ORIGINAL ARTICLE

Implementing Rapid Antibody Test to Identify Asymptomatic SARS-CoV-2 Infection as Initial Screening in Admitting Pregnant Women, Yes or No?

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ABSTRACT

Introduction: Assessing patient history is solely insufficient to identify the asymptomatic Covid-19 cases in pregnancy. Therefore, regular laboratory examinations should be deemed to find the actual case. However, this strategy might be more challenging for a limited-resource area. Hence, finding the most effective laboratory screening is beneficial. This study aimed to collate the effectiveness of rapid antibody and universal reverse transcriptase-polymerase chain reaction (RT-PCR) for asymptomatic Covid-19 testing among pregnant women in low-resource settings. **Methods:** We performed a study using one-year retrospective data of asymptomatic Covid-19 cases among pregnant women admitted in Dr. Soetomo General Academic Hospital Surabaya, conducted with the paired rapid antibody test and RT-PCR SARS-CoV-2 result. **Results:** Of 265 cases included, 217 samples had a reactive rapid antibody test (81.89%). There was a significant association between rapid antibody test and RT-PCR (p=0.026) with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 89%, 22%, 38%, and 79%, respectively. Thus, it can identify more asymptomatic cases compared to identification by history and symptoms only. This study also revealed a higher significant efficiency cost (p<0.001) by reducing the overall expense up to IDR 36,180,000 (USD 2,514) or 15% lower than the universal RT-PCR SARS-CoV-2 testing strategy. **Conclusion:** This study suggests that implementing a rapid antibody test has favour in identifying more asymptomatic Covid-19 cases in pregnancy and evince more cost-effective than universal PCR testing

Keywords: Covid-19, SARS-CoV-2, Pregnancy, Asymptomatic, Rapid antibody test

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INTRODUCTION

An emergency can occur at any time during pregnancy, labor, and delivery. Hence, the condition puts pregnant women into groups that cannot be adjourned to get health services, unlike other non-essential health services that can be deferred during the pandemic. Considerable evidence from China showed that most Covid-19 patients were asymptomatic and had mild symptoms (1). In line with some Covid-19 studies in pregnancy, most cases detected in hospitals were asymptomatic and had mild symptoms (2). However, unlike the symptomatic case, identifying such cases will be a challenge of its own. Therefore, RT-PCR for SARS-CoV-2 test solely based on the patient's history through symptoms and close contact was insufficient to identify asymptomatic cases. Additionally, pregnant women were still possibly demanding treatment at the hospital even with mild illness (3, 4).

The recommendation from a prior study suggests the universal RT-PCR SARS-CoV-2 test for all patients who need hospitalization (5). However, this strategy will be challenging to implement in areas with limited facilities and countries with low testing capacity. Consequently, it may take a long time to obtain the examination results in an emergency obstetric setting that can not be delayed and require prompt decisions and immediate treatment. In addition, although rapid antibody test was

no longer recommended in detecting Covid-19 cases, rapid antibody test as an alternative screening was relatively easy, fast, cheap, and did not require specific staff for the sampling (6, 7). Therefore, this study aimed to analyze the effectiveness and benefit of this screening test for identifying the asymptomatic Covid-19 cases of pregnancy in an emergency setting which can also be a risk of transmission if not detected during hospitalization.

MATERIALS AND METHODS

This retrospective case-control study was performed using one-year medical records data (1st April 2020 – 31st March 2021) in Dr. Soetomo General Academic Hospital Surabaya, one of Indonesia's central tertiary referral hospitals. We included pregnant women who were admitted to the emergency delivery room with asymptomatic SARS-CoV-2 infection and had paired rapid antibody and RT-PCR SARS-CoV-2 tests.

Rapid antibody tests were performed using lateral flow method with an immunochromatographic assay for detecting SARS-CoV-2 antibody (Wondfo One Step Covid-19 rapid test kit), while RT-PCR SARS-CoV-2 examination was performed using Abbott real-time SARS-CoV-2 assay for the qualitative detection of SARS-CoV-2. This study has been approved and granted exemption by the ethical committee of Dr. Soetomo General Academic Hospital (IRB 0446/LOE/301.4.2/V/2021). The information recorded included demographic data, medical history, comorbidity, referral classification, and laboratory findings (including white blood cell count, neutrophils count, lymphocyte count, neutrophil-to-lymphocyte ratio, and rapid antibody result RT-PCR SARS-CoV-2 tests). All laboratory tests were carried out at the discretion of the treating physician.

This study calculated the SARS-CoV-2 rapid antibody test performance as a screening test and compared the cost between screening strategy using initial rapid antibody test followed by RT-PCR SARS-CoV-2 if the rapid antibody test was reactive with estimation cost of universally RT-PCR SARS-CoV-2 test for all admitted asymptomatic pregnant women. The cost reference used in this study uses the rates available at Dr. Soetomo General Academic Hospital with the following details: rapid antibody test (IDR 30,000 / USD 2.09), RT-PCR SARS-CoV-2 test (IDR 900,000 / USD 62.69), positive rapid antibody test followed by RT-PCR SARS-CoV-2 test (IDR 930,000 / USD 64.78).

Categorical variables were reported as numbers and percentages, while continuous variables were presented as mean and standard deviation (SD) or median and interquartile ranges (IQR). For the statistical analysis, this study used Chi-Square and Fisher Exact Test as an alternative to compare the difference in the categorical variables, while independent T-Test, paired T-Test, and Wilcoxon – Mann-Whitney Test as an alternative was used to compare the continuous variables between groups. All of the statistical analysis was performed using SPSS version 24.0 software for Windows (IBM Corp., Armonk. N.Y., USA) with p-value of <0.05 was taken to signify statistical significance. In addition, we extracted 2x2 contingency table data and calculated the performance of a rapid antibody screening test for asymptomatic pregnant women (sensitivity, specificity, Positive Predictive Value [PPV], and Negative Predictive Value [NPV]).

RESULT

From one-year data obtained in the study, we had a total of 298 pregnant women admitted to the obstetric emergency room of Dr. Soetomo General Academic Hospital Surabaya. We subsequently excluded 33 pregnant women diagnosed with symptomatic Covid-19 from the study. Thus, in total, this study included 265 pregnant women who had paired testing of rapid antibody tests along with RT-PCR SARS-CoV-2 test. During the study period, we also collected 135 Covid-19 cases among pregnant women whom the majority of patients were asymptomatic (89%), as shown in Figure 1. Therefore, cumulatively, the characteristics from 265 asymptomatic pregnant women who had paired testing of rapid antibody tests along with RT-PCR SARS-CoV-2 test were provided in Table I.

Table I. Distribution of asymptomatic patient characteristics

Characteristics	RT-PCR SARS-CoV-2 (+) (n = 92)	RT-PCR SARS-CoV-2 (-) (n = 173)	*p*
Maternal age, median (IQR)	29 (8.75)	29 (10)	0.748
Gestational age, median (IQR)	38 (3)	38 (5)	0.185
Parity, no. (%)			
Primigravida	28 (30.4)	56 (32.4)	0.747
Multigravida	64 (69.6)	117 (69.6)	
Comorbidities, no. (%)			
Any	29 (31.5)	68 (39.3)	0.21
Obesity	21 (22.8)	35 (20.2)	0.622
Hypertension in pregnancy	9 (9.8)	29 (16.8)	0.123
Heart disease	0 (0)	4 (2.3)	0.302
Autoimmune disease	1 (1.1)	0 (0)	0.347
Diabetes in pregnancy	1 (1.1)	1 (0.6)	0.649
Referral Classification, no. (%)			
by herself	30 (32.6%)	42 (24.3%)	0.273
rejected by other hospital	27 (29.3%)	50 (28.9%)	
referred by other hospital	35 (38.0%)	81 (46.8%)	

CONTINUE

Table I. Distribution of asymptomatic patient characteristics cont)

Characteristics	RT-PCR SARS-CoV-2 (+) (n = 92)	RT-PCR SARS-CoV-2 (-) (n = 173)	*p*
Rapid antibody test, no. (%)			
Reactive	82 (89.1%)	135 (78.0%)	**0.026**
Laboratory parameter, median (IQR)			
White blood cell count (x10^3/µL)	11.85 (11.25)	13.43 (6.53)	**0.021**
Neutrophils (x10^3/µL)	10.56 (7.14)	9.21 (6.3)	**0.025**
Lymphocyte (x10^3/µL)	1.54 (0.84)	1.66 (0.79)	0.41
Neutrophil to lymphocyte ratio (x10^3/µL)	5.68 (5.9)	6.73 (6.62)	0.35

Abbreviations: IQR, interquartile range; RT-PCR, reverse-transcriptase polymerase chain reaction, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

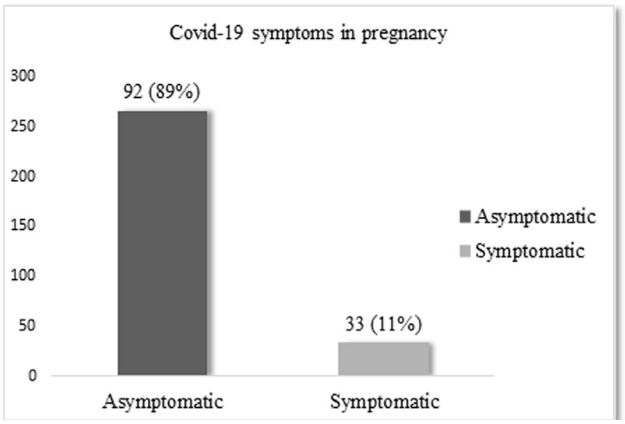

Figure 1. The proportion of pregnant women with Covid-19 based on the presence of symptoms

The majority of patients included in this study were aterm and admitted for labor and delivery. The laboratory parameters obtained showed a significantly lower number of leukocytes (p=0.021) accompanied by higher neutrophils (p=0.025) in Covid-19 pregnant patients. There was also a significant association between the rapid antibody test and RT-PCR SARS-CoV-2 test (p=0.026). This study conducted an evaluation of rapid antibody screening capabilities for the asymptomatic Covid-19 pregnant cases with high sensitivity (89.13%) and low specificity (21.97%) (Table II).

This study explored the calculation of required costs using the first strategy, rapid antibody test screening followed by SARS-COV-2 RT-PCR test if the rapid antibody results were reactive compared to the second strategy, universal RT-PCR SARS-COV-2 testing for all admitted patients. As a result, it was a significantly more efficient cost (IDR 766,363.64 ± 347,784.45 vs. IDR 900,000; p<0.001) with a decrease in expense of IDR 36,180,000 (USD 2,514) or 15% lower using rapid antibody screening method compared directly to the universal RT-PCR test.

Table II. Rapid antibody test screening performance on asymptomatic pregnant women with Covid-19

Rapid Antibody Test	RT-PCR SARS-CoV-2 (+) (n = 92)	RT-PCR SARS-CoV-2 (-) (n = 173)
Reactive, no. (%)	82 (89.1)	135 (78)
Non-reactive, no. (%)	10 (10.9)	38 (22)
Sensitivity, % (95%CI)	89.13 (80.92-94.66)	
Specificity, % (95%CI)	21.97 (16.04-28.88)	
Positive predictive value, % (95%CI)	37.79 (35.52-40.32)	
Negative predictive value, % (95%CI)	79.17 (66.51-87.91)	

Abbreviations: CI, confidence interval.

DISCUSSION

This one-year retrospective study was conducted since the Covid-19 case began to be identified in Dr. Soetomo General Academic Hospital until the end of March 2021 before the protocol was changed by replacing the use of rapid antibody test with rapid antigen test as a screening protocol. Among 298 Covid-19 cases in pregnancy obtained during the study period, the majority of the patients did not have any symptoms (89%). This finding was in line with several studies which reported higher asymptomatic proportion (2, 8). Our initial two-months study in the same center also showed similar results, although the proportion was smaller (9). A systematic review from 67,271 pregnant women revealed that pregnant women with Covid-19 were less likely to have symptoms (10). Some other studies showed opposite results with the majority of symptomatic proportions (11, 12). These different results are likely to be due to the differences in research design, especially the strategy for Covid-19 testing in each facility. If the Covid-19 testing is obtained only for symptoms or close contact history will undoubtedly cause a higher symptomatic proportion in the study. Therefore, it can be estimated that the detection of asymptomatic cases can be underestimated using this protocol. This study similarly found that most pregnant women with Covid-19 came to the hospital in aterm condition with the purpose of labor that concordant with the previous studies (2, 13, 14). This condition causes challenges in detecting the asymptomatic Covid-19 cases because most patients who came for labor and delivery did not have respiratory disorders that cannot be anticipated if we do not actively identify the cases.

There is no significant difference in pregnant comorbidity such as diabetes and hypertension in pregnancy, obesity, heart disease, and autoimmune with Covid-19

incidence. Similar to other studies, obesity is the significant comorbidity found in the covid-19 pregnant woman (2, 15). Several studies showed that maternal comorbidity could impact the severity of Covid-19 but need further studies to confirm this association (12, 16). Prior meta-analysis showed that chronic hypertension, preeclampsia, and preexisting diabetes were associated with more severe symptoms in pregnancy (10). Some laboratory parameters showed a significant difference in Covid-19, including the lower white blood count and the high neutrophil. However, many studies showed opposite results, Chen et al. revealed 25% leukocytosis in severe cases, while Huang et al. found an increase of leukocyte count in 54% (17, 18). An increase in the neutrophil count is commonly found in Covid-19 cases, correlated with cytokine storm (19). However, using this parameter as a differentiator of Covid-19 patients is challenging because the results were inconsistent. In addition, physiological changes in leukocyte count from 6,000-17,000/mm3 and even higher until 25,000/mm3 might confuse the use of white blood cells as a parameter on Covid-19 (20).

In this study, there was a significant association between rapid antibody tests with the results of the RT-PCR SARS-COV-2 with good screening sensitivity (89.13%) but low specificity (21.97%). With this high sensitivity, rapid antibody tests can detect 82 out of 92 cases of asymptomatic Covid-19 in pregnancy, which is certainly very important to be identified to control the possibility of Covid-19 transmission from patients in the hospital. Some other studies with larger samples showed lower sensitivity (21). Our previous study also showed lower sensitivity in both symptomatic and asymptomatic Covid-19 pregnant cases (9). It should be noteworthy that PPV on this antibody screening is only 37.79%. On the other hand, our study revealed 135 false-negative cases that showed that this antibody test examination solely could not be used as the only test in identifying Covid-19 without RT-PCR SARS-CoV-2 to confirm the acute Covid-19 case, which is likely to be infectious (6). Moreover, this high false-negative showed that the seroprevalence of Covid-19 cases in pregnant women, which can be interpreted as pregnant women who have previously been infected, was relatively high compared with other studies (22).

Some earlier research advocates universal screening by using RT-PCR based on conditions with high infection transmission in the population (5). This study attempted to compare the costs required using the initial rapid antibody test screening strategy and followed by the SARS-CoV-2 RT-PCR test if it obtained reactive results with the strategy of universal RT-PCR test upon all pregnant women. To the best of our knowledge, no study discussed the cost-effectiveness of testing, especially in the obstetric population with Covid-19. This study found that financing is more efficient if we carried out an initial rapid antibody screening strategy than directly examining all patients with RT-PCR. The saved cost can reach up to IDR 36,180,000 (USD 2,514) or reduce financing up to 15%.

Although most of the health facilities have replaced screening strategy using rapid antigen test instead of rapid antibody test, according to the WHO target, the rapid antigen diagnostic of SARS-CoV-2 should be at minimum 80% sensitivity to detect SARS-CoV-2. However, a prior study compared the diagnostic accuracy of a commercial SARS-CoV-2 antigen detection kit and showed lower antigen detection in cycle threshold value more than 30 (compared to RT-PCR diagnosis) (23). Therefore, the rapid antigen kit might not detect an asymptomatic population in pregnancy, while the antibody is still detected in this population.

From this study, the performance of antibody detection sensitivity is above 80% (89,1%), which is still needed to screen patients, especially in the pregnant population. The obstetric patients in our hospital undergo either cesarean section or normal pregnancy. Hence, screening remains needed to divide the personal protective equipment (PPE) needs. Therefore, antibody detection can reduce the cost and help to screen such populations.

Generally, this study found out that if we only performed Covid-19 tests in symptomatic cases, it would leave 92 cases of pregnancy with asymptomatic Covid-19 infection, which is undoubtedly very precarious for the patients and health workers in the health institution. By using screening based on the rapid antibody test, we can detect 82 asymptomatic cases. In contrast, if universal RT-PCR were used, it would detect all asymptomatic cases but with a higher cost and potentially interfere with the RT-PCR test capacity in the health facility, especially in the area with limited testing capacity. In addition, our study has several limitations. Notably, the study was conducted only in a single-center hospital, based on the experience at our institution so that sometimes it cannot represent the conditions in the population. However, the hospital chosen in this study is the largest Covid-19 referral hospital in the second largest province in Indonesia. Furthermore, this study is not likely to be done in areas that have already implemented vaccinations in most citizens, including pregnant women, as already recommended in many countries (24, 25). Nevertheless, in our country, vaccination was still limited to health workers and the aged population at the time of this study. All patients who have been examined have never received any SARS-CoV-2 vaccine yet.

CONCLUSION

Numerous asymptomatic Covid-19 cases in pregnant women explicated the importance of case identification management, which is not likely to be done with the testing solely based on symptoms and contact history.

Implementing initial rapid antibody tests in low support circumstances has advantages in identifying higher asymptomatic Covid-19 case in pregnancy with good sensitivity. However, the high false-positive result showed that this test could not be used individually without confirming the RT-PCR SARS-CoV-2 test as a gold standard. Furthermore, this initial screening strategy evince more cost-effective than implementing universal PCR testing simulated from this study.

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