (0) | 0/3 (0) | 2/3 (67) |
| Remdesivir | 3 | 3/3 (100%) Treatment | 4440 | 1/3 (33) | 0/3 (0) | 0/3 (0) | 2/3 (77) |
| Vaccines | 10 | 10/10 (100%) Prophylaxis | 7157 | 10/10 (100) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Other drugs, combined treatments or multiple active comparators | 183 | 9/183 (5%) Prophylaxis 173/183 (94.5%) Treatment 1/183 (0.5%) Treatment and prophylaxis | 86 605 | 146/183 (80)* | 0/183 (0) | 0/183 (0) | 37/183 (20) |
| Overall | 310 | 41/310 (13%) Prophylaxis 265/310 (86%) Treatment 4/310 (1%) Treatment and prophylaxis | 261 745 | 235/310 (75.8) | 0/310 (0) | 1/310 (0.3) | 74/310 (23.9) |
| ***Non-pharmacological interventions*** | | | | | | | |
| ECMO, $ECCO_2R$, or CytoSorb therapy | 4 | 4/4 (100%) Treatment | 264 | 3/4 (75) | 0/4 (0) | 0/4 (0) | 1/4 (25) |
| Prone positioning or respiratory devices | 11 | 1/11 (9%) Prophylaxis 10/11 (91%) Treatment | 2497 | 4/11 (36) | 1/11 (9) | 0/11 (0) | 6/11 (55) |
| Other non-pharmacological interventions | 46 | 40/46 (87%) Other 6/46 (13%) Treatment | 47 889 | 9/46 (20) | 1/46 (2) | 0/46 (0) | 36/46 (78)† |
| Overall | 61 | 1/61 (1%) Prophylaxis 20/61 (33%) Treatment 40/61 (66%) Other | 50 650 | 16/61 (26) | 2/61 (3) | 0/61 (0) | 43/61 (71) |

contraindications to determine whether a pregnant patient may be included. This tactic effectively deflects all responsibility (and liability) to the clinician. Even trials investigating drugs with a relatively favourable safety profile (e.g. ascorbic acid), interventions or drugs already being used in pregnant women (e.g. extra-corporeal membrane oxygenation [ECMO], steroids) or those investigating low-risk non-pharmacological interventions (e.g. biological sampling for diagnostic/basic science purposes) exclude pregnant women. Most importantly, there is a global lack of differentiation between the risks at various developmental stages of pregnancy (Table 1).

A commonly cited excuse for non-inclusion of pregnant women in clinical trials is that pregnant women would be unwilling to participate. Adult women and their families should not be patronised because they are pregnant; they should be given the choice to participate. They may be willing to participate if the intervention is presented favourably, it is not available outside the trial, and when their contribution to scientific research is highlighted. As with any other patient, fulfilment of inclusion/exclusion criteria and informed consent are mandatory to safeguard the patient. On the one hand, experimental drugs are being used to treat pregnant women with COVID-19 anyway.[2,5] On the other hand, pregnant women with COVID-19 are dying, perhaps with no treatment attempted.

Declarations regarding the need to include pregnant women in clinical research and obvious concerns for the well-being of this population time and time again fail to translate to actual practice. What should we learn from this situation? Clarification of the approach to pregnant women should be mandatory during trial registration. Trials excluding pregnant women should be required to justify doing so. Referral to alternative sources with regard to risk should not be allowed. Industry should be expected to cover insurance for all patients, including pregnant women. In the specific context of the COVID-19 pandemic, experimental treatments offered to deteriorating patients within the context of a clinical trial in the hope that they may be of benefit should also be offered to pregnant women who deteriorate.

We could learn much from the management of pregnant women whose lives are at stake during this pandemic wave. This opportunity should be embraced lest we need to explain to our daughters why we have learned nothing of use to them during this pandemic wave when they are pregnant during the next pandemic.

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## Declarations of interest

The authors declare that they have no conflicts of interest.

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# COVID-19: novel pandemic, novel generation of medical students

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Editor—As the novel coronavirus disease 2019 (COVID-19) pandemic continues throughout the world, and while healthcare professionals fight frontline battles and systems leaders negotiate public health measures, the needs of medical students at various stages of training cannot be forgotten. Preclinical students, removed from in-person sessions, have transitioned to rapidly adapted online curricula and assessments. Final-year students' experiences differ widely by jurisdiction, ranging from early graduation and provisional registration to entering residency despite postponed board