REVIEW ARTICLE

Is it time to start COVID-19 vaccination in pregnant women?

Muhammad Ilham Aldika Akbar*
Department of Obstetrics Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
Universitas Airlangga Hospital - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

COVID-19 pandemic has been lasting for years, and pregnant women encounter an increased risk of mortality and morbidity. Until now, vaccine COVID-19 has been developed and shows a promising result. Unfortunately, pregnant women are consistently excluded from receiving a new vaccine. Because pregnant women are excluded from participating in a clinical trial of vaccines related to safety issues, this exclusion cycle prevents pregnant women from receiving the vaccine that may benefit them. In this review article, the author provides evidence, data, and the reason why vaccination of pregnant women should be started in Indonesia, at least in a clinical trial, especially for health workers and women with comorbidities.

Keywords: Covid-19; vaccine; maternal health; infectious disease; medicine

ABSTRAK

Pandemi COVID-19 telah berlangsung selama beberapa tahun, dan ibu hamil menghadapi risiko kematian dan kesakitan yang tinggi. Sampai saat ini, vaksin COVID-19 telah dikembangkan dan menunjukkan hasil yang baik. Sayangnya, ibu hamil selalu diekslusi untuk menerima vaksin baru. Karena ibu hamil dieklusi untuk berpartisipasi pada penelitian klinis vaksin terkait isu keamanannya, ini akan menciptakan siklus ekslusi yang mencegah ibu hamil untuk mendapatkan vaksin yang bermanfaat untuk mereka. Pada telaah artikel ini, penulis menunjukkan bukti, data, dan alas an mengapa vaksinasi pada ibu hamil harus dimulai di Indonesia, paling tidak pada uji klinis, terutama pada tenaga Kesehatan dan ibu hamil dengan penyakit penyerta.

Kata kunci: Covid-19; vaksin; kesehatan ibu; penyakit infeksi; pengobatan

***Correspondence:** Muhammad Ilham Aldika Akbar, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia.
E-mail: muhammad-i-a-a@fk.unair.ac.id@fk.unair.ac.id

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INTRODUCTION

Since the start of the COVID-19 pandemic, pregnant women became the susceptible group with an increased risk of mortality ad morbidity. Pregnancy outcomes of COVID-19, in general, are better compared to the SARS, MERS, H1N1, Ebola, and Zika infections.[1] However, the risk of ICU admission, mechanical ventilator used, and maternal death is increased compared to normal pregnant women without COVID-19.[2] There has been no official government report about the prevalence, morbidity, and mortality of COVID-19 in pregnancy. Still, our unpublished study result from Universitas Airlangga Hospital show a maternal mortality rate of 9.8% (six maternal death from a total sixty-one confirmed cases). Morbidity presence in this study includes preeclampsia, gestational hypertension, preterm premature rupture of the membrane (PPROM), and preterm birth.

Vaccination (primary prevention) is still the best strategy to overcome any pandemic, including COVID-19.[3] Unfortunately, although pregnant women are a high-risk group, they do not have access to the COVID-19 vaccine. This problem is caused by the fact that pregnant women are permanently excluded from a clinical trial of a new therapy, drugs, including vaccination. The consideration of excluding pregnant women from many clinical trials is primarily related to fetal-neonatal safety and adverse pregnancy outcomes. However, the exclusion of pregnant women from vaccine clinical trials will create a repeated and continuous exclusion cycle. Pregnant women can not participate in a vaccine trial, which leads to no vaccine efficacy and safety data in pregnancy, resulting in no vaccine recommendation in pregnancy.[4] This cycle is unfair for pregnant women: 1. Pregnant women are rejected from vaccine study which may benefit maternal and fetal, and 2. Lack of evidence will decrease vaccine used in pregnant women, lead to decrease protection of the population (pregnant women, fetal) from COVID-19.[4] Therefore a complete review is needed to discuss this problem so that pregnant women and fetuses are not harmed in this pandemic situation. This article will discuss any aspect of the COVID-19 vaccine in pregnancy and why vaccination should be started soon in pregnant women.

VACCINATION IN PREGNANCY

Since the early 19th century, pregnant women's vaccination has been done to protect mother and baby from smallpox infection, pertussis, and tetanus. The maternal vaccination program has been accelerated since the start of an influenza pandemic in 2009. Vaccination increases the specific antibody vaccine level in maternal blood when the baby is delivered. It can protect until the susceptible periods pass or until the baby has finished their routine immunization program.[5] Until now, three vaccines were recommended in pregnancy: tetanus, pertussis, and influenza. The most critical issue in pregnancy vaccination is the safety concern. The vaccine safety assessment becomes a problem because of adverse events related to pregnancy complication itself. When this event happens in clinical trials, it is essential to examine the association with the vaccine or pregnancy carefully. Many studies have provided evidence of vaccine safety, such as tetanus, influenza, and pertussis[5]. The emerging of the COVID-19 pandemic raises new challenges related to pregnancy vaccination. Considering this is a very recent disease, the lack of evidence from clinical trials makes a vaccination program in pregnancy not yet performed[8].

COVID-19 VACCINE

Until now, many countries have developed a variety of COVID-19 vaccines. These vaccines can be classified based on the type, mechanism, and media used, including mRNA vaccine, viral vector vaccine, recombinant protein vaccine, and inactivated viral vaccine.[6] Vaccines that used mRNA media are Pfizer-Biotech (BNT162b2) and Moderna (mRNA-1273), the viral vector is AstraZeneca Oxford (AZD1222), and Johnson & Johnson-Janssen Pharmaceuticals (Ad26.COV2.S), a recombinant protein with Baculovirus are Novavax and GSK-Sanofi; also the inactivated viral vaccine is Coronavac-Sinovac Biotech. mRNA vaccine is a relatively new type of vaccine which brings genetic information to create a protein spike SARS-CoV-2, which the maternal immune system will recognize. mRNA vaccine never enters the cell nucleus and merges into the DNA, and in the periods of hours until days, this vaccine will be degraded in the cell cytoplasm. mRNA vaccine does not alter the human DNA, and either causes genetic changes.[7] Theoretically, based on this mechanism, the safety risk to the fetus or newborn is minor. Since Dec 13, 2020, FDA has approved the Emergency Use of Authorization (EUA) for the Pfizer dan Moderna vaccine to be used in the community in an emergency state. The EUA approval needs a tight review and test from four agencies/panels and has shown that the benefit of vaccine exceeds the risk from phase 3 clinical trial[6-8].

Astra Zeneca and Johnson & Johnson vaccine mechanism involve a modified viral vector that gives a protein spike SARS-CoV-2 into the cell and induces an immune response. This monovalent vaccine contains a recombinant human adenovirus type 26 (Ad26) vector,

which encodes a stabilized form of protein spike (S) SARS-CoV-2. The vector vaccine is not a live virus so that it unable to replicate in human body cells. This mechanism has been used in the Ebola HIV vaccine, which has been applied to pregnant women and shows a tolerable safety profile and reactogenicity.[3,7] Two adenovirus vector vaccine COVID-19 studies (phase 1/2 dan phase 2) show a neutralizing antibody and T-cell response to the protein spike SARS-CoV-2.[8] ChAdOx1, a viral platform that uses a chimpanzee adenovirus vector used in the Oxford study, shows an ability to safely induce a cellular and humoral immune response and protect pregnant sheep. They were vaccinated in the first trimester against Rift Valley fever disease, without risk of maternal viremia or miscarriage.[8]

Coronavac vaccine (China Sinovac Biotech) receive a EUA from The Food and Drugs Monitoring Agency Indonesia (BPOM) to be used in Indonesia.[9] Phase 3 clinical trials in Indonesia, Turkey, and Brazil show that the Coronavac is safe with minor-moderate adverse effects in the form of local impact (pain, induration, redness, and edema in injection site) and systemic effect (fever, myalgia, and fatigue). The Coronavac has also shown efficacy in three clinical trials Indonesia (65.3%), Turkey (91.25%), and Brazil (78%).[9] This vaccine uses the additional platform of inactivated virus, which has been proven a safety profile in pregnancy as shown in an influenza vaccine.[10–12] Coronavac has shown immunogenicity reactogenicity to mice, rats, and non-humans primates by inducing antibody SARS-CoV-2 who neutralized ten strains of SARS-CoV-2. The study shows Coronavac gives partials/complete protection on macaques from severe interstitial pneumonia interstitial after intentionally infected by SARS-CoV-2, which supports the next step to human clinical trial.[13] Indonesia is developing a national vaccine (Merah Putih vaccine - Eijkman Institute -Biofarma) in phase 1 clinical trial. The trial is expected complete in September-October 2021.[14]

Evidence of COVID-19 vaccine in pregnancy

COVID-19 pandemic has shown the risk and susceptibility of pregnant women when excluded from vaccine trials and limits their access to vaccines. Vaccination on pregnant women protects the pregnancy outcomes, mother and baby, simultaneously.[15] However, because pregnant women are permanently excluded from vaccine trial cause lack of evidence for the recommendation of COVID-19 vaccine to this susceptible group. Fetal safety issues always become the first consideration to exclude vaccination to pregnant women. Many proposals have been sent to NIH and US FDA to permit pregnant women involves in the clinical trial with a tight protocol and prioritize their pregnancy safety.

Evidence from previous used of similar vaccine

Inactivated viral vaccine (SINOVAC's Coronavac) is an established vaccine platform that has been used for a long time. This vaccine type has a proven safety profile in pregnant women and fetuses. The safety profile of Coronavac presumed will be similar to other inactivated viral vaccines such as the influenza vaccine. Inactivated influenza vaccine has been proven safe to the fetal-neonatal and does not increase the risk of adverse pregnancy outcomes such as preeclampsia, preterm birth, IUGR, and congenital malformation.[16] The most frequent adverse effect found are injection site pain and edema, fever, and myalgia. The absolute contra-indication is a severe allergic reaction to the vaccine or its ingredients.[16] Oppermann et al. evaluate the safety profile and pregnancy outcomes after influenza vaccination A (H1N1)v2009 on 323 pregnant women compared to 1329 control. The study shows no difference between both groups in risk of spontaneous miscarriages, major fetal malformation from exposure in any trimester, or first trimester only, or preconception periods.

Moreover, the risk of preeclampsia, preterm delivery, and IUGR are not increased in the vaccinated group. Oppermann et al. conclude that the H1N1 vaccine does not increase maternal and fetal risk.[10] From this study, the safety profile of Coronavac is expected to be similar. Pregnant women should have a chance to participate in the inactivated viral vaccine's clinical trial because this vaccine type's safety profile is already established.

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY STUDY

FDA recommends a developmental and reproductive toxicology study (DART) on the animal to evaluate the vaccine's adverse effect potential on a reproductive function.[6] So far, only Moderna that already submit their DART study and indicate that mRNA1273 vaccine, which is given to mice before or during pregnancy with a dose of 100 ug do not show a poor effect on the female reproductive system or interfere with fetal, embryonal, or postnatal development except general skeletal variations which can be resolved without intervention after delivery.[6,7] A DART study of a rabbit who gave a 1 ml injection of Janssen COVID-19 vaccine shows no poor adverse effect on female fertility or developmental problems in fetal, neonatal, and postnatal until day 28.[7] At the same time, the Ad26 vector vaccine is already used in HIV, Ebola on

pregnant women and has been proven its safety profile and reactogenicity. These DART study results indicate the first safety data of the COVID-19 vaccine used in pregnancy.

V-SAFE PREGNANCY REGISTRY DATA

Although pregnant women are permanently excluded from vaccine trials, many reproductive ages women who are vaccinated became pregnant. In US, in a group of women who were vaccinated with Pfizer-Biotech, there are 12 pregnancies and in Moderna vaccinated group, there is 13 pregnancy. Pregnancy outcomes still in observation, and until now, there are no signs of disturbance in fetal development.[6] In UK, there is 53 accidental pregnancy after vaccination. The miscarriage rate is similar between vaccinated and unvaccinated groups, as seen in Table 1.[1]

Until Feb 16, 2021, 30.494 pregnancy has been reported to CDC v-safe post-vaccination health checker and shows no sign of specific safety issues.[7] CDC has include pregnancy in the v-safe pregnancy registry study and, up to Feb 19, 2021, already recruit 1800 pregnant women.[17] This study aims to evaluate the safety profile of Pfizer-Biotech and Moderna vaccine in pregnancy in the US. As far the reactogenicity and adverse event in pregnancy do not show a significant safety problem. The adverse event is also similar between pregnant and non-pregnant women. There is no difference in adverse pregnancy outcomes between pregnant women who participate in the v-safe pregnancy registry and the general pregnant women population. This preliminary result can be seen in Table 2.[17]

CLINICAL TRIAL

Phase 1/2 clinical trial already performed to evaluate safety, tolerability, and immunogenicity of Coronavac to 18-59 years old healthy adult in China.[18] In this randomized, double-blind, placebo-controlled trial, 144 participants are recruited in the phase 1 trial and 600 participants in the phase 2 trial. Zhang et al. show that two doses of Coronavac given in a different concentration and schedule are well tolerated and indicate moderate immunogenicity in a healthy adult. The incidence of adverse reaction between 3 ug and six ug doses is not different and shows no dose-effect safety concern. However, long-term follow-up is needed to ascertain this finding. The majority side effect found in this study is primarily mild pain in the injection site. Compared to another COVID-19 vaccine, such as viral vector and mRNA, fever incidence in Coronavac is lower.[18]

Table 1. Miscarriages rate in accidental pregnancy after COVID-19 vaccine in UK.[1]

Vaccine	Control Group		Vaccinated Group	
	Miscarriages n (%)	Pregnancies/ Total Participants	Miscarriages n (%)	Pregnancies/ Total Participants
Pfizer-Biotech	1 (8)	12/18.846	0	11/18.860
Moderna	1 (14)	7/15.170	0	6/15.181
AstraZeneca	3 (33)	9/5.829	2 (17%)	12/5.807

Table 2. V-safe pregnancy registry outcomes in COVID-19 vaccinated pregnant women.[17]

Outcomes	Background Rates (%)	V-safe Pregnancy Registry Overall (%)
Pregnancy Outcomes		
Miscarriage (< 20 weeks)	26	15
Stillbirth (≥ 20 weeks)	0.6	1
Pregnancy Complications		
Gestational Diabetes	7-14	10
Preeclampsia or gestational hypertension	10-15	15
Eclampsia	0.27	0
Intrauterine Growth Restriction	3-7	1
Neonatal Outcomes		
Preterm birth	10.1	10
Congenital Anomalies	3	4
Small for Gestational Age	3-7	4
Neonatal death	0..38	0

Coronavac also shows a humoral immune response and produces sufficient neutralizing antibodies, which supports the emergency use of this vaccine in China, and phase 3 trial in Indonesia, Turkey, and Brazil. Phase 1/2 trial has also been done in older adults (>60 years old), show a good safety profile, tolerability, and induce an excellent humoral immune response.[19] Pregnancy vaccination with Coronavac is predicted to show a similar safety and immunogenicity result.

Clinical vaccine trials on pregnant women are now in progress. Kathryn et al. study evaluate the immunogenicity and reactogenicity of mRNA COVID-19 vaccine on pregnant and lactating women compared to 1. control unpregnant women, 2. control pregnant women who are infected naturally.[20] This study involves 131 reproductive-age women who were vaccinated, consisting of 84 pregnant women, 31 breastfeeding women, and 16 non-pregnant women. The study shows that antibody titer post-vaccination is not different between pregnant, breastfeeding, and non-pregnant women (5.59 vs. 5.74 vs. 5.62). However, all titers are still higher compare to antibody titers induced by natural infection of COVID-19. Vaccine-induced antibodies are also found in the umbilical blood cord and breastmilk. Second doses vaccine increase Ig G SARS-CoV-2 titer but not the Ig A, in maternal blood and breastmilk. The adverse effect found in pregnant and lactating women are relatively lower compare to non--pregnant group, include pain and redness in the injection site, headache, myalgia, fatigue, and fever. During study periods, only 13 pregnant women gave birth, one patient experienced spontaneous preterm birth, and no other complication was found, such as preeclampsia and IUGR. Newborn morbidity was found to include one case of transient tachypnea of the newborn (TTN), and two babies need NICU admission. In general, this study shows that the mRNA COVID-19 vaccine shows good immunogenicity, reactogenicity, and safety profile, although the sample size is small.

Pfizer-Biotech already starts a phase 2/3 trial to evaluate the safety, tolerability, and immunogenicity COVID-19 vaccine (BNT162b2) on healthy pregnant women over 18 years old. On Feb 18, 2021, the first participant received the first dose of vaccine for this trial. At the end of the study, the sample is expected to reach 4000 pregnant women.[21,22] This study completes the initial phase 1/2 trial, which has shown a good safety result.[22] This study hopefully will give evidence about the safety of the mRNA vaccine in pregnancy soon.

CONSIDERATION OF VACCINATION IN PREGNANCY

The primary consideration of vaccination on pregnant women is the balance between risk and benefit. COVID-19 significantly increases maternal, neonatal mortality and morbidity and the risk of adverse pregnancy outcomes.[23] The clinical trial has shown a vaccine efficacy of around 55-95%, depend on vaccine type.[6,9,24] Vaccination in pregnant women will significantly decrease pregnancy complications, adverse pregnancy outcomes, and maternal death risk. Vaccine COVID-19 may potentially give early protection to the newborn, based on Ig anti spike SARS-CoV-2 finding in a baby born from a vaccinated mother.[25] However, further study is needed to evaluate this antibody's protective role in newborns from COVID-19 infection.

In addition to efficacy/effectivity, vaccine safety always becomes a priority consideration for pregnancy vaccination. Based on the type and mechanism of the existing COVID-19 vaccine, theoretically, it is safe for pregnancy. All vaccines do not consist of living viruses, so they do not replicate in the human body either change genetic material.[6] Adenovirus 26 vector has been proven as safe as it used in Ebola vaccination in pregnancy.[26] The inactivated vaccine has also been established as a safe platform vaccine in pregnancy, as used in an influenza vaccine.[10,11,27] An animal study, DART study, clinical phase 1/2 trial of the COVID-19 vaccine shows a promising result in terms of safety and tolerability.[21,22,28] Clinical phase 3 trial is still in progress in many countries, and the official result is not published yet. However, clinical phase 3 trials in healthy non-pregnant women show a reassuring safety profile, and no significant safety issues arise.[17,21,22] The summary of consideration matter in COVID-19 vaccination in pregnancy can be seen in table 3.

The available data about the risk and benefit of COVID-19 vaccination can be used to determine our next step in managing this pandemic, especially in pregnant women. The clinical phase 3 vaccine trial involving pregnant women should be started in Indonesia, parallel with many other countries. The pregnant health workers and pregnant women with comorbidities need to be the first prioritized participant in this vaccine trial before a more extensive scale trial involving the population are performed. Meanwhile, health workers should support pregnant women who want to be vaccinated after full informed consent about the risks and benefits. Health workers should not obstruct the pregnant women's will to have a COVID-19 vaccine for their (maternal & fetal) own benefit.

Table 3. Summary consideration of COVID-19 vaccination in pregnant women

COVID-19 Infection Risk in Pregnancy
1. Pregnancy increase the risk of severe COVID-19, ICU admission, mechanical ventilator used, and maternal death 2. COVID-19 complications risk increase if pregnant women have a comorbid/underlying disease such as obesity, hypertension, diabetes, older age, cardiovascular disease, and autoimmune disease 3. Vertical transmission risk to fetal (although small and rare) 4. Pregnancy complication risk (preterm birth and intrauterine growth restriction)
Safety of COVID-19 Vaccine
1. Theoretical risk based on the COVID-19 vaccine mechanism is small 2. The use of a similar type of COVID-19 vaccine has been proven safe in pregnancy (adenovirus vector, inactivated viral vaccine) 3. DART study on Moderna and Pfizer-Biotech vaccine have shown a good safety profile 4. Phase 1/2 clinical trial on COVID-19 vaccine shows a good tolerability and safety profile 5. Phase 3 clinical trial is in progress, and a pre-preliminary result of the V-safe pregnancy registry study shows no increase in the risk of adverse pregnancy outcome in vaccinated women 6. The risk of vaccine reactogenicity includes fever may affect fetal in the first trimester. This problem can be resolved with the addition of antipyretic drugs.
Efficacy of COVID-19 Vaccine
1. Limited data on pregnancy; however, vaccine efficacy are expected to be similar with healthy unpregnant women (55% - 95%) 2. Decrease risk of adverse pregnancy outcomes, maternal morbidity, and mortality 3. Prevent severe manifestation of COVID-19 4. Protective potential of antibody transfer through placenta to the fetal

CONCLUSION

Pregnant women and medical staff shall use the limited data available dan consider the risk and benefit of the COVID-19 vaccine in pregnancy, including specific individual patients risk exposed to SARS-CoV-2. Available data show reassuring evidence about the possibility of safe COVID-19 vaccination in pregnant women. CDC, ACOG, and SMFM recommend COVID-19 vaccination for pregnancy, considering its benefit outweighs the risk. Pregnancy medical staff should be the priority to obtain the COVID-19 vaccine. While waiting for the result of phase 3 clinical trial in many countries, Indonesia can start the vaccine trial involving pregnant medical staff or pregnant women with comorbidities before performing a larger scale study in the population. In addition, pregnant women who want to get the COVID-19 vaccine should be supported after complete informed consent of the risk and benefit.

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