EDITORIAL

Pregnancy and Covid vaccine trials: Gender justice compromised

SAROJINI NADIMPALLY

Keywords: *Covid-19, vaccination, vaccination for pregnant women, clinical trials*

On June 11, 2021, a pregnant woman approached the Delhi High Court seeking vaccination for pregnant women on a priority basis. The petitioner also sought directions to the Union government for setting up of separate vaccination centres for pregnant women who are at high risk, and the creation of a registry for monitoring their medical condition post vaccination (1). The case was a pivotal point in the history of Covid-19 vaccine rollouts in India, because it demanded a clear communication from the Union Government for vaccination of pregnant women. The Union Government's counsel informed the Court that while the Government would consider the May 28 recommendations of the National Technical Advisory Group on Immunisation (NTAGI) in favour of vaccinations for all pregnant women based on a risk vs benefit assessment, no timeline was in place for this yet (2). Based on this statement, the Court disposed of the petition, passing no further orders.

The debate on Covid-19 vaccinations for pregnant women in India is not a recent phenomenon. Just before the vaccine rollouts started in January, the Ministry of Health and Family Welfare (MoHFW) issued an advisory that pregnant and lactating women should not be vaccinated as they had not been part of any Covid-19 vaccine trials, and no data were available that proved vaccines to be safe in pregnancy (3). The Delhi Commission for Protection of Child Rights (DCPCR) had moved the Supreme Court challenging this advisory as based on unreasonable classification, arbitrary, and violative of the right to life of a class of women, and called for the inclusion of pregnant and lactating women in vaccination drives, as also their categorisation as a high-risk group. The petition noted that this policy should have changed with "later evidence, medical research and studies all demonstrating the need to vaccinate pregnant and lactating women, to protect them from COVID-19" (4). Recently, MoHFW, in an Operational Guidance dated July 2, 2021, has recommended Covid-19 vaccination for pregnant women, but is ambiguous about the timelines (5), especially amidst the concerns raised by medical experts about its safety if administered during the first trimester (6).

Concerns about Covid-19 vaccination for pregnant women and lactating mothers are actually not limited to India alone. In fact, the exclusion of pregnant and lactating women from biomedical research, including clinical trials, is a long-standing global problem. And, it is a glaring reflection of the gender blindness implicit in clinical research and health policy making.

Covid-19 vaccines and pregnancy: recent global developments

In January, the World Health Organization (WHO) recommended "the use of the mRNA-1273 vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks." It further said that pregnant women should be provided detailed information to help them make this assessment. But, the WHO guidance itself did not quite recommend vaccinations for "all" pregnant women, and left it rather open-ended (7). In April, the UK Joint Committee on Vaccination and Immunization (JCVI) advised that pregnant women be offered Covid-19-vaccines along with the rest of the population, in line with the age group roll out. JCVI further noted that they should preferably be offered the Pfizer-BioNTech or Moderna vaccines (8). In June, the US Centre for Disease Control and Prevention (CDC) also said that vaccines should be available to pregnant people (9). Italy, France, Brazil, Spain, Mexico, and the Netherlands have also issued similar guidelines (10).

While there was not enough data from vaccine trials for these countries to arrive at this decision, they seem to have relied

Author: **Sarojini Nadimpally** (sarojnipr@gmail.com), Public health researcher and Founder, Sama Resource Group for Women & Health, J-291, First Floor, Saket, New Delhi-110 017, INDIA.

To cite: Nadimpally S. Pregnancy and Covid vaccine trials: Gender justice compromised. *Indian J Med Ethics.* 2021 Jul-Sep; 6(3) NS: 189-192. DOI: 10.20529/IJME.2021.051.

largely on a risk vs benefit formula then. But now, emerging research is providing better and more reliable data.

Countries are also attempting to track and monitor adverse implications after vaccinating pregnant women, such as the US CDC's v-safe registry for women vaccinated in their periconception period (ie within 30 days from their last menstrual period through 14 days after), and who are 18 years of age or older during pregnancy (11).

A safety study, published by Shimabukuro et al in the *New England Journal of Medicine (NEJM)* in April, relies on several vaccine surveillance systems from December 2020 to February 2021, to assess the safety of the mRNA Covid-19 vaccines in over 35,000 pregnant women. They found no increased risks during pregnancy, or birth complications, or identifiable risks because of the vaccine (12).

Additionally, several studies have demonstrated the effects of Covid-19 on pregnant women. Among these:

- The *Lancet* review of 40 published studies from 17 countries, on collateral impact of the pandemic on pregnancy outcomes, found increased chances of stillbirth and maternal death in those infected (13).
- A 2021 study by the University of Washington on 2,100 Covid-19-positive pregnant women, found they were 20 times more likely to die than those who did not contract the virus (14).
- A cohort study, by Villar et al, of 2,130 pregnant women in 18 countries had similar findings (15).

Given the urgent need and demand for such data, some attempts are being made by vaccine manufacturers to initiate clinical research on pregnant women. The Pfizer/BioNTech trial in the US hopes to recruit women from 24 to 34 weeks of pregnancy (16). Johnson & Johnson, after being mired in reports of its vaccine causing blood clots, also has plans for a trial in pregnant women (17).

Available data on Covid-19 effects on pregnant women in India

The harsh national lockdown in India created an upheaval in almost all aspects of people's lives and livelihoods. Researchers had warned that Indian policymakers had no plans whatsoever for the estimated 70,000 women due to give birth each day (18). Data shared by the MoHFW also illustrates that the government "failed to keep track of almost 40 lakh pregnant women and 47.5 lakh new-born children during the nationwide lockdown imposed in late March" (19).

Several other studies corroborated the vulnerability of pregnant women to the virus: A study by ICMR in June 2021, which compared pregnant and postpartum women during the first and second waves of the pandemic, found that symptomatic cases were higher during the second wave (28.7 per cent) as compared to 14.2 per cent during the first wave of the pandemic (20). The study also found that the case fatality rate among pregnant and postpartum women during the second wave (5.7%) was significantly higher than in the first wave (0.7%), with maternal deaths being mainly due to "pneumonia and respiratory failure" (21). The ICMR study recommended that pregnant and lactating women should be vaccinated against Covid-19. Further, the Federation of Obstetric and Gynaecological Societies of India (FOGSI), in a statement said, "The very real benefits of vaccinating pregnant and lactating women seem to far outweigh any theoretical and remote risks of vaccination." FOGSI clearly underlines the vital importance of vaccination of pregnant and breastfeeding women against Covid-19 with preparations to manage adverse events (22).

Clinical research and pregnancy: Ethical frameworks

Prescribing of thalidomide for pregnant women in the late 1950s and early 1960s caused deformities in thousands of infants. This had raised many concerns and ethical issues. Stringent rules and regulations were put in place post the thalidomide tragedy due to potential risks to pregnant women and the developing foetus (23). Macklin notes that the US FDA reversed this policy in 1993 on the grounds that the exclusion of the majority of women from most clinical trials had resulted in a lack of scientific data on the risks and benefits to women of drugs that had been studied exclusively in men (24).

Ethics guidelines also responded to this unscientific exclusion of pregnant and lactating women. For instance, the Council for International Organizations of Medical Sciences (CIOMS) guidelines of 2016 (25) recommended the inclusion of pregnant and breastfeeding women "only after careful consideration of the best available data from preclinical research in pregnant animal models, research in nonpregnant women, retrospective observational studies, and pregnancy registries." CIOMs emphasises that researchers and research ethics committees "must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies, their foetuses, and their future offspring".

Cautioning about ethical issues in clinical trials on pregnant women, the ICMR revised ethical guidelines of 2017 (26) state that

they "must only take place when the object of the research is to obtain new knowledge directly relevant to the foetus, the pregnancy or lactation." Yet, the ICMR National Guidelines of April, 2020 for biomedical research ethics review committees during the pandemic fails to mention anything about "pregnant" or "lactating" women leaving a lot of scope for ambiguity (27).

A study of Phase III trials of drugs from the Clinical Trial Registry of India (CTRI) by Sama indicated that there are very few pharmaceutical company-sponsored drug intervention studies in areas other than pregnancy-associated conditions; that Phase III trials with only women were on breast cancer, cervical cancer, female infertility, post-menopausal osteoporosis, bacterial vaginosis, uterine myomas, but alarmingly poor in case of inclusion of pregnant women (28). Another study by Karekar et al, which reviewed CTRI registered studies, suggested that less than two per cent of all the studies involved pregnant women and only one per cent were testing pharmacological interventions (29). These studies clearly indicate an exclusion or underrepresentation of pregnant women in clinical research.

Pregnant women have also been excluded from vaccine trials. Except for the 2009 H1N1 influenza vaccines, pertussis vaccines, and those for maternal immunisation, pregnant women have rarely been considered for trials (30). For instance, the Ebola vaccine trials excluded pregnant women in 2015-2016 despite clear data indicating the particularly devastating impact of Ebola on this group (31). This exclusion from research and the generation of evidence then leads to exclusion from vaccine delivery programmes.

According to Dr Vineeta Bal, a scientist at the Indian Institute of Science Education and Research (IISER), carrying out clinical trials for drugs on pregnant women is not easy as it requires prediction of what tissue, organ, or type of cells can be affected as an off-target effect of the drug. But, vaccines have fewer, if any, off-target effects. "During pregnancy, there are very focused and localised changes in the uterus and the placenta which help in prevention of the foetal rejection. While some spill over from the localised effects is expected and seen at the population level, the consequences are not due to a radical systemic [ie outside of the uterus in this case] effect. The changes in the immune system of the pregnant woman hardly ever affect her ability to respond to and tackle routine, minor infections. Most of them do not even progress to illness or disease. Depending upon specific infectious agents, the developing foetus may or may not be affected." Dr. Bal further points out, "Randomised trials of vaccines on pregnant women are very few. However, based on safety concerns, vaccinologists and vaccine developers play safe – choose the most healthy population for initial testing [18-45, non-pregnant healthy individuals], then expand the net. For Covid-19 vaccines, this is being done. It is important to make a distinction between drug trials and vaccine trials" (32).

Conclusion

Given the scale of the Covid-19 pandemic and to avoid further human costs, a public health obligation exists to include pregnant women in therapeutic and vaccine trials for appropriate prevention and care (33). For pharmaceutical companies, researching the effect of drugs or vaccines on pregnant women present considerable risks and little reward. It requires extra expertise and cost, and poses potential liability problems. However, the exclusion of pregnant and lactating women from clinical trials, and subsequently from policymaking is not just a result of logistical limitations, it is indicative of systemic gender blindness among the scientific community and inadequate attention paid to ethics and reproductive rights. After all, the challenges neither were, nor are, insurmountable.

Acknowledgements: *The author would like to thank Sweta Dash for her inputs, information and edits, Dr Subha Sri and Dr Vineeta Bal for going through the draft, and Neelanjana Das for all her support with material collection*

References

1. India Legal. No time-bound direction can be given to Govt for including pregnant women in COVID-19 vaccination: Delhi HC. *India Legallive.com.* 2021 Jun 12 [cited 2021 June 15], Available from: https://www.indialegallive.com/constitutional-law-news/courts-news/no-time-bound-direction-can-be-given-to-govt-for-including-pregnant-women-in-COVID-19-vaccination-delhi-hc/
2. NDTV. Centre's stand on COVID-19 vaccine for pregnant women as matter reaches court. 2021 Jun12 [cited 2021 Jun 15]. *NDTV.com.* Available from: https://www.ndtv.com/india-news/centres-stand-on-COVID-19-19-vaccine-for-pregnant-women-as-matter-reaches-court-2462120
3. Additional Secretary, Union Ministry of Health and Family Welfare. Letter No. T-22020/14/2020-IMM. Precautions and Contraindications for COVID-19-19 vaccination. 2021 Jan 14 [cited 2021 Jun 15]. Available from: https://www.mohfw.gov.in/pdf/LetterfromAddlSecyMoHFWregContraindicationsandFactsheetforCOVID-1919vaccines.PDF
4. Supreme Court of India. Delhi Commission for Protection of Child Rights vs. Union of India and Anr. WP No -- of 2021. 2021 May 18 [cited 2021 June 15]. Available from: https://www.livelaw.in/pdf_upload/wp5722021-1-pages-1-32-393760.pdf
5. Ministry of Health and Family Welfare. Government of India. Operational Guidance for COVID-19 Vaccination of Pregnant Women. New Delhi: MoHFW; 2021 Jul 2 [cited 2021 Jul 6]. Available from: https://cdnbbsr.s3waas.gov.in/s3850af92f8d9903e7a4e0559a98ecc857/uploads/2021/07/2021070559.pdf
6. Rao SR. Avoid vax in first trimester of pregnancy, say experts. *Times of India.* 2021 Jun 30[cited 2021 Jul 2]. Available from https://timesofindia.indiatimes.com/city/bengaluru/avoid-vax-in-first-trimester-of-pregnancy-say-experts/articleshow/83976614.cms
7. World Health Organization. Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19. Geneva: WHO; 2021 Jan 25, updated Jun 15[cited 2021 Jun 28]. Available from: file:///D:/Admin/Downloads/WHO-2019-nCoV-vaccines-SAGE-recommendationm-RNA-1273-2021.2-eng.pdf
8. Public Health England. Press release. JCVI issues new advice on COVID-19 vaccination for pregnant women. 2021 Apr 16[cited 2021 June 15]. Available from: https://www.gov.uk/government/news/jcvi-issues-new-advice-on-covid-19-vaccination-for-pregnant-women

9. Centres for Disease Control and Prevention. COVID-19 Vaccines While Pregnant or Breastfeeding. U.S. Department of Health & Human Services. 2021 Jun 16 [cited 2021 Jun 28]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html
10. Yadavar S. Why India cannot delay vaccinating pregnant women against Covid-19. *India spend.com.* 2021 Jun 9[cited 2021 Jun 15]. Available from: https://www.indiaspend.com/covid-19/why-india-cannot-delay-vaccinating-pregnant-women-against-covid-19-754076
11. Centres for Disease Control and Prevention, V-safe COVID-19 Vaccine Pregnancy Registry. Atlanta: CDC; Updated 2021 Jun 28[cited 2021 Jul 2]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html
12. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med.* 2021 Apr 21[cited 2021 Jun 15]. Epub ahead of print. DOI: 10.1056/nejmoa2104983
13. Chmielewska B, Barratt I, Townsend R, Kalafat E, van der Meulen J, Gurol-Urganci I, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health*. 2021 Jun; 9(6): e759–e772. Epub 2021 Mar 31. DOI:10.1016/S2214-109X(21)00079-6.
14. University of Washington School of Medicine/UW Medicine. Pregnant women with COVID-19 face high mortality rate: Worldwide study also found that 11 percent of babies contracted the novel coronavirus from their mothers. *ScienceDaily.* 2021 Apr 22[cited 2021 Jun 25]. Available from: www.sciencedaily.com/releases/2021/04/210422181856.htm
15. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection. The INTERCOVID Multinational Cohort Study. *JAMA Pediatr.* 2021 Apr 22[cited 2021 Jun 15]. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2779182
16. Pfizer Press Release. Pfizer and BioNTech commence global clinical trial to evaluate COVID-19 vaccine in pregnant women. 2021 Feb 18[cited 2021 Jun 15]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate%2083.|
17. J&J website. Johnson & Johnson Expands Phase 2a Clinical Trial of COVID-19 Vaccine Candidate to Include Adolescents. 2021 Apr 2[cited 2021 May 30]. Available from: https://www.jnj.com/johnson-johnson-expands-phase-2a-clinical-trial-of-COVID-19-19-vaccine-candidate-to-include-adolescents
18. Dasgupta J. Maternal health matters. *The Hindu.* 2020 Jun 18[cited 2021 Jun 15]. Available from https://www.thehindu.com/opinion/op-ed/maternal-health-matters/article31854774.ece
19. Shahina KK. Missing in Lockdown: Lakhs of pregnant women and newborns. *The Federal*. 2020 Jul 1[cited 2021 Jun 15]. Available from: https://thefederal.com/health/missing-in-lockdown-lakhs-of-pregnant-women-and-newborns/
20. The Week. Pregnant and lactating women should be vaccinated against COVID-19, says ICMR study. 2021 Jun 16 [cited 2021 Jun 17]. Available from: https://www.theweek.in/news/india/2021/06/16/pregnant-and-lactating-women-should-be-vaccinated-against-covid-19-says-icmr-study.html
21. India.com News Desk. Pregnant, postpartum women more severely affected during second Covid wave than first: ICMR study. 2021 Jun 16 [cited 2021 Jun 17]. *India.com.* Available from: https://www.india.com/news/india/pregnant-postpartum-women-more-severely-affected-during-second-COVID-19-wave-than-first-icmr-study-4745615/
22. Federation of Obstetric and Gynaecological Societies of India. Position statement, COVID-19 vaccination for pregnant & breastfeeding women. FOGSI website;2021 [cited 2021 Jun 15]. Available from: https://www.fogsi.org/wp-content/uploads/covid19/fogsi-statement-on-covid-vaccination-in-pregnancy-and-bf.pdf
23. Kim JH, Scialli AR. Thalidomide: The tragedy of birth defects and the effective treatment of disease. *Toxicol Sci.* 2011 Jul;122(1):1–6. Doi: https://doi.org/10.1093/toxsci/kfr088
24. Macklin R. Enrolling pregnant women in biomedical research. *Lancet*. 2010 Feb 20;375(9715);P632-3. Doi: https://doi.org/10.1016/S0140-6736(10)60257-7
25. Council for International Organizations of Medical Sciences (CIOMS) & WHO. (2016). International Ethical Guidelines for Health-related Research Involving Humans. Fourth Edition. Geneva: CIOMS/WHO; 2016[cited 2021 Jun 15]. Available from: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf
26. Indian Council of Medical Research. (2017). National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. New Delhi: ICMR; 2017[cited 2021 Jun 15]. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf
27. Indian Council of Medical Research (2020). National Guidelines for Ethics Committees Reviewing Biomedical & Health Research during COVID-19 Pandemic. New Delhi: ICMR: 2020[cited 2021 Jun 15]. Available from: https://www.icmr.gov.in/pdf/COVID-19/techdoc/EC_Guidance_COVID-1919_06052020.pdf
28. SAMA Resource Group for Women and Health. Circle of Medicines: Development to Access. 2016[cited 2021 Jun 15]. Available from: http://www.samawomenshealth.in/circle-of-medicinesdevelopment-to-access/ page no 47
29. Karekar SR, Pooja SG, Marathe PA, A review of clinical studies involving pregnant women registered in the Clinical Trials Registry of India. *Perspect Clin Res.* 2020 Jan-Mar [cited 2021 Jun 15];11(1): 8–12. Available from: https://www.picronline.org/article.asp?issn=2229-3485;year=2020;volume=11;issue=1;spage=8;epage=12;aulast=Karekar
30. Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, et al. The need for inclusion of pregnant women in COVID-19 vaccine trials.*Vaccine.* 2021 Feb 5; 39(6): 868–70. Doi: 10.1016/j.vaccine.2020.12.074.
31. Schwartz DA. 2018, Clinical trials and administration of Zika virus vaccine in pregnant women: Lessons (that should have been) learned from excluding immunization with the Ebola vaccine during pregnancy and lactation, *Vaccines* (Basel). 2018 Dec 4[cited 2021 Jun 15]; 6(4): 81. doi: 10.3390/vaccines6040081. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313913/
32. Bal V. (Visiting Faculty, Indian Institute of Science education and Research, Pune) Personal communication to the author in emails dated June 13 &24, 2021. Cited with permission.
33. Taylor MM, Kobeissi L, Kim C, Amin A, Thorson AE, Bellare NB, et al 2020. Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action, *Lancet Glob Health.* 2020 Dec 16[cited 2021 Jun 15]. Doi: https://doi.org/10.1016/S2214-109X(20)30484-8