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Safety of COVID-19 Vaccines During Pregnancy: A Short Communication

Rupa Lakshmi Vijayan M.D[1], Andrelle Senatus M.D[2], Swostik Pradhananga M.B.B.S[3], Chhaya Kamwal M.B.B.S[4], Madiha Zaidi M.D[5], Ali Sanaullah Choudhry M.B.B.S[6], Syed Adeel Hassan M.B.B.S[7], Marcos Sanchez Gonsalez MD PhD[7], Miguel A Diaz[7] and Efrain Garcia[7]

[1]*Kasturba Medical College, Mangalore, India.*

[2]*Pontificia Universidad Católica Madre y Maestra, Dominican Republic.*

[3]*Weifang Medical University, China.*

[4]*PramukhSwami Medical College, India.*

[5]*Dow International Medical College, Pakistan.*

[6]*Lahore Medical and Dental College, Pakistan.*

[7]*Larkin Health System, South Miami, FL, USA.*

***Correspondence:**

Rupa Lakshmi Vijayan, 7000 SW 62nd Ave, Suite 601, South Miami, FL 33143, Tel: +1 8143152522.

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ABSTRACT

Background: *COVID-19 a novel viral infection has taken many lives worldwide in a very short period. The first case of SARS CoV-2 was reported in December 2019 in Wuhan, China. The number of infected cases subsequently increased, leading to a pandemic declaration by WHO in March 2020. Several clinical trials are currently underway to produce effective vaccines to fight against this virus; however, a few of them include pregnant women; leaving us to question the efficacy of the vaccine. Pregnant women are immune-compromised and considered a high-risk group for SARS-CoV-2 and therefore experience maternal and fetal consequences. It seems to be essential to incorporate them in these clinical trials. This study was led to understand the factors preventing pregnant women from participating in such trials and to assess the safety of potential COVID-19 vaccines during pregnancy.*

Methods: *This study was conducted using the available literature was done in May 31 2021 by searching databases: PubMed, WHO, clinicaltrials.gov and Google Scholar. Keywords such as COVID-19 Vaccine, COVID Vaccine Clinical Trials, COVID prevention in pregnancy, and their combinations were used. We included patients with a positive COVID-19 test and excluded systematic reviews on COVID-19 negative pregnant patients. The search was comprehensive according to the cross-checking of reference lists from the articles retrieved.*

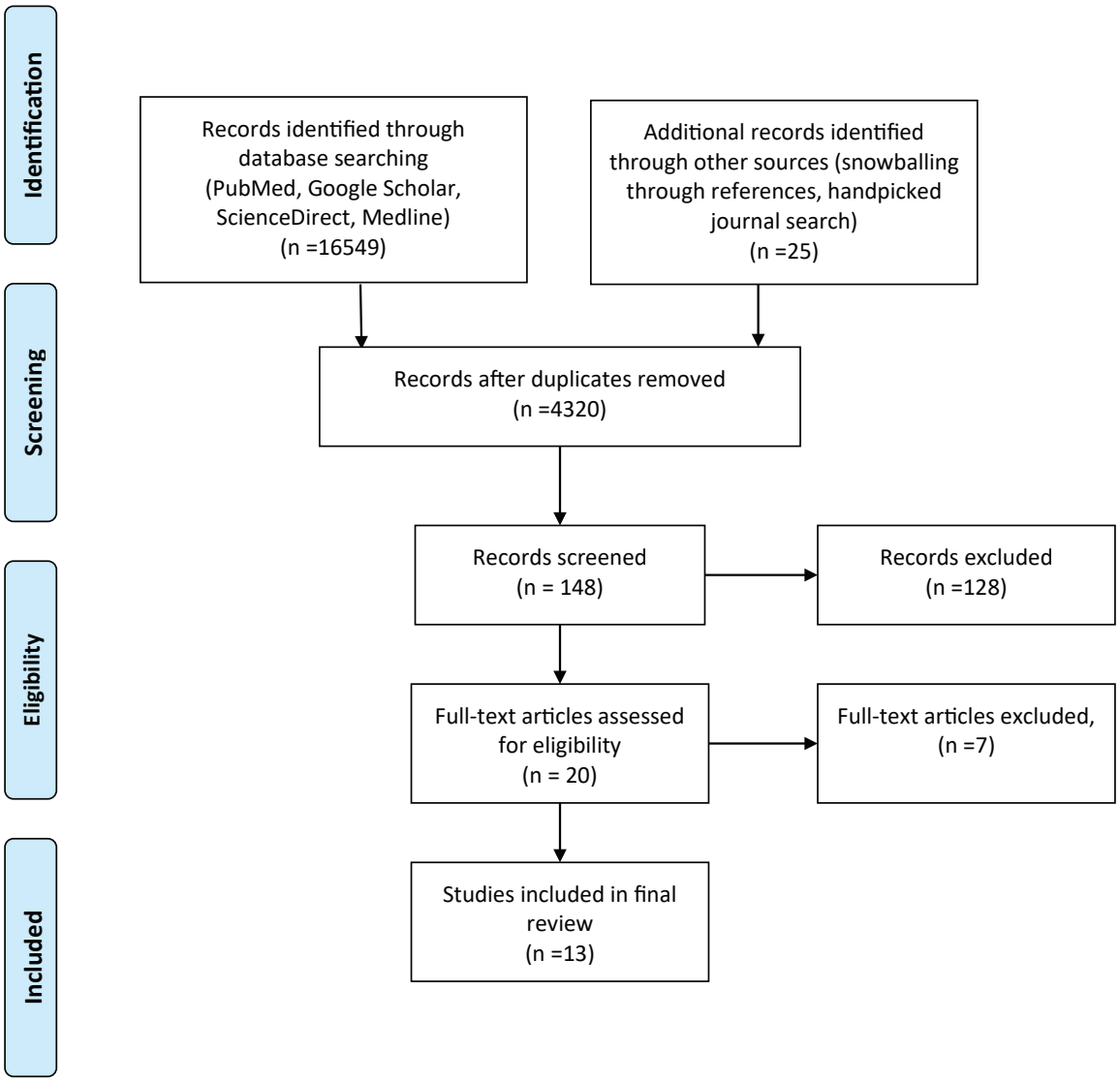
Results: *Our search results led to 4320 studies after removing duplicates; title and abstract screening were done for 20 studies. We also performed the manual search to look for related articles and 13 studies were included in the final analysis.*

Conclusion: *To enable and ameliorate the participation of pregnant and lactating women for the development of vaccines against COVID-19, we are left with a question pertaining to the short as well as long term prognosis of COVID-19 in pregnant women, their fetus, and also the infants. With such approach we can establish and enable a proper guidance and framework to emphasize the inclusion of pregnant women in the development of future vaccine.*

Keywords
COVID-19 Vaccine, COVID Vaccine Clinical Trials, COVID prevention in pregnancy.

Introduction
In a very short period Coronavirus Disease (2019) (COVID-19), a novel viral infection has taken many lives worldwide. The first case of SARS CoV-2 was reported in December 2019 in Wuhan, China. The number of infected cases subsequently increased, leading to a pandemic declaration by the World Health Organization (WHO) in March 2020. Several clinical trials are currently underway, with numerous completed, to produce effective vaccines. However, the effectivity among young females, particularly pregnant women has been questioned, leading to questions about vaccine efficacy and side effects [1]. It is essential to incorporate all groups in global vaccine clinical trials across all gender and racial groups. We performed an extensive database search to review and assess previously published or currently underway studies addressing COVID-19 vaccine trials. This communication aims to understand the factors preventing pregnant women from participating in such trials and to assess the safety of COVID-19 vaccines during pregnancy. Pregnant women are a high-risk group for SARS CoV-2 and are at risk of experiencing maternal and fetal consequences during and post pregnancy.

Methods
The literature review was done from December 2019 through May 31st, 2021 by searching 4 databases: PubMed, WHO, clinicaltrials.gov and Google Scholar. We used keywords including COVID-19 Vaccine, COVID Vaccine Clinical Trials, COVID prevention in pregnancy, and their combinations. We included patients with a positive COVID-19 test and excluded systematic reviews consisting of COVID-19 negative pregnant patients. The search was comprehensive with an umbrella method employed; a cross-checking of reference lists was conducted from the articles retrieved.



Flow chart 1: PRISMA flow chart for studies included.

The following inclusion criteria were fulfilled for the included studies:

1. Full text, peer-reviewed articles (Meta-analysis, case-studies and case series, systematic reviews, randomized controlled trials).
2. Articles in English.

Articles that lacked in patient data, those limited to specific comorbidities, and organ dysfunctions were excluded to avoid selection bias. After exclusion, 9 articles were selected for the final review. Selected articles were independently reviewed by two authors. All disagreements were resolved with a discussion between the two authors, or with input from a third independent reviewer and mutually agreed upon by the authors.

Our review search included studies from various countries across the globe. Endnote X9 was used to remove duplicated. Ethical approval was not required for this study as already available databases were used for obtaining data and patients were not directly involved.

The study was conducted to understand factors preventing pregnant women from participating in vaccine clinical trials, thus leading to skewed vaccine efficacy.

Results

Of the 4320 articles retrieved, data was tabulated for thirteen articles reviewed (Table 1). Possible factors preventing pregnant women from being included in vaccine trials were extracted. Several clinical trials are currently underway while others are complete to produce effective vaccines to fight against COVID-19. However, only a few of them included pregnant women during the initial phases, leading to questions about the efficacy of the vaccine (Table 1).

Discussion

Pregnancy in itself is an immunocompromised state that places pregnant women at a higher risk of acquiring COVID-19 and causes them to face fetal and maternal consequences. According to data provided by Disease Control and prevention of the US Centers, amongst the total hospitalized cases of COVID-19 from 1st March

Table 1: Characteristics of included studies.

Citation #	Title	Authors	Type of literature	Year of publication	Summary
1	Why are pregnant women susceptible to COVID-19? An immunological viewpoint	Hong Liu et al.	Review	2020	Attributed increased risk of COVID-19 infection to changes of immune system during pregnancy and cytokine-storm characteristic of COVID-19
2	Risks associated with viral infections during pregnancy	Karen Racicot and Gil Mor	Review	2017	Discussed effects of maternal, placental, and fetal viral infection to pregnancy outcomes including maternal health and fetal development
3	Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome	Shell F Wong et al.	Multi-center observational	2003	Summary of adverse pregnancy outcomes during SARS epidemic
4	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Chaolin Huang et al.	Case cohort	2020	Summarized epidemiology and sequelae of COVID-19 infection
5	Is COVID-19 receiving ADE from other coronaviruses?	Jason A. Tetro		2020	Introduced the possible association between previous exposure to other forms of coronavirus and antibody-dependent enhancement during COVID-19 infection
6	The unique immunological and microbial aspects of pregnancy	Gil Mor et al.	Review	2017	Discussed the dynamics of immune responses during pregnancy
7	Coronavirus disease 2019 (COVID-19) pandemic and pregnancy	Dashraath et al.	Review	2020	Review of COVID-19 infection in pregnancy woman, and assessed the use of chloroquine as possible treatment
8	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	Chen et al.	Review	2020	Investigated intrauterine transmission of COVID-19 by analyzing perinatal and neonatal outcomes
9	Effects of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcomes: a systematic review	Juan et al.	Review	2020	Assessed perinatal and neonatal outcomes of COVID-19 infection in pregnancy women
10	Coronavirus disease 2019 (COVID-19) and pregnancy: a systematic review	Yang et al.	Review	2020	Reported the similarities of the clinical characteristics of pregnant women and non-pregnant population,
11	Clinical Presentation and Outcomes of Pregnant Women with Coronavirus Disease 2019: A Systematic Review and Meta-analysis	Matar et al.	Review & Meta-analysis	2020	Reported increased rate of preterm birth and cesarean delivery in pregnant COVID-19 patients
12	Pregnancy and Perinatal Outcomes of Women with Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis	Liu et al.	Original research	2020	Attempted to provide initial evidence for treatment guidance of pregnancy women with COVID-19 pneumonia by reporting early findings of chest CT and lab abnormalities
13	Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis	Mascio et al.	Review & Meta-analysis	2020	Reported increased risk of adverse perinatal outcomes in pregnant women with COVID-19 infection

to 22nd August, 2020 in women at reproductive-age (15-19 years), one quarter were pregnant. Among the hospitalized women in this group, compared to non-pregnant women, pregnant women were more likely to need mechanical ventilation [2]. Therefore, it is vital for this high-risk group to be included in vaccine related clinical trials, given that the individual consents to inclusion and understands any potential side effects [3]. Limited data is available on clinical trials of COVID-19 vaccines in pregnant women due to extensive data on exposure, but inadequate data is published for evidence-based care [4]. A common assumption is the unwillingness of pregnant women to participate due to the fear of having to experience adverse effects such as vomiting, fever, seizures and body aches [5].

For example, out of 1486 COVID-19 investigations, only 28 included pregnant women and of those only four underwent pharmacological interventions. Thus, this leaves pregnant women with a 0.3% chance of access to participate in clinical trials for COVID-19 [6]. This again emphasizes the importance of the participation of pregnant women in vaccine trials.

Since its appearance, COVID-19 has caused a notable healthcare burden around the world. Despite it being a major risk in immunocompromised individuals, pregnant women are not included in the clinical trials against COVID-19 [4]. The data collected through this review supports that despite many ongoing and completed trials related to COVID-19 vaccines, there are very few accepting the participation of pregnant women. To ameliorate the inclusion of pregnant women in clinical trials, clarification and/or education of the trials is essential [7]. This implies that we are missing out on the opportunity to collect valuable data that could later be very beneficial when it comes time to make decisions about the health of pregnant women at risk of COVID-19 [8]. Since vaccine prevention is essential to curb the effects of COVID-19, there may not be robust data to prove safety of vaccines in pregnant women.

If data for safety and toxicology are provided in animal model preclinically, there is no ethical reason to exclude pregnant women to participate clinical trials for COVID-19 vaccines except for the live virus vaccines. [9] It is recommended that the inclusion of pregnant women be evaluated under current ethical rules aimed at protecting pregnant women and the fetus, to adapt trials to her condition, to allow them to make informed decisions [10]. Appropriate consideration of inclusion and exclusion criteria to minimize the obstetric risk and also increase the inclusion of this population is essential. Determining population of choice (healthy or at risk), analyzing and interpreting if the rates of events in obstetric and neonatal population potentially increases due to vaccination can aid in inclusion and exclusion criteria [11].

Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) group has been currently focusing on COVID-19 vaccination in pregnant women [12]. However, it still has to encounter many barriers in developing countries. The challenges for vaccine delivery in developing countries is not only for who gets the vaccine but there are bigger barriers along the way. Developing countries cannot afford to invest the cost required for the development of the vaccine which is a costly affair. It has been noted that 39 billion US$ has been committed for the development of vaccine globally [13]. The procurement, vaccine allocation, inequities in distribution and its uptake are the major challenges developing countries are facing during the COVID pandemic. [14] The countries lacking resources also has to deal with factors like the lack of trained logistical personnel, difficulty to provide a perfect environment for the storage and transportation of vaccines and lastly the vaccine hesitancy amongst the people. [14].

One of the limitations of our study is that we have only included studies completed all across the world. The ongoing studies weren't discussed. Another one noted was no interventions were done and no outcome parameters were fixed. This study was done as a mode to be an eye opener to the challenges of the vaccinations and how some considerations can be brought about.

Conclusion

To enable and ameliorate the participation of pregnant and lactating women for the development of vaccines against COVID-19, three key questions should be considered: what is the prognosis of COVID-19 in pregnant women, their fetus, and also the infants in short as well as in long term basis (including all ethnic groups); Are pregnant women willing to be vaccinated against COVID-19 and participate in trials on COVID-19; and lastly which pregnant women are suitable for COVID-19 vaccines. Moreover, the focus should be to educate pregnant women on clinical trials and should be included early in such trials. With such approach we can establish and enable a proper guidance and framework to emphasize the inclusion of pregnant women in the development of future vaccine.

Author Contributions

Authors RV, AS, SW, CK, SW and MZ contributed equally in defining the study outline and manuscript writing. Data review and collection were done by CK, AS, MZ, AS, ZS. Manuscript writing, and final checks were done by RV, AS, ZS. The critical review is done by RV, AS and SW. ZS and RV are the guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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