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Serum Antibodies SARS-CoV-2 Spike (S) Protein Receptor-Binding Domain in OBGYN Residents and Effectiveness 3 Months after COVID-19 Vaccination

Rima Irwinda[1], Achmad Kemal Harzif[1], Natasya Prameswari[1], Rabbania Hiksas[1]*, Angga Wiratama Lokeswara[2], Noroyono Wibowo[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [2]Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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***Correspondence:** Rabbania Hiksas, Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia. E-mail: rabbaniahiksas@gmail.com
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Abstract

BACKGROUND: The health care workers are considered as vulnerable people who had higher infecting dose of SARS-CoV-2 infection compared to other society. Among more than 500 deaths of Indonesians physicians, obstetrics and gynecologist (OBGYN) has become the most specialists who died in this pandemic.

AIM: The objective of our study is to evaluate the antibodies of SARS-CoV-2 in serum OBGYN residents post-vaccination as well as the presence of infection 3 months after the vaccination.

METHODS: A prospective cohort study was conducted in OBGYN residents Universitas Indonesia. Serum antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) was measured using electrochemiluminescence immunoassay, 21 days after Sinovac vaccination, with basic characteristics being recorded. Within 3 months follow-up, the participants were monthly checked related to post-vaccination infection.

RESULTS: The median antibodies SARS-CoV-2 for all participants were 50.72 (19.09–98.57) U/mL. There were 20 residents (24.1%) who had post-vaccination infection within 3 months and dominated by asymptomatic to mild symptoms. Body mass index ($r = –0.221$, $p = 0.044$) and sleep hours ($r = –0.225$, $p = 0.041$) were found to be inversely correlated with antibodies SARS-CoV-2 S RBD.

CONCLUSION: Antibodies SARS-CoV-2 S RBD found to be correlated with BMI and sleep hours. The 3-month post-vaccine infection among OBGYN residents was almost similar to Jakarta's positivity rate and the efficacy rate was higher than expected by National Agency of Drug and Food Control.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a very wide spectrum of clinical manifestation, from the asymptomatic infection to severe respiratory infection that leads to systemic multiorgan failure and even death [1]. This infection was first detected in Wuhan, China, in 2019. After that, the transmission increased globally and become a worldwide pandemic. Studies have shown that during the first 6 months of the pandemic, the mortality rate was up to 1 million and might continue to increase [2]. In Indonesia, until June 2021, there were 1.8 million people got infected with more than 50.000 deaths [3].

Health care workers are considered as vulnerable people who had a likelihood to receive SARS-CoV-2 exposure as well as higher infecting dose compared to other society. Although they have easier access to personal protective equipment, the increasing rate of the infection might still an issue for them. Based on the mitigation team of Indonesian Medical Association, there were more than 500 deaths of Indonesian's physician. Among 245 deaths of specialists, 41 of them were obstetrics and gynecologists, making OBGYN specialists in the 1st rank of specialists' case of deaths due to SARS-CoV-2 infection. In our center, among 83 OBGYN residents in Faculty of Medicine, Universitas Indonesia (FMUI), 11 of them got infected with SARS-Cov-2, though without any severe symptoms.

The urgency of this pandemic leads to the needs of effective and efficient SARS-CoV-2 vaccination, to reach the herd immunity. An effective SARS-CoV-2 vaccination could prevent the infection, disease, as well as the transmission. However, there are numbers of individual factors which might contributes in different immune response post-vaccination, including intrinsic host factors such as sex and comorbidities, behavioral factors such as smoking or alcohol consumption habit, nutritional factors, environmental factors/stress, vaccine factors, and administration factors [4].

Up to this time, there is still a limited study in quantitative SARS-CoV-2 antibody assay performance,

in post-vaccination population, both in with and without previous infections [5]. Thus, the aim of our study was to evaluate the serum antibodies SARS-CoV-2 SRBD in OBGYN FMUI residents and efficacy 3 months after COVID-19 vaccination, as well as its relation with their individual factors.

Objective

The objective of this study is to evaluate the antibodies of SARS-CoV-2 in serum OBGYN residents' post-vaccination as well as the presence of infection 3 months after the vaccination.

Methods

A prospective cohort was conducted in OBGYN residents FMUI post-vaccination, with age ranged from 25 to 40, from March to June 2021. The collection of data performed in accordance with the ethical guideline laid down in the Declaration of Helsinki.

It has been approved by the Ethical Committee for Research in Human from the Faculty of Medicine, Universitas Indonesia (No. 349/UN2.F1/ETIK/PPM.00.02/2021). All participants had been given an informed consent prior their inclusion for the study.

The inclusion criteria include all active obstetrics and gynecology FMU/RSCM residences in 2021, which already administered two dosages of SARS-CoV-2 vaccine. For residents with previous infection, they should at least 3 months free from the infection to be able received vaccination. The exclusion criteria were the rejection of subjects to join the study.

Basic individual characteristics was obtained from all participants such as sex, body mass index (BMI), year of educational level, blood type, comorbidities, previous SARS-CoV-2 infections, as well as habits including smoking, alcohol consumption, working hours, and sleep hours. The calculated BMI were then categorized based on Asia-Pacific BMI criteria which include underweight (<18.5), normal (18.5–22.9), overweight (23–24.9), and obese (≥25).

The collection of serum was performed 21 days after the second dose of CoronaVac (Sinovac Life Sciences, Beijing, China) vaccine. Samples were collected using venous puncture into 5 mL tubes (Vacutainer; Becton-Dickinson) and directly transfer to the laboratory for measurement. Serum antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) was measured using electrochemiluminescence immunoassay (ECLIA). The method was standardized against the internal Roche standard for anti-SARS-CoV-2-S, which consists of an equimolar mixture of two monoclonal antibodies that bind Spike-1 RBD at two different epitopes. A 1 nM of these antibodies corresponds to 20 U/mL of the Elecsys Anti-SARS-CoV-2 S assay. The quantification ranged from 0.4 to 250.0 U/mL. The test results were considered non-reactive if the value <0.8 U/mL, and reactive if the value reached ≥0.8 U/mL. Furthermore, within 3 months post-vaccination follow-up, the participants were monthly checked whether they had SARS-CoV-2 infection or not. Symptom, severity rate, and CT value of post-vaccination infection were recorded.

The data were then analyzed using Statistical Package for the Social Sciences (SPSS) version 25. The normality test was first checked using Kolmogorov–Smirnov test. Since the numeric data were considered abnormal, it was presented as median (interquartile interval [IQR]). To find the differences among characteristics, unpaired t-test or Mann–Whitney was performed in variables with two categories, and one-way ANOVA or Kruskal–Wallis test in variables with more than 2 categories. Following that, classification and correlation between numeric variables were analyzed using a Spearman or Pearson test.

Results

Post-vaccination antibody results related to residents' characteristics

All of the participants results were analyzed. The median antibodies SARS-CoV-2 results for all participants were 50.72 (19.09–98.57) U/mL. Among all, there were 10 of participants whose antibody quantification level 250.0 U/mL, with three of them with previous SARS-CoV-2 infection.

The antibody results and characteristics of subjects are shown in Table 1. More than a half of participants were obese (56.6%), with median BMI 25.65 (23.25–28.73). Residents with normal body weight had a higher antibody level 81.00 (19.15–129.50) U/mL, and the number decreased along with the increase of BMI category. In addition, there were 14.5% participants who had comorbidities, which were mainly asthma and anemia. There were 10.8% of participants with previous history or currently active smokers and 8.4% of participants with previous history or currently active alcohol drinker. However, the antibody level was found no differences in various blood types as well as the presence of other comorbid disease. Related to smoking and alcohol consumption habits, patients no history of actively do those habits had lesser antibody quantity level compared to residents with no exposure.

Related to BMI, the correlation with the antibody result was also found significantly negative ($p = 0.044$) in Table 2. The median of working hours of residents was 12 (10–12) h/day, with sleep hours 6 (5–6) h/day. However, the correlation result was found insignificant.

Pre- and post-vaccine infection antibody results

As much as, 13.3% (11 residents) of the participants had previous SARS CoV-2 infection, as shown in Table 3. Whereas within 3 months follow-up, there were 20 residents had post-vaccination infection. The severity was dominated by asymptomatic to mild infection, with length of infection ranged from 8 to 18 days.

Table 1: Antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) 21 days in residents' characteristics

Residents characteristics	n (%)	Antibodies SARS-CoV-2 (U/mL)	p-value
Sex			
Male	41 (49.4)	49.65 (17.63–125.22)	0.256
Female	42 (50.6)	55.2 (21.7–123.80)	
BMI			
Underweight	0 (0)	-	0.320
Normal	19 (22.9)	81.00 (19.15–129.50)	
Overweight	17 (20.7)	68.65 (19.75–88.36)	
Obese	47 (56.6)	41.38 (18.48–76.32)	
Blood type			
A	29 (34.9)	18.57 (12.08–50.72)	0.136
B	19 (22.9)	20.84 (1.57–73.66)	
O	26 (31.3)	29.08 (7.22–59.51)	
AB	9 (10.8)	6.75-(0.00–20.97)	
Level education			
Basic	11 (13.3)	66.67 (20.84–75.76)	0.06
T1–2	35 (42.2)	68.65 (32.74–129.50)	
T3–4	37 (44.6)	29.09 (12.76–85.96)	
Comorbidities			
Yes	70 (85.5)	77.24 (23.10–105.11)	0.783
No	12 (14.5)	49.92 (18.98–98.67)	
Diabetes Mellitus	1		
Hyperthyroid	1		
Autoimmune diseases	2		
Asthma	3		
Hypertension	1		
Anemia	4		
Rhinitis allergy	2		
Smoking			
Yes/history	74 (89.2)	74.00 (16.32–144.25)	0.652
No	9 (10.8)	50.72 (19.12–92.31)	
Alcohol			
Yes/history	76 (91.6)	50.20 (28.13–143.20)	0.04
No	7 (8.4)	18.48 (1.96–49.65)	

Data presented as median (IQR).

Although, there was one resident who had severe symptoms with shortness of breath and O_2 saturation up to 86%. She had been given non-rebreathing oxygen face mask with O_2 15 lpm for a day followed by nasal cannula O_2 4 lpm. She was discharged after 3 days of hospitalization. She was categorized obese with BMI 25, 14, and an alcohol consumer. In addition, there was no significant difference in antibody quantity among residents with or without previous SARS-CoV-2 infection nor among residents with or without post-vaccination infection.

Table 4 shows CT value of residents having infections. Table 3 shows the correlation between the antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) and the PCR cycle threshold (CT) values of the residents with pre-vaccine and post-vaccine infections. The antibodies showed a weak, positive correlation with the CT values of residents with post-vaccine infections (r = 0.201), and a negative, but stronger correlation with the CT values of residents with pre-vaccine infections (r = –0.527). Neither correlation was statistically significant.

Table 2: Correlation antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) with residents characteristics

Residents characteristics	*r*	p-value
BMI	**–0.221**	**0.044**
Working hours	0.075	0.500
Sleep hours	**–0.225**	**0.041**

Table 3: Antibodies of subjects with SARS-CoV-2 infection

Infections	n (%)	Antibodies SARS-CoV-2 (U/mL)	CT value
Pre-vaccine infection			
Yes	11 (13.3)	68.65 (0.04–250.0)	33.00 (27.75–36.75)
No	72 (86.7)	50.72 (19.15–93.57)	-
Post-vaccine infection			
Yes	20 (24.1)	55.84 (21.17–75.32)	17.00 (15.00–29.50)
No	63 (75.9)	47.00 (18.67–121.50)	-

Data presented as median (IQR).

Table 4: Correlation antibodies SARS-CoV-2 spike (S) protein receptor-binding domain with CT value of pre-vaccine and post-vaccine infection

Residents characteristics	*r*	p-value
CT value of pre-vaccine infection	–0.527	0.118
CT value of post-vaccine infection	–0.259	0.315

Discussion

SARS-CoV-2 antibody assessment has become a pivotal tool in measuring individual seroconversion response to COVID-19 vaccination. Measurement of the level of a person's specific antibody after vaccination may depict the level of protection that the person has gained against the virus post-vaccination. Vaccination is expected to induce neutralizing antibodies, thus it could prevent the virus to bind with ACE2 receptor, through the surface of spike protein. The spike (S) proteins are types of protein which mediates the contact with the host cells, during the virus entry process, through the binding of ACE2 receptors. One of S protein subunits, called S1N terminal domain, is important for receptor binding [6]. Quantitative antibody measurement, which calculates the spike (S) protein receptor-binding domain (RBD), could become one of the markers of SARS-CoV-2 protection. At days 0 and 28 vaccination, the immune response seems to be higher than day 0 and 14. Another study also assesses antibody quantification at day 21 post-vaccination as it was considered for the body to create sufficient antibody response [7], [8]. Therefore, we performed the assessment of the antibody quantification on day 21.

In our study, we found that the median (IQR) for antibody quantification in all participants was 50.72 (19.09–98.57) U/mL. This was considered lower than the other study that using the same antibody quantification in post-vaccination participants whose never got infected, in which the mean was 96.4 U/mL [7]. Regarding the participants characteristics, we found that there was no significant different of antibody level on

sex and blood type. This was in conjunction with other study in health-care practitioners which also found no difference in sex [9]. In contrast, other studies showed that women have more sustained antibody response than male [8], [10]. Since they used Pfizer BNT162b2 mRNA vaccine, which was still unavailable in Indonesia, this may become another important consideration to determine the effect.

Nutritional status has a strong association with immune response in SARS-CoV-2 infection [11]. In our study, we found a negative correlation between BMI level and antibody quantity amount. This finding was conjunction with other studies which have shown that the increase of BMI level is conversely correlated with antibody response, such as in hepatitis vaccination [4]. Not only BMI level, the level of micronutrients content may also influence the innate, humoral, and cellular immune response [12], [13]. Almost all micronutrients are important, but especially Vitamins C, D, and zinc, which had the strongest immune support [14]. However, low number of participants may influence the weak correlation results. Therefore, a wider range of population may represent better understanding.

In addition, we found a negative correlation between sleep duration and antibody quantity level. This was in contrast with a previously published study which suggested that short duration and low quality of sleep during the vaccination week are associated with lower response from antibody, such us during hepatitis A and hepatitis B vaccination [15], [16]. This includes better Th1 immune response in adequate length of sleep, as Ag-specific Th cell response after sleep occurring within 24 h post-vaccination [17]. Nevertheless, further studies are required to evaluate the relationship between sleep hours and the antibody quantity levels as the correlation found in our study, although statistically significant, was a weak correlation.

Related to pre- and post-vaccination infection, we found people with previous SARS-CoV-2 infections had a higher of antibody quantification level compared to residents without previous infection, though the value was only slightly. Other studies have suggested that patients with previous infection tend to have a significantly higher antibody level [8], [18]. In addition, there was also no significant difference found in 3 weeks antibodies values on 3 months post-vaccine infection. We found 20 residents got infected post-vaccination, with median 55.84 (21.17–75.32) U/mL. This number of infected people was only a few less than the average of positivity rate in Jakarta within 3 months (April–June 2021) was 24.7% [3]. Meaning that among 83 people, there were 21 people could be found positive.

In January 2021, Indonesian National Agency of Drug and Food Control was released that the CoronaVac (Sinovac) vaccine efficacy in Indonesia was 65.3% [19]. This means that this vaccine is expected to be effective in at least 54 people among 83 people. As there were 63 participants with no post-vaccine infection, the result from our participants was found higher that the efficacy rate. In addition, the severity of majorly infected subjects found asymptomatic to mild. As vaccination is not only to prevent the presence of infection but also prevent severe infection, this vaccine might be considered effective enough. This was in line with another study which showed that vaccination among health workers was found effective to shorten detectable of viral RNA, lower risk of febrile symptoms, and shorten duration of symptoms [20]. However, since our result showed a non-reactive antibody result from participants with previous infection, the effectivity of the vaccine needs to be analyzed further. The measurement of antibody levels directly after the initial dose could become an important data to determine whether the participant had seropositive or seronegative baseline.

Interestingly, despite the absence of significant difference in antibody levels of residents with history of previous infection ($p = 0.230$), our study shows that the CT values of previous infection has a moderate, inverse relationship with the antibodies of the residents in 3 weeks after receiving vaccination ($r = –0.527$), though the value was not considered significant (0.118). This finding means that residents with lower CT values during their previous infection, which can be interpreted as having higher viral loads, tend to have higher levels of antibodies after receiving vaccination. This is not surprising, as the previous studies have found that higher viral loads are associated with stronger antibody response [21]. However, in this study, we did not take into account how far ago was the CT value of the prior infection recorded from the measurement of the antibody levels after vaccination, as the previous studies have suggested that the antibodies of SARS-COV-2 reduce variably within days of infection and are limited to only about 40 days after the onset of the symptoms [22], [23], [21]. In fact, this may also explain why the correlation we found was only moderate, as well as our findings on the insignificant difference in antibody levels of residents with history of previous infection.

In addition, our study found that the antibodies of the residents' post-vaccination also had a negative and weak correlation with the CT values of post-vaccination infection of the residents ($r= –0.259$). This means that residents with higher antibodies post-vaccination tend to have lower CT values, which are associated with higher viral loads, when infected with SARS-CoV-2 after vaccination. This inverse correlation goes against previous studies which have found that vaccinations, including the CoronaVac, lead to better protection against symptomatic and severe COVID-19 infection, and lower viral load (higher CT values) in post-vaccination infection [24], [25]. However, the correlation that we found was statistically insignificant ($p= 0.315$),

thus explaining its difference from the previous studies. This may be attributed to the low number of samples and the timing of CT value measurements with regard to the onset of infection or symptoms in our subjects. The previous studies have found that the CT value varies with the progression of the disease, and a 1-time measurement may not fully represent its peak value [26].

Overall, there are certain limitations need to be considered to interpret our study. We did not measure baseline antibody quantity before or directly after the first dose of vaccination and the number of participants also limited. Therefore, to achieve more information throughout this topic, this type of measurement should be account in wider range of population. The assessment could be both in vulnerable subjects such as health workers and common people in the society. Prior antibody quantification before vaccination should also be measured to identify, as people who got asymptomatic infection might also develop an antibody reaction. Nevertheless, since there is still a limited study regarding SARS-CoV-2 antibody quantification, especially in Indonesia, this could become the preliminary study for further Indonesian SARS-CoV-2 research progress.

Conclusion

Antibodies SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) among OBGYN residents post-vaccination has been calculated and found to be inversely correlated with BMI and sleep hours. The implications of these results include that BMI and sleep hours may be contributing factors determining the levels of response toward vaccination and hence should be taken into account when measuring antibody response. The 3-month post-vaccine infection among OBGYN residents was almost similar to Jakarta's positivity rate and the efficacy rate was higher than expected by the BPOM. Although there were inverse correlations on CT values pre- and post-vaccination infection with the level of antibody, no significant found in this relationship. Therefore, further studies are required to ensure the effect of vaccination, especially in health care workers.

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