Review Artikel

ACE2 Receptors Finding in Placenta with Intrauterine Fetal COVID-19 Infection: A Meta-Analysis

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Abstract

Objective: Association between ACE2 receptors in the placenta and the incidence of intrauterine COVID-19 infection in pregnant women infected with COVID-19

Methods: Systematic review and meta-analysis of placenta in pregnant women with COVID-19 infection, ACE2 receptor in placenta, and RT-PCR of neonates from COVID-19 pregnant women. This study followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) protocol.

Results: 6 journals meet the inclusion criteria. ACE2 receptors were found in syncytiotrophoblasts 72/72 (100%), cytotrophoblasts 41/72 (56.9%), extravillous trophoblasts 24/72 (33.3%), decidual cells 2/72 (2.7%), villous stromal cells 1/72 (1.3%), and 1/72 stromal cells (1.3%) with the incidence of neonates infected with SARS-CoV-2 from pregnant women with COVID-19 10.5%, odds ratio (OR) between ACE2 receptors and neonates infected with COVID-19 is 1.97 (95%CI 0.05–81.09), the pooled proportion of ACE2 receptor findings in 72 placentas in pregnant women with COVID-19 infection, syncytiotrophoblast 98.3 (95% CI 94.3–99.9), cytotrophoblast 40.3 (95% CI 2.3–88.9), and extravillous trophoblast 35.2 (95% CI 0.2–88.5).

Conclusion: Expression of ACE2 receptors is always present in the placenta of pregnant women, and there is an association but non-significant between ACE2 receptors in the placenta and the incidence of COVID-19 intrauterine infection with an odds ratio of 1.97 (95%CI 0.05-81.09).

Keywords: COVID-19 infection, Intrauterine, ACE2 receptor placenta.

Reseptor ACE2 Pada Plasenta dengan Kejadian Infeksi COVID-19 Intrauterine pada Janin: *A Meta-Analysis*

Abstrak

Tujuan: Hubungan antara reseptor ACE2 di plasenta dengan angka kejadian infeksi COVID-19 *intrauterine* pada ibu hamil yang terinfeksi COVID-19.

Metode: Tinjauan sistematis dan meta-analisis plasenta pada ibu hamil COVID-19, reseptor ACE2 pada plasenta, dan hasil uji RT-PCR neonatus dari ibu hamil COVID-19. Penelitian ini mengikuti protokol *Preferred Reporting Items for Systematic Review and Meta-analyses* (PRISMA).

Hasil: 6 jurnal memenuhi kriteria. Reseptor ACE2 ditemukan di sinsitiotrofoblas 72/72 (100%), 41/72 sitotrofoblas (56.9%), trofoblas ekstravili 24/72 (33.3%), sel desidua 2/72 (2.7%), sel stroma vili 1/72 (1.3%), dan sel stroma 1/72 (1.3%) dengan insidensi neonatus yang terinfeksi SARS-CoV-2 dari ibu hamil dengan COVID-19 sebanyak 10.5%, odds ratio (OR) antara reseptor ACE2 dan neonatus terinfeksi COVID-19 adalah 1.97 (95%CI 0.05–81.09), proporsi gabungan penemuan reseptor ACE2 pada 72 plasenta ibu hamil COVID-19, sintiotrofoblas 98.3 (95%CI 94.3 – 99.9), sitotrofoblas 40.3 (95%CI 2.3 – 88.9), dan trofoblas ekstravili 35.2 (95%CI 0.2 – 88.5).

Kesimpulan: Ekspresi reseptor ACE2 selalu ditemukan di plasenta ibu hamil, dan terdapat hubungan yang tidak bermakna antara reseptor ACE2 di plasenta dengan kejadian infeksi intrauterine COVID-19 dengan *odds ratio* 1.97 (95%CI 0.05-81.09).

Kata kunci : Infeksi COVID-19, Intrauterine, reseptor ACE2 plasenta.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first reported in Wuhan, China in December 2019 and spread from China throughout the worldwide.[1] It has been confirmed that angiotensin converting enzyme 2 (ACE2) on host cells is considered as the main receptor the corona virus uses to enter and transmit in human bodies.[2-3] Expression of ACE2 can be found on the outer surface of cells (membranes) on various organs, such as the lungs, arteries, heart, and others. [4]

Pregnant women are categorized at higher risk to severe SARS-CoV-2 infection, this occurs due to physiological changes in pregnancy that can significantly impact the immune system, respiratory system and cardiovascular function and coagulation.[5-6] Expression of ACE2 as a SARS-CoV-2 can be found in the placenta during pregnancy, especially in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of the primary and secondary villi, with the finding of higher ACE2 expression in the placenta in early pregnancy.[7] Recent reports using immunohistochemical techniques have shown positive results through the findings of S protein and N protein from SARS-CoV-2 in the cytoplasm of the syncytiotrophoblast and N protein in intervillous macrophages along with hofbauer cell in the placenta of pregnant women with COVID-19, this may suggests SARS-CoV-2 can possibly infect the placenta and be transmitted to the fetus before delivery.[5,7-8] Intrauterine vertical transmission of COVID-19 from mother to fetus through the placenta is still contoversial, although several studies have shown the possibility of intrauterine transmission of COVID-19 infection, however there are studies that did not indicate the vertical transmission, thus the data SARS-CoV-2 can pass through the placenta and infect the fetus through interaction with the placental ACE2 receptor is lacking.[5-8] Therefore, the author wanted to know about the association between ACE2 receptors in the placenta with the incidence of intrauterine infection in pregnant women infected with COVID-19.

Method

Search strategy

On December 30th 2021, systematic review of journal searches has been conducted through five electronic databases, namely *PubMed*, *Science Direct*, *Scopus*, *Google Scholar* dan *Research Gated* with the topic of ACE2 receptors in the placenta with the intrauterine COVID-19 infection using the MeSH keywords listed in table 1. The journals taken were published from January 2020 – December 30th 2021. The search for articles was limited to incomplete research articles.

- **Study selection**

Journals with cohort study designs, case reports, and case series examining ACE2 receptors in the placenta with COVID-19 intrauterine infection were considered eligible for this analysis. The exclusion criteria were: 1) Review of articles and narrative articles; 2) Journal with non-pregnant population; 3) Journals that did not report ACE2 receptors on the placenta via placental biopsy; 4) Journals that do not report RT-PCR tests on fetuses.

The identified articles were managed by EndNote 20 software to exclude duplicate journals. Researchers (HHW) and (THW) already reviewed the titles and abstracts based on the articles inclusion and exclusion criteria above, which supervised by other researchers (TPS). The selected full-text assessment and the extraction of relevant data were carried out by the same researcher.

Table 1 Keywords of This Systematic Review

Databases	Keywords	Hits
PubMed	sars-cov-2 OR covid-19 OR cov-19 OR 2019-ncov AND ace2 receptor placenta OR ace2 receptor maternal-fetal OR ace2 receptor vertical transmission OR ace2 receptor placenta infection OR ace2 intrauterine infection	115
Science Direct	sars-cov-2 OR covid-19 OR cov-19 OR 2019-ncov AND ace2 receptor placenta OR ace2 receptor maternal-fetal OR ace2 receptor vertical transmission OR ace2 receptor placenta infection OR ace2 intrauterine infection	2209
Scopus	sars-cov-2 OR covid-19 OR cov-19 OR 2019-ncov AND ace2 receptor placenta OR ace2 receptor maternal-fetal OR ace2 receptor vertical transmission OR ace2 receptor placenta infection OR ace2 intrauterine infection	114
Google Scholar	sars-cov-2 OR covid-19 OR coronavirus AND histopathology ace2 receptor placenta OR ace2 receptor maternal-fetal OR ace2 receptor vertical transmission OR vertical transmission placenta	1
Research Gate	sars-cov-2 OR covid-19 OR coronavirus AND histopathology ace2 receptor placenta OR ace2 receptor maternal-fetal OR ace2 receptor vertical transmission OR vertical transmission placenta	1

– **Data Extraction**

We extracted the following data: 1) Author and Year of publication; 2) Study location; 3) Study design; 4) Pregnancies; 5) Neonates; 6) Gestational day/age when the pregnant women get infected by COVID-19 before giving birth; 7) The severity of COVID-19 symptoms in pregnant women; 8) COVID-19 RT-PCR test results in neonates; 9) Placental samples; 10) Types of ACE2 receptors assessment on the placenta; 11) Number & Location of ACE2 receptors found in the placenta. Then we used a meta-analysis to perform a comparative analysis and pooled proportion of the data by calculating the 95% percentage confidence intervals (CI) and $P<0.05$ as the association measure between ACE2 receptors in the placenta and the incidence of intrauterine COVID-19 infection. CI represents the range of values of an effect estimate and $P<0.05$ is statistically significant.

MedCalc 20012 software and Review Manager 5.4.1 was used for the meta-analysis. The results of data processing are presented in the form of a forest plot graphic. Heterogeneity between studies will be assessed using the I^2 statistic, a value <50% indicates the study can be considered homogeneous and a fixed effect model can be used in this meta-analysis, while a value >50% is observed that there is substantial heterogeneity and uses a random effects model. Egger's Test and funnel plots were used to identify publication bias in the distribution of articles from those included in the study. However, the funnel plot asymmetry test was not used for the number of publications included in the study <10, which fits the scenario of this study.

– **Study quality assessment**

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were used to perform this systematic review and meta-analysis.[9] The quality case reports and case series were assessed using the methodological quality and synthesis of case-series and case-reports quality scale.[10]

Result

From five databases (*Pubmed, Science Direct, Scopus, Google Scholar* and *Research Gate)*, we found 2440 articles were scanned

for 115 Pubmed articles, 2209 Science Direct articles, 114 articles from Scopus, and one each from Google Scholar and Research Gate. (Fig 1). The collected journals were taken according to the inclusion criteria and selected according to the PRISMA method. First, checking the duplication of article data, it is found that there are 2117 duplicate articles. Second, 323 articles were screened and selected for research titles and abstracts in journals, a total of 268 articles were excluded based on titles and abstracts for the following reasons: (1) 263 journals did not report on placental ACE2 receptors, review articles, narrative articles; (2) 5 journals do not use English. The next stage, screening, assessment and research selection was carried out on 55 journals with full text, 49 journals were excluded on the grounds of: (1) 3 journals were not found; (2) 18 journals are review articles; (3) 11 journals did not perform RT-PCR tests on fetuses; (4) 14 journals did not report ACE2 receptors on the placenta via placental biopsy; (5) 3 non-population journals of pregnant women. The final stage, 6 final journals with all the inclusion criteria and included in this systematic review were found.

In 72 pregnant women infected with COVID-19 alongside 76 neonates from pregnant women based on six selected articles (Table 2), it was found that 8/76 (10.5%) neonates were infected with COVID-19 with RT-PCR confirmation. There are five studies that report the days and gestational age of pregnant women when infected with SARS-CoV-2 before giving birth, 4 of the 5 studies reported the gestational age of pregnant women when infected with SARS-CoV-2 are during 23 weeks + 1 day to 40 weeks[11-12, 15-16] and 4 days – 17 antepartum.[13] Five of the six studies reported the severity of COVID-19

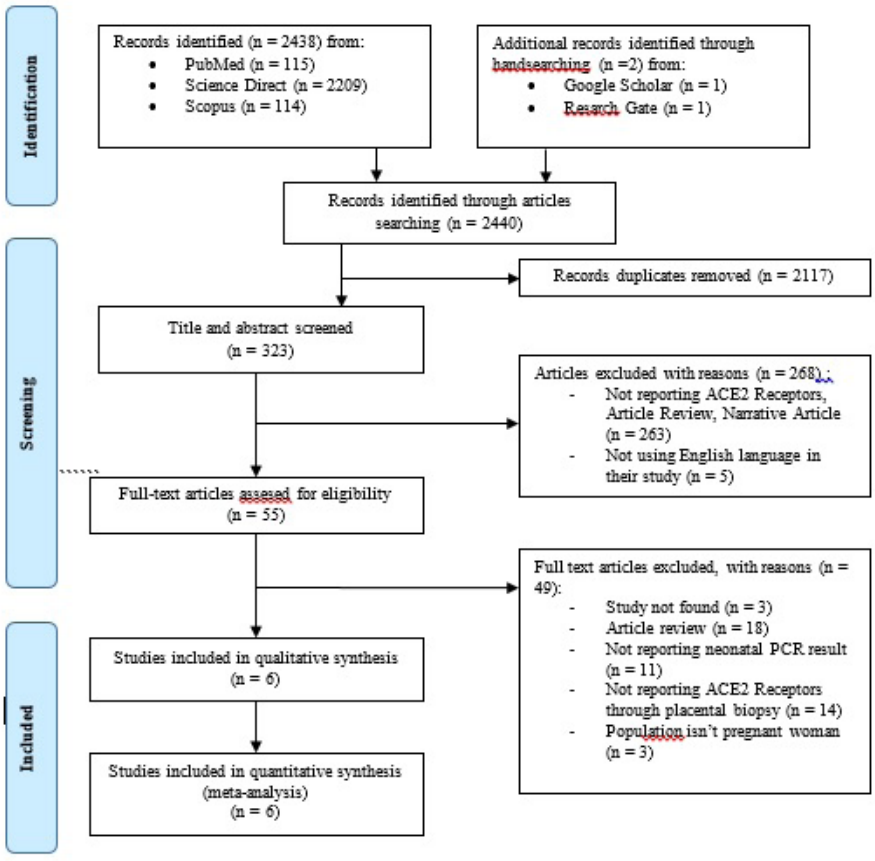

Figure 1 PRISMA Flowchart

Table 2 Published Studies on the ACE2 Receptor and the Incidence of Intrauterine Infection with COVID-19

Author/ Year	Study Location	Study Design	Pregnancies, n	Neonates, n	Gestational Day/Age (+)COVID-19*	Severity of COVID-19	RT-PCR Test Results in Neonates	Placental Samples, n	Types of ACE2 Receptor Assessment in the Placenta	Number & Location of Findings ACE2 Receptor in Placenta
Colson *et al.*[11]/2021	Belgium	Cohort	30	30	23W+1D until 40W	18 asymptomatic, 23 symptomatic	30 Negative	30	IHC, *Western Blot*, & RT-PCR	+ : STB (30) + : CT (30)
Hetch *et al.*[12]/2020	USA	Cohort	17	19 (2 Multiple pregnancy)	30W until 41W+1D	6 asymptomatic, 11 symptomatic	1 Positive, 18 Negative	17	IHC	+ : STB (17) + : CT (10) + : EVT (17)
Dong *et al.*[13]/2021	China	Cohort	7	7	4D–17D antepartum	4 asymptomatic, 3 symptomatic	7 Negative	7	IHC	+ : STB (7) + : EVT (7)
Taglauer *et al.*[14]/2020	USA	Cohort	15	15	NR	NR	5 Positive. 10 Negative	15	IHC & IF	+ : STB (15)
Disse *et al.*[15]/2021	Germany	Case Report	1	3 (Triple pregnancy)	28W+3D	1 symptomatic	2 Positive, 1 Negative	1	IHC	+ : STB (1) + : CT (1) + : VSC (1) + : STC (1)
Zhao *et al.*[16]/2020	China	Case Series	2	2	24W+1D Until 26W+3D	2 symptomatic	2 Negative	2	IHC & RT-PCR	+ : STB (2) + : DC (2)

*in weeks and/or day. D: Day; W: Weeks; IHC: Immunohistochemistry; IF: Immunofluorescence; RT-PCR: Real Time Polymerase Chain Reaction; STB: Syncytiotrophoblasts; CT: Cytotrophoblasts; EVT: Extravillous Trophoblast; DC: Decidual Cells; VSC: Villous Stroma Cell; STC: Stromal Cells

symptoms in pregnant women infected with SARS-CoV-2, one study had a higher proportion of patients with asymptomatic disease[13], whereas the other four studies had a higher proportion of patients with symptomatic disease.[11-12, 14-16]

These six studies[11-16] (Table 2) showed that there are expression of ACE2 receptors in 72 placental samples from 72 pregnant women infected with COVID-19 using the immunohistochemical analysis method, the results of the analysis is ACE2 receptors can be found on syncytiotrophoblasts from 72/72 (100%), cytotrophoblasts 41/72 (56.9%), extravillous trophoblast 24/72 (33.3%), decidual cells 2/72 (2.7%), stromal cells and villous stroma cell 1/72 (1.3%).

Six studies[11-16] (table 3) reported on analyzing the findings of ACE2 receptors in the placenta. The combined proportions showed that the proportion of ACE2 receptors found in placental syncytiotrophoblast was 98.3 (95% CI 94.3–99.9), cytotrophoblast 40.3 (95% CI 2.3–88.9), and extravillous trophoblast 35.2 (95% CI 0.2–88.5) of 72 samples placenta.

Two studies[12,14] (table 4) showed an odds ratio of 1.97 (0.05–81.09) between the findings of ACE2 receptors in placenta and neonatal outcomes of COVID-19 positive pregnant women and COVID-19 negative pregnant women with a statistical value (P = 0.72). The results of the heterogeneity test showed that significant heterogeneity was found between studies (I^2=60%). (2/6) the other study did not perform a meta-analysis, due to the absence of a control group.

Discussion

Six research articles[11-16] reported between 76 babies that were born from mothers infected with COVID-19, 10 babies among them were found infected with COVID-19 (10.5%), the diagnosis of COVID-19 in pregnant women and infants was based on RT-PCR, which

Table 3 Pooled Proportion of ACE2 Receptor Finding Locations in 72 Placenta Samples

ACE2 Receptor Finding Location	Studies (n)	Placental Samples (n=72) and Distribution	I^2 (%)	Pooled Proportion (95% CI)
Syncytiotrophoblast	6	72	0%	98.3 (94.3-99.9)
Cytotrophoblast	6	41	95%	40.3 (2.3-88.9)
Trophoblast extravillious	6	24	95.8%	35.2 (0.2-88.5)

Table 4 Meta-Analysis of Odds Ratio Between the Findings of ACE2 Receptors in Placenta and Neonatal Outcomes of COVID-19 Positive Pregnant Women And COVID-19 Negative Pregnant Women

	Neonates/Pregnancies (n) (%)			
Studies (n)	Pregnancy with COVID-19	Pregnancy without COVID-19	I^2, %	Odds Ratio (95% CI)
2	6/32 (18.75%)	0/11 (0%)	60%	2

proves that even though the placenta has ACE2 receptors does not cause the baby to be directly infected, this may be related to the function of the placenta which has physical and immunological defense functions as a barrier, and the presence of decidual macrophages for antimicrobial function, as well as placental T cells for regulation of maternal-fetal tolerance and virus-specific CD8+T cells. The decidua protects the fetus from infection, while the syncytiotrophoblast and cytotrophoblast in the placenta act as an additional barrier to the passage of infection and exhibit varying resistance to pathogens.[17]

Vertical transmission of the virus from mother to fetus has several potential causes, including the destruction of the villous tree with damage to the lining of the fetus. syncytiotrophoblast protection, induces apoptosis in addition, viral infection and damage to blood vessels in the placenta can occur as a result of infected maternal immune cells in all layers of the syncytiotrophoblast, paracellular or transcellular, and vertical transmission of viral infection due to aspirated amniotic fluid.

Expression of ACE2 receptors in 72 placenta samples combined from six research articles[11-16] by pregnant women infected with COVID-19 was found in the syncytiotrophoblast (100%), cytotrophoblast (56.9%), extravillous trophoblast (33.3%), decidual cells (2.7%), villous stromal cells (1.3%), and stromal cells (1.3%) from the placenta, this is in line with the evidence of the presence of ACE2 receptors in the placenta at the maternal-fetal interface including parts of the syncytiotrophoblast, cytotrophoblast, decidual perivascular cells, and stromal cells.[20]

In Colson et al.[11] study, ACE2 receptor expression was found to be quite high in syncytiotrophoblasts at <30 weeks' gestation and decreased >30 weeks' by histological score (H-score), it was also found in Zhao et al.[16] Study that ACE2 receptor expression was high in early pregnancy, the different findings on ACE2 receptor expression because ACE2 receptors tend to be found to be high in early gestation, but relatively low ACE2 receptors

in pregnant women with COVID-19 are associated with premature placentas and severe infections, thus, the placenta not only expresses ACE2 receptors as a portal of entry for the virus, but is also responsive to infection and results in downregulation which is an indication of infection.

The study of Taglauer et al.[14] reported that ACE2 receptor expression was present in syncytiotrophoblasts in the placenta widely both in positive and negative infection of COVID-19, but it was found that there was a significant decrease in the level of ACE2 receptor expression in placenta of pregnant women with COVID-19 compared to placenta tissue of pregnant women negative for COVID-19 as a control, this may be due to ACE2 being the main receptor for SARS-CoV-2, the S protein from SARS-CoV-2 can bind to ACE2 as a receptor with high affinity, ACE2 that bound to the S protein from SARS-CoV-2 can cause ACE2 endocytosis with viral particles that enter the endosome, this can cause a decrease in the expression of ACE2 receptors on the membrane surface.[8,22]

The structural proteins of SARS-CoV-2, namely S and N proteins, were found by Dong et al.[13] in syncytiotrophoblasts, as well as Taglauer et al.[14] who found S protein in all villous compartments of the placenta, and Disse et al.[15] who found Protein N were strongly found in syncytiotrophoblast cells, while in the study of Zhao et al.[16] Said the RNA nucleic acid test in the placenta was not found. In the study of Dong et al.[13], Taglauer et al.[14], and Disse et al.[15] the N and/ or S proteins of SARS-CoV-2 in the placenta tended to always be found in COVID-19 pregnant women with COVID-19-infected neonates.

A pooled meta-analysis of the proportion of six studies that reported finding placental ACE2 receptor expression in the syncytiotrophoblast of 72 placentas of pregnant women infected with SARS-CoV-2 was 98.3% or 98.3 (95% CI 94.3 – 99.9) of 72 placentas tested. In six studies, it was found that ACE2 receptors found in placental syncytiotrophoblasts were almost always found, whereas the pooled proportion of ACE2 receptors found in placental cytotrophoblast was 40.3% or 40.3 (95%CI 2.3 – 88.9) and extravillous trophoblast 35.2% or 35.2 (95%CI 0.2 – 88.5) indicating the finding of ACE2 receptors in the cytotrophoblast and trophoblast extravillous placenta is not always found.

The results of a comparative meta-analysis of data extracted from (2/6) cohort studies using the statistical method of odds ratio were 1.97 (95%CI 0.05–81.09) indicating that neonates in pregnant women infected with COVID-19 with the presence of ACE2 receptors in the placenta had a 1.97 times risk of developing COVID-19 infection than neonates with COVID-19 negative mothers with the findings of ACE2 receptors in the placenta, but the horizontal line CI deviated with the vertical line 1 and the P value=0.72, so there is an association but non-significant between ACE2 receptors in the placenta and the incidence of COVID-19 intrauterine infection.

Based on these reports, this suggests that there is a possibility that the placenta can be infected and indicates the presence of a virus that can infect the placenta and penetrate the placental barrier by the presence of the S and N proteins of SARS-CoV-2 in the syncytiotrophoblast which is in direct contact with maternal bleeding and is the lining of the placenta. First, the virus must pass to the fetus, but not all cases result in vertical transmission between the mother and the neonate, so that the placenta can indeed be infected, but the cases are very rare, and not always the fetus can be infected.

Conclusion

Expression of ACE2 receptors is always present in the placenta of pregnant women,

and there is an association but non-significant between ACE2 receptors in the placenta and the incidence of COVID-19 intrauterine infection with an odds ratio of 1.97 (95%CI 0.05-81.09).

Limitations

A more comprehensive systematic review is needed, because the authors found several research articles that were inaccessible in this systematic review due to language limitations, incomplete research articles, and non-free access articles.

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