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COVID-19 and Impact on Pregnant Women

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Coronavirus disease 2019 or COVID-19 is the viral infection pandemic that has spread all over the world. Although all people are prone to the infection almost equally, some of them after catching infection may produce more severe clinical symptoms. These are called vulnerable groups and pregnant women are one of them.

Summary: Pregnant women were thought to be not affected by the COVID-19 pandemic in the first wave, but recent observations from the second wave which harbors the mutated versions of novel coronavirus, said to be more virulent and lethal, suggests that pregnant women are not only vulnerable to catching the infection but they can show severe clinical outcomes. Also case fatalities, preterm births are also high among COVID-19 infected pregnant women.

Conclusion: More vaccination among pregnant women is needed to safeguard them as the severity of the symptoms is lowered post-vaccination. To solidify more results, more comprehensive and frequent studies are needed so that correlation can be established.

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1. INTRODUCTION

Coronavirus disease 2019 or COVID-19 is an extremely contagious infection caused by a novel coronavirus which is a member of coronaviridae family. Coronaviruses are not new to the world and has caused previous outbreaks of severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome. In December 2019 in Wuhan city of Hubei province in China, an unknown flu was detected which killed many people in the wet market. Then it was identified as COVID-19. The spike proteins which gave the specific shape like crown is the reason behind the name coronavirus. Since then spread through all over the world it affecting billions of people directly as well as indirectly. As of April 25, 2021, 146,615,147 infection cases has been reported and 3,102,588 case fatalities due to COVID-19 related complications been reported has from across 220 countries and regions of the world [1]. It was declared as pandemic on March 11, 2020, after assessing its spread and extent [2,3]. The declaration was unique in past hundred years as no other disease outbreak was so lethal and had extent as huge as COVID-19. United States of America, India, Brazil, Russia, Turkey and France have more than half COVID-19 infections and deaths attached due to its complications [4]. Although all the people are prone to the infection, certain section of the population is more vulnerable to the infection and complications attached to COVID-19 [5]. These are high-risk category people which includes elderlies, comorbid patients and pregnant and lactating women. Pregnant women are more prone to obtain severe clinical outcome especially during second wave of COVID-19 [6]. The second wave which is said to be brought about by mutations in the virus and various factors attached to human behavior and negligence has targeted more pregnant women than the first wave. Also there are severe observations which are pointing towards the vertical transmission of the COVID-19 through mother to neonates. Major consequences like still births, pre term births and other medical complications can be seen among COVID-19 infected pregnant women. Vaccination is seemingly helping the pregnant women to lower the severity of symptoms and patients can be easilv managed.

2. COVID-19 AND VULNERABLE POPULACE

COVID-19 is an extremely contagious disease which can happen to anyone. But certain section of population are more vulnerable and prone to the infection than others. This section can be protected with extra caution so that overall infection cases and case fatalities due to COVID-19 remains low as these are people which are major contributors to the numbers. If these people or section of society is protected then overall pandemic will weaken by its core. The vulnerable groups so far identifies contains elderlies which are above 50 years of age, comorbid patients which are patients having underlying medical illness and pregnant women along with others. All these group of people are going through their immunosuppressive state and are low on immunity and bodily functions. If these people get infected by COVID-19 then it is difficult to medically manage such patients. Such patients require sophisticated medical attention which can include intensive care unit care. ventilators and oxygen support system. Case fatalities are mostly contributed from this section of people [7].

3. COVID-19 AND PREGNANT WOMEN

Pregnant women are among the vulnerable section of population which needs extra attention to cope up with the situation. Pregnant women are already on their immunosuppressive state and are harboring another life. Studies have shown that pregnant women are prone not only to infection of the COVID-19 but also to complications which arises from the infection. During pregnancy, various changes in the body takes places. ??? In a multi country study, observations suggested that pregnant women with COVID-19 infections are more vulnerable to higher risk of fatalities, pre term birth, long haul?? in ICU, and other related complications. Almost 700 COVID-19 infected pregnant women and 1400 without COVID-19 pregnant women were assessed . This is a serious cause of concern as fetus is also under threat. According to this study there is 20 times more risk of death in COVID-19 pregnant women than non-Covid-19 one [8]. The findings are from April and august of 2020. Each infected pregnant women were tallied with two non-COVID-19 infected pregnant women which is one of its kind study in obstetrics. 11.5 percent of the babies from positive pool of pregnant women tested positive for COVID-19. Although study points out that the vulnerability of catching the infection is no more than any other group but after infection is contracted to the pregnant women then the medical management becomes difficult in most of the cases. In pregnant women itself, those were having underlying medical illness like hypertension obesitv. diabetes. were extremely vulnerable in developing critical symptoms which requires sophisticated medical attention and care. In some countries like Brazil [9] the situation in general is so grave that the government urged its local women to defer their pregnancies till worst of the pandemic gets over [10]. In the previous outbreaks of Severe acute respiratory syndrome (SARS) caused by SARS-COV and Middle Eastern respiratory syndrome (MERS), the pregnant women were also at higher risk of developing fatal clinical outcomes. Pregnant women of all trimesters are equally prone to all the stated conditions. Various changes in systems like cardiorespiratory and immune system can make pregnant women more susceptible. the Estrogen sourced hyperemia develops nasal congestion which is similar to the COVID-19 symptoms. Therefore if unchecked can make the clinical situation more grave as it can be mistaken as normal during pregnancy. It also increases the risk of transmission to the immediate contacts of the pregnant women resulting in unknowing transmission of the COVID-19 disease. Due to fetal oxygen demand, heightened metabolism, gestational anemia dyspnea is regarded as normal during pregnancy. But same symptom of COVID-19 can get neglected making condition graver as time passes. Breathlessness due to physiology and pathology must be identified early enough to treat. Due diaphragmatic pressure resulting from fetus containing uterus, the resultant capacity of the lungs gets reduced while in pregnancy. Therefore proper care is already needed to make sure the safety of the women. Pregnant women are also unable to clear secretions from pulmonary system which gets accumulated over time and needs medical intervention. In first wave, there was almost none deaths due to COVID-19 and pregnant women were not considered as soft target for the novel coronavirus. The fatality rates when compared to the previous outbreaks of SARS and MERS were found to be lower. But as soon as second and successive waves struck the world, this assessment were overturned and now many

latest studies are tagging the pregnant women as high risk category patients [11].

4. COVID-19 AND NEONATES

Along with pregnant women, there is another major stakeholder in this pandemic situation and that is the new born child. The mother is vulnerable so as child. But infected mothers can show severe clinical symptoms like pre term birth which can hinder the growth potential of the child. Although no comprehensive study is available to show the impact of COVID-19 during pregnancy on child. Infants and neonates are already vulnerable as all their systems are very nascent and are in forming stage. Critical care is required for new born especially those from infected mothers. They are also in vulnerable category. A study conducted in 22 different countries threw some light on the possible correlation between the COVID-19 infection and physiological state of mother and neonate. According to the given study 11 percent of the infected women were shifted to ICU and three of them met with fatal outcome making case fatality rate to stand at 0.8 percent. 70 pre term births were reported but most of them were requested by the pregnant women to avoid the COVID-19 situation. 2.3 % saw miscarriages meaning 5 neonatal deaths.. Although the study was limited, it can offer a valuable insight. Generally, adhering to protocol, new born babies are being separated from the infected mothers to safeguard the neonate from the infection. But this has been resulted into catastrophic scenario [12].??? Babies who are underweight or pre term births needs to be with parents for longer duration. Kangaroo mother care in which skin to skin contact is ensured between new born babies and mothers is necessary for the survival of the babies. Also exclusive breastfeeding by mothers is the key to lower the infant mortality rates. It has been seen that, in the group of new born babies having low birth weight or pre term births, the kangaroo mother care is helping to reduce the infant mortalities by 40 percent, hypothermia by 70 percent and severe grade infections by 65 percent. There is already a lot of hindrance in accessing the non-COVID-19 health care especially new born care, therefore we have to spread the best practices like kangaroo mother care, otherwise it can wash away all the gains made by humans in lowering infant mortality rates. Although the infections that are being confirmed are mostly mild in nature among neonates and babies, therefore steps like kangaroo mother care should be continued.

Many countries have included separation of new born babies from the infected mothers in their guidelines and standard operating procedures for hospitals for safety of neonates. Some health authorities even forbid the infected mothers to breastfeed the babies to avoid infection. This can catastrophic and should be discontinued or we will see another wave of infant mortalities. Various studies and observations have shown that there is low chance of neo natal deaths and infection among them is of extremely mild nature. COVID-19 infection among pregnant women facilitate pre term births therefore it is more important to care the babies as stated earlier [13].

5. VERTICAL TRANSMISSION

The most debated topic of the pregnancy in COVID-19 is vertical transmission. Till date no concrete correlation between the two has emerged but studies are ongoing. As the rate of positivity of the neonates and new born are increasing, vertical transmission concept is gaining more and more traction. Vertical transmission basically means transmission of COVID-19 from mother to offspring while in the womb. COVID-19 infected pregnant women are already vulnerable to pre term births and various other complications, vertical transmission only adds up to woes of the pregnant women. In some cases where the new born babies were tested positive after the birth, the samples of amniotic fluid and placenta were tested and it had no viral strains on it ruling out the vertical transmission [14]. But several other cases have raised suspicion over the positivity of the neonates. Transmission through breast feeding also ruled out as breast milk also tested negative for the novel coronavirus. But in several cases, IgM antibodies were found in the blood of neonates. But the antibodies cannot transmit from mother to offspring via placenta which raised suspicion upon vertical transmission of COVID-19. But there are various other reasons which can be attributed to the infection in new born babies. After birth, the negligence in handling the babies after birth by the paramedic staff can result in the transmission of the infection. Also infected mothers while breast feeding can transmit the infection via sneeze and cough. All these can average into positivity rate among neonates going higher. More studies needs to be done in order to correlate the two more comprehensively and results can be shown with empirical backing [15].

6. PSYCHOLOGICAL IMPACT OF COVID-19 ON PREGNANT WOMEN

The less talked about impact of COVID-19 is psychological impact. The social distress can be seen all over the world which is attributed to various pharmacological as well as non-pharmacological interventions like lockdown, physical distancing, isolation, quarantine and so on. Pregnant women are more prone to fall to such pressure as they are worried about the wellbeing of their offspring. Also lots of hormonal changes has been undergoing??? in pregnant women which can also affect their mood in adverse way. Constant listening to negative news about passing of close relatives or various other case fatalities due to COVID-19 makes them more prone to negative thoughts. This can affect the wellbeing of mother as well as children which is projected to come. In COVID-19 positive women, the situation is even pregnant worse as they are confronting to situation like viral attack, long isolation and ICU time. Also isolation makes them more distanced from their family members which also have a negative impact on the patient [16]. More than 70 percent pregnant women showed anxiety and low grade depressions and requested doctors and medical professions to pre pone?? their delivery to ensure safety of the new born. Socioeconomic strata in which different women are on different levels suggests some more insights. The pregnant women from lower socioeconomic strata have to work for livelihood even if they are in pregnant state. Sometimes they are ill still they have to work round the clock. Due to lockdown the livelihoods washed away ??? so they got shifted from livelihood work to house hold work. Rural women are expected to do all the household chores even if they are pregnant. This affect their mental condition as no proper medical intervention is available where they can seek help. Domestic abuse is yet another brunt that pregnant women have to bear. into can culminate All these negative thoughts and depressions which is not good for expected mothers and babies. Psychological intervention is as important as medical interventions. Often it is considered as taboo to seek psychological help professionally. The stigma attached to the psychological distress is huge and needs to be tackle on urgent basis [17].

7. PREVENTIVE MEASURES FOR COVID-19

There are two types of measures which can be taken to control any disease outbreak or illness. One is curative measure which can be taken after the disease has been contracted to the person and second one is preventive measures which can be taken to prevent the disease from happening at first place. Considering novelty of COVID-19 and many complications which is attached to it, preventive measures are more suitable than curative measures for various reason. The transmission rate of the novel coronavirus is so huge that the entire healthcare sector has been collapsed under the severe strain from the incoming demand. In second wave more and more people are being infected and more complications is attached to it as mutations has been the key killer [18]. Not only has this, the survivors of the COVID-19 had to bear the brunt of the disease even after the recovery from the disease. The long COVID-19 is haunting millions of patients who got recovered from the novel coronavirus disease 2019. Therefore it is always advisable to follow preventive measures to stav away from all this Various guidelines and agony. standard operating procedures has been issued from time to time by World Health Organization (WHO) and national level health authorities to tackle the spread of the COVID-19. The nonpharmacological interventions (NPI) like lockdown and physical distancing along with wearing of masks and face shields, avoiding touching public surfaces have immense impact in stopping the spread of COVID-19. This can be strictly followed by the people so that they can safeguard themselves from the infection. Also avoiding going out unnecessarily, following balanced diet, doing some exercise can also act as preventive measure. In case of pregnant women, more care has to be taken to avoid infection. Strict wearing of masks while in proximity of the pregnant women must be done. While going for checkup ensure that all the preventive measures are being followed. the physical intervention can be converted into tele medicine intervention so as to minimize the external contact with doctors. Staying in regular touch with the concern doctor and avoiding selfmedication without consulting the competent authority can also help. Infected mothers who are expecting their babies or lactating mothers can be very cautious while handling the baby. While breastfeeding there is a chance of transmission of COVID-19 to new born baby, therefore

mothers should wear all the protective equipment's such as masks, face shield, protective gown, so that the droplets cannot travel to the neonates. Along with vaccines like whooping cough and flu pregnant women can get the COVID-19 vaccination. Many studies have stated that vaccination have no adverse impact on pregnant women and it is safe to have jabs during pregnancy. 35691 subjects were assessed and no side effects of vaccines were seen. The two candidates which was tested were Pfizer and Moderna vaccines. The participants were aged from 16 to 54 years old. No safety concern were observed for any trimester and also for babies. It becomes important when the second wave is supposedly killing more pregnant women than the first wave [19]. Studies on pregnant women and their exposure to radiation [20], knowledge about influenza and vaccination [21] and effects of amoebiasis [22] were reported. Studies on different aspects of healthcare situation in Covid-19 were reported by Pasari et. al. [23], Patel et. al. [24], Phansopkar et. al. [25], Dhok et. al. [26] and Nibudey et. al. [27].

8. CONCLUSION

Preventive care is more important than curative care especially during COVID-19. Pregnant women must be extra cautious and family members must be aware of all the preventive measures that can be employed to prevent the infection. As infection can lead to any degree of severity, so proper care must be taken. Vertical transmission is not yet established with empirical backing but all care must be taken to ensure safeguard of new born. Neonate handling protocols must be strictly adhered so as to minimize hospital acquired infection of COVID-19. Taking lessons from SARS and MERS outbreaks, every stake holder must be consulted and efficient policy must be drawn so as to amplifv the benefit to highest extent. Vaccinations has been approved for pregnant women as no side effects and observations raising concern has been seen. Also it has effectiveness in lowering the adverse impact of the COVID-19 as well as protecting the new born babies from the infection. Measures like kangaroo care must be employed among babies who had preterm birth or low weight which is extremely necessary according to several reports. Telemedicine must be preferred over physical visit among pregnant women of first and second trimester so as to minimize the risk of contracting infection. Self-medications must be avoided at any cost as it can create unmanageable medical complications.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- COVID-19 Map [Internet]. Johns Hopkins coronavirus resource center. [Cited 2021 Apr 25]. Available:https://coronavirus.jhu.edu/map.h tml
- WHO Director-General's opening remarks at the media briefing on COVID-19; 2020.pdf.
- Dushyant Bawiskar, Pratik Phansopkar, Ayurva Vilas Gotmare. COVID-19 facets: Pandemics, curse and humanity. ijrps. 2020;11(SPL1):385–90.
- WHO Coronavirus (COVID-19) Dashboard [Internet].
 [Cited 2021 Apr 25].
 Available:https://covid19.who.int
- Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: A report based on 116 cases. American Journal of Obstetrics and Gynecology [Internet]. 2020; 223(1):111.e1-111.e14 [Cited 2020 Oct 17] Available:https://linkinghub.elsevier.com/re trieve/pii/S0002937820304622

- Grubaugh ND, Hanage WP, Rasmussen AL. Making sense of mutation: What D614G means for the COVID-19 pandemic remains unclear. Cell. 2020;182(4):794–5.
- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J. 2020;55(5).
- Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA. 2020 May 12;323(18):1848–9.
- 9. Paulo R in S. Brazil warns women to delay pregnancy amid COVID-19 surge [Internet]. the Guardian; 2021. [Cited 2021 Apr 25]. Available:http://www.theguardian.com/worl d/2021/apr/16/brazil-warns-women-todelay-pregnancy-amid-covid-19-surge
- Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: What obstetricians need to know. American Journal of Obstetrics and Gynecology [Internet]. 2020;222(5):415– 26.

[Cited 2021 Apr 24] Available:https://www.ajog.org/article/S000 2-9378(20)30197-6/abstract

- 11. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521–31.
- Rao SPN, Minckas N, Medvedev MM, Gathara D, N PY, Estifanos AS, et al. Small and sick newborn care during the COVID-19 pandemic: Global survey and thematic analysis of healthcare providers' voices and experiences. BMJ Global Health [Internet]. 2021;6(3):e004347. [Cited 2021 Apr 25] Available: https://db.bmi.com/content/6/3/e0

Available:https://gh.bmj.com/content/6/3/e0 04347

 Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The intercovid multinational cohort study | Neonatology | JAMA Pediatrics | JAMA Network [Internet].

[Cited 2021 Apr 24].

Available:https://jamanetwork.com/journals /jamapediatrics/fullarticle/2779182?guestA ccessKey=fed2ea98-6893-42aa-87e4-9664222f3842&utm_source=For_The_Me dia&utm_medium=referral&utm_campaign =ftm_links&utm_content=tfl&utm_term=04 2221

- Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18):1846– 8.
- Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. American Journal of Obstetrics and Gynecology [Internet]. 2021;0(0). [Cited 2021 Apr 24]

Available:https://www.ajog.org/article/S000 2-9378(21)00187-3/abstract

- Wang Y, Chen L, Wu T, Shi H, Li Q, Jiang H, et al. Impact of COVID-19 in pregnancy on mother's psychological status and infant's neurobehavioral development: A longitudinal cohort study in China. BMC Medicine [Internet]. 2020;18(1):347. [Cited 2021 Apr 24] Available:https://doi.org/10.1186/s12916-020-01825-1
- Durankuş F, Aksu E. Effects of the COVID-19 pandemic on anxiety and depressive symptoms in pregnant women: A preliminary study. J Matern Fetal Neonatal Med. 2020;18:1–7.
- Allam M, Cai S, Ganesh S, Venkatesan M, Doodhwala S, Song Z, et al. COVID-19 Diagnostics, tools, and prevention. Diagnostics [Internet]. 2020;10(6):409. [Cited 2020 Dec 16] Available:https://www.mdpi.com/2075-4418/10/6/409
- Kaushik M, Agarwal D, Gupta AK. Crosssectional study on the role of public awareness in preventing the spread of COVID-19 outbreak in India. Postgraduate Medical Journal [Internet]; 2020. [Cited 2020 Dec 16]; Available:https://pmj.bmj.com/content/early /2020/09/10/postgradmedj-2020-138349
- Singh, Pradeep K. Perioperative radiation exposure in a pregnant woman. Iranian Journal of Radiation Research. 2011;8(4):253–55.
- 21. Arriola, Carmen S, Piyarat Suntarattiwong, Fatimah S Dawood, Giselle Soto, Prabir

Das, Danielle R Hunt, Chalinthorn Sinthuwattanawibool, et al. What do pregnant women think about influenza disease and vaccination practices in selected countries. Human Vaccines and Immunotherapeutics, n.d.

Available:https://doi.org/10.1080/21645515 .2020.1851536

- 22. Karadbhajne, Priti, Anil Tambekar, Abhay Gaidhane, Zahiruddin Quazi Syed, Shilpa Gaidhane, and Manoj Patil. Amoebiasis in pregnant woman: A case report. Medical Science. 2020;24(104): 1814–17.
- Pasari, Amit S, Amol Bhawane, Manish R Balwani, Priyanka Tolani, Vishal Ramteke, Nishant Deshpande. Knowledge about COVID-19 and practices among hemodialysis technicians in the COVID-19 Pandemic Era. International Journal of Nephrology; 2020. Available:https://doi.org/10.1155/2020/671 0503
- 24. Patel, Mohan P, Vivek B Kute, Jitendra Goswami, Manish R Balwani. Hospitals may become 'disease hotspots' for COVID-19 amid shortage of personal protective equipment. Indian Journal of Critical Care Medicine. 2020;24(11):1145– 46.

Available:https://doi.org/10.5005/jpiournals-10071-23645.

- 25. Niran J. The impact of combining therapy and medication on bipolar disorder incidence and prevalence. International Journal of Respiratory Care. 2016;12(1):10–13.
- 26. Ali Say. The impact of adolescent pregnancy on the quality of life: Focusing on medication intervention implications. International Journal of Respiratory Care. 2016;12(1):14–18.
- Phansopkar, Pratik Arun, Waqar Mohsin Naqvi, Arti Isherkumar Sahu. COVID-19 pandemic- a curse to the physical wellbeing of every individual in lock-down. Journal of Evolution of Medical and Dental Sciences-JEMDS. 2020;9(35): 2561–66.

Available:https://doi.org/10.14260/jemds/2 020/556.

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