

Systematic Review**Maternal and Perinatal Outcomes of COVID-19 in Pregnant Women*****Luaran Maternal dan Perinatal pada Ibu Hamil dengan COVID-19*****Putu H. I. Pramana¹, Gede B. S. Wirawan², Made Y. D. Astiti³, Kaspan¹**

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Abstract

Objective: To describe and identify risk factors of maternal and perinatal outcome of COVID-19 in pregnant women.

Methods: Literature search was conducted on MEDLINE and Google Scholar databases for articles published in December 2020 to January 2021. Keywords used includes 'COVID-19', 'pregnant women', 'maternal outcome' and 'fetal outcome.' Critical appraisal and selection were conducted to identify articles that fulfill inclusion criteria. The selected articles were analyzed thematically to answer the research questions.

Results: Literature search yielded 124 articles with 11 included in final analysis. The results showed low to moderate risk of maternal and perinatal adverse outcomes, including low risks for maternal and perinatal mortality coupled with moderate risk for maternal ICU admission and preterm birth with NICU admission for the newborn. Higher risk was observed for pregnant women with symptomatic COVID-19 infection, which points to the necessity for awareness of the risk and targeted early detection efforts.

Conclusions: There are low risk for adverse maternal and perinatal outcomes, including mortality and ICU/NICU admission, associated with COVID-19 infection in pregnant women. Risk factors for adverse outcomes included pregnant women with symptomatic COVID-19 infection.

Keywords: COVID-19, ICU, maternal mortality, NICU, perinatal mortality, preterm birth.

Abstrak

Tujuan: Mendeskripsikan dan mengidentifikasi faktor risiko luaran maternal dan perinatal COVID-19 pada ibu hamil.

Metode: Penelusuran literatur dilakukan di database MEDLINE dan Google Scholar untuk artikel yang diterbitkan pada Desember 2020 hingga Januari 2021. Kata kunci yang digunakan meliputi 'COVID-19', 'wanita hamil', 'keluaran ibu' dan 'hasil janin'. Penilaian dan seleksi kritis dilakukan untuk mengidentifikasi artikel yang memenuhi kriteria inklusi. Artikel yang dipilih dianalisis secara tematis untuk menjawab pertanyaan penelitian.

Hasil: Penelusuran literatur menghasilkan 124 artikel dengan 11 termasuk dalam analisis akhir. Hasil penelitian menunjukkan risiko rendah hingga sedang untuk luaran buruk maternal dan perinatal, termasuk risiko rendah untuk kematian maternal dan perinatal ditambah dengan risiko sedang untuk masuk ICU ibu dan kelahiran prematur dengan masuk NICU untuk bayi baru lahir. Risiko yang lebih tinggi diamati untuk wanita hamil dengan infeksi COVID-19 bergejala, yang menunjukkan perlunya kesadaran akan risiko dan upaya deteksi dini yang ditargetkan.

Kesimpulan: Terdapat risiko rendah untuk luaran buruk maternal dan perinatal, termasuk kematian dan rawat inap di ICU/NICU, terkait dengan infeksi COVID-19 pada wanita hamil. Faktor risiko untuk luaran buruk adalah wanita hamil dengan gejala infeksi COVID-19.

Kata kunci: COVID-19, ICU, kelahiran preterm, mortalitas maternal, mortalitas perinatal, NICU.

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INTRODUCTION

COVID-19 has infected over 100 million people worldwide, causing over 2 million deaths. In many countries, its spread is uncontrolled with most nations in the world reporting community transmissions.¹ In such countries, every members of community are considered at risk population, regardless of known contact to an infected person, including pregnant women.²

There has been no definitive data on the extent pregnant women make up COVID-19 confirmed cases worldwide. An early screening study in New York, United States, found 13.5% asymptomatic infections and 1.9% symptomatic infections from 215 screened obstetric patients presenting for delivery.³ However, an epidemiological update by Pan-American Health Organization (PAHO) in September 2020 presented much lower rate with 60,458 cases in pregnant women from over 6 million cumulative cases, a much lower proportion.⁴

Nevertheless, infection of a novel virus to pregnant women population opens up various unknown risks. The most immediate being to the pregnancy, maternal, and perinatal outcomes. Reviews on early reports of COVID-19 impacts on pregnancy showed differing results. One review reported over 90% pregnant women with COVID-19 required caesarean sections with 10.7% fetal distress and 21.3% preterm birth.⁵ Another reported much bleaker situation with over 60% fetal distress.⁶

These early reviews relied much on case reports and case series, each reporting few cases. As demonstrated by aforementioned PAHO report, COVID-19 cases in pregnant women were quite rare. As situation developed, more reports emerged which included larger sample size and more accurately described the outcome of COVID-19 infection among pregnant women.

In accordance to these new emerging evidences, we aimed to review it to make a more cohesive picture. Our primary objective in this review is to describe maternal and perinatal outcome of COVID-19 infection in pregnancy. Meanwhile, our secondary objective is to describe risk factors for adverse outcomes for pregnant women with COVID-19 infection.

METHODS

We conducted a review on open-access literatures on COVID-19 infection in pregnant

women. Literature search was conducted on MEDLINE and Google Scholar databases from December 2020 to January 2021 using keywords that included 'COVID-19', 'pregnant women', 'maternal outcome' and 'fetal outcome.' Results was limited to those published after May 1st 2020.

For analysis, we included descriptive and analytic studies describing maternal and fetal outcome of confirmed COVID-19 infection during pregnancy. We excluded case reports, case series, and studies with sample size less than 50 to give more accurate picture of the situation. We also excluded studies which conflated the statistics of confirmed and suspected COVID-19 cases among pregnant women.

Variables of interest for maternal outcome included ICU admission and maternal mortality rate. Meanwhile, variables of interest pregnancy and perinatal outcomes included percentage of live birth, preterm birth, NICU admission, and mortality. Included studies do not have to report on all these variables. Report one at least one variable was sufficient for inclusion.

Studies were appraised for quality before inclusion and analysis. Quality appraisal was conducted using CASP (Critical Appraisal Skills Programme) Checklist for appropriate study design reported. The checklist included questions on research questions, methodology, and analysis technique employed to assess validity of results.

Data extraction was conducted with pre-piloted forms by both authors independently of each other. Extracted data included date of publication, study design, sample size, and description of variables of interest. The results were compared between the two authors and duplicates were reconciled. Inclusion or exclusion was discussed and agreed upon by all authors before effected.

RESULTS

As visible in Figure 1, literature search identified 124 studies, of which 77 was immediately excluded due to having 'review', 'case report', or 'case series' on the title and/or abstract. We reviewed the abstract for the remaining 47 studies and excluded 19 more for describing case report or case series results. From 28 studies with underwent data extraction, another 17 studies were excluded for having sample size less than 50 or results that conflate confirmed and suspected COVID-19 cases. The remaining 11 studies was

included for analysis.

There are variations between included studies, based on design and inclusion criteria. By design, there were 4 cohorts, either prospective or retrospective, 5 retrospective studies, either analytic or descriptive, and 2 case-control designs.

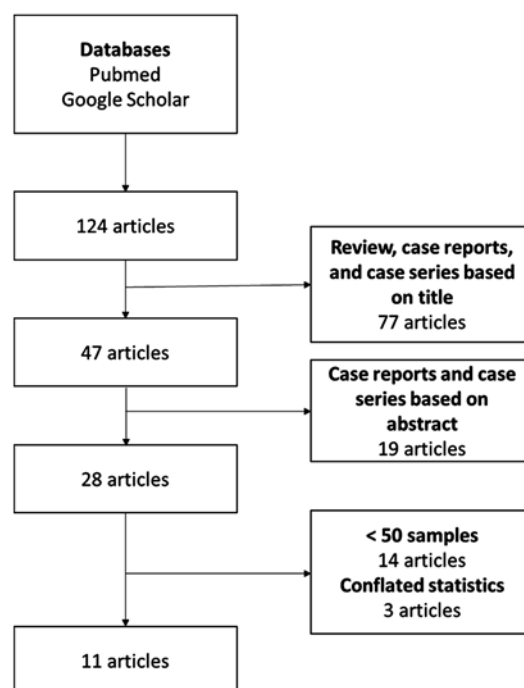


Figure 1. Literature search and selection diagram.

Inclusion criteria varies, even between studies with similar design. Some analytic studies included both confirmed, suspected, and/or non-COVID-19 cases,⁷⁻⁹ as well as pregnant and non-pregnant COVID-19 cases.¹⁰ For these studies, we only extracted data for pregnant women with confirmed COVID-19 cohort or group.

Table 1. Characteristics of included studies

Author	Title	Design	Sample Size	Ref.
Di Mascio <i>et al.</i>	Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19	Prospective cohort	388 pregnant women with confirmed COVID-19, 266 of which completed their pregnancy	11
Gabriel <i>et al.</i>	Maternal, Perinatal and Neonatal Outcomes With COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns During Their First Month of Life	Retrospective cohort	242 women who gave live birth while having confirmed COVID-19	12
London <i>et al.</i>	The Relationship between Status at Presentation and Outcomes among Pregnant Women with COVID-19	Retrospective cohort	68 pregnant women with confirmed COVID-19, 56 of which completed their pregnancy	13
Adhikari <i>et al.</i>	Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Prospective cohort	252 pregnant women with confirmed COVID-19 who completed their pregnancy	7
Ayed <i>et al.</i>	Maternal and perinatal characteristics and outcomes of pregnancies complicated with COVID-19 in Kuwait	Retrospective analytic	185 pregnant women with confirmed COVID-19, 169 of which completed their pregnancy	14

Delahoy <i>et al.</i>	Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020	Retrospective analytic	598 pregnant women with confirmed COVID-19, 458 of which completed their pregnancy	15
Woodworth <i>et al.</i>	Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy — SET-NET, 16 Jurisdictions, March 29–October 14, 2020	Retrospective analytic	4,442 completed pregnancy with confirmed COVID-19	16
Nayak <i>et al.</i>	Impact of the Coronavirus Infection in Pregnancy: A Preliminary Study of 141 Patients	Retrospective analytic	141 completed pregnancy with confirmed COVID-19	9
Yen <i>et al.</i>	Coronavirus disease 2019 in pregnant women: a report based on 116 cases	Retrospective descriptive	65 pregnant women with confirmed COVID-19, 50 of which gave live birth	8
Badr <i>et al.</i>	Are clinical outcomes worse for pregnant women at < 20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching	Case control	83 pregnant women with confirmed COVID-19	10
Yang <i>et al.</i>	Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan, China	Case control	65 pregnant women who gave live birth with confirmed COVID-19	17

Due to different in design and inclusion criteria, there were also difference in outcome of observation reported between included studies. Most studies included pregnant women with COVID-19 regardless of pregnancy completion.^{11,13–16} Some studies included only women who give live birth with concurrent COVID-19 infection, thus did not report incidences of adverse pregnancy outcomes such as miscarriage or stillbirths.^{10,12,17}

As much as 7 studies reported both variables of interest on maternal outcome, namely ICU admission and mortality, while 2 studies reported only maternal mortality rate. There are wide variation in reported ICU admission rate for pregnant women with confirmed COVID-19, ranging from 1.1%¹⁴ to 17.6%.¹³

Accounting for sample size variation, however, the reports indicate there was a cumulative of 125 ICU admission from 1,629 observed pregnant women in the seven studies that reported this variable.^{8,10–15} This translates to an ICU admission rate of 7.67%.

Table 2. ICU Admission and Maternal Mortality Rate Reported in Included

Authors	ICU admission (%)	Maternal mortality rate (%)	Ref.
Di Mascio <i>et al.</i>	11.1	0.8	11
Gabriel <i>et al.</i>	2.9	0.4	12
London <i>et al.</i>	17.6	0	13
Adhikari <i>et al.</i>	-	0	7
Ayed <i>et al.</i>	1.1	0	14
Delahoy <i>et al.</i>	7.4	0.3	15
Nayak <i>et al.</i>	-	2.12	9
Yen <i>et al.</i>	9.2	0	8
Badr <i>et al.</i>	13.34	0	10

Meanwhile, from 9 studies which reported maternal mortality rate, 6 reported no deaths.^{7,8,10,13,14} The others reported very low mortality rate, ranging from 0.3%¹⁵ to 2.12%.⁹ Overall, there was only 9 mortality events from 2,022 observed pregnant women observed by studies that reported this variable.^{7–15} This translates to maternal mortality rate of 0.5%.

Almost all included studies reported one or both of rate of live and preterm births from observed pregnant women with COVID-19. Most reported high live birth rate, in excess of 95%.

The lowest reported live birth rate was 94.4%¹¹ while the highest was 99.3%.¹⁶

Table 3. Pregnancy outcomes reported in included studies

Authors	Live births (%)	Preterm births (%)	Ref.
Di Mascio et al.	94.4	27.9	11
Gabriel et al.	-	14.5	12
London et al.	98.2	16.4	13
Adhikari et al.	97	11	7
Ayed et al.	97.6	26.7	14
Delahoy et al.	97.8	12.5	15
Woodworth et al.	99.3	12.9	16
Nayak et al.	92.9	-	9
Yen et al.	-	32	8
Yang et al.	-	14	17

Some of these studies included multiple pregnancies, which leads to the number of live births to exceed the number of observed mothers. A significant proportion of these births was preterm, however, with preterm births making up around 20% of live births. The lowest reported proportion of preterm births was 11%⁷ and the highest was 32%.⁸ From 5,439 observed live births with known gestational age, there was 773 preterm infants, translating to preterm birth rate of 14.2%.

Meanwhile, there was 8 studies who followed up on the newborn and reported either one or both of NICU admission and perinatal mortality. Similar to ICU admission for pregnant women, there was wide variation of NICU admission rate among newborn of these women. The lowest reported NICU admission rate was 3%¹⁴ while the highest was ten-times that at 34%.⁸ Mortality was low, however, with most studies reported zero death and the highest reported 2% perinatal mortality rate.^{8,11}

Table 4. Perinatal Outcomes Reported in Included Studies

Authors	NICU admission (%)	Perinatal mortality (%)	Ref.
Di Mascio et al.	27.5	2.0	11
Gabriel et al.	11.3	0	12
Adhikari et al.	3.3	0	7
Ayed et al.	3.0	0	14
Delahoy et al.	-	0.4	15
Woodworth et al.	9.3	0.2	16
Nayak et al.	17.9	-	9
Yen et al.	34.0	2	8

Several included studies reported comparison between pregnant women with Some included studies reported comparison between pregnant women with confirmed COVID-19 with outside

groups, which may include pregnant women with suspected, but not confirmed, COVID-19⁸ or pregnant women without COVID-19.^{7,9,10,17} Others reported comparison between two subgroups of symptomatic and asymptomatic pregnant women with COVID-19.^{13,15,16}

Comparison of maternal outcomes between confirmed and suspected groups showed no difference in mortality rate. However, pregnant women with confirmed COVID-19 were more likely to be admitted to ICU compared to suspected group (9.2% vs 3.9%). However, no statistical tests were conducted to see the significance of this difference.⁸

Nayak *et al.* reported higher risk of maternal mortality in COVID-19 confirmed pregnant women (2.12% vs 0.95%) although the difference was not statistically significant ($p > 0.05$).⁹ However, Badr *et al.* reported higher risk of ICU admission for pregnant women with confirmed COVID-19.¹⁰ Meanwhile, conflicting evidence was presented on risk of preterm birth between the two groups, with one study reporting no statistically significant difference⁷ while another reporting significant increased risk of preterm birth in confirmed group with OR of 3.71 (95% CI 1.70 – 8.03).¹⁷

Results on comparison between symptomatic and asymptomatic confirmed COVID-19 pregnant women painted a more cohesive picture. Women with symptomatic confirmed COVID-19 was more at risk for ICU admission necessitating ventilation support (26.1% vs 0%)¹³ and mortality (0.7% vs 0%).¹⁵ Women with symptomatic COVID-19 was also less likely to give live birth compared to their asymptomatic counterparts (95% vs 99.1%).¹⁵ Meanwhile, conflicting evidence was reported on risk of preterm birth with Delahoy *et al.* reporting increased risk among symptomatic group while Woodworth *et al.* reporting no difference.^{15,16}

DISCUSSION

Our review result showed relatively low risk of adverse outcomes for pregnant women with concurrent COVID-19 infection. While there was moderate risk of ICU admission, there was relatively low risk of maternal mortality. Similarly, there was high chance of successful pregnancy with live birth although it was accompanied with moderate risk of preterm pregnancy and NICU admission. Perinatal mortality rate, however, was low.

This result was not much different from early

reviews, although early reviews tend to report higher proportion of mortality or other adverse events. One early review reported preterm birth rate of 63.8% and NICU admission rate of 76.92%.⁶ Another review reported 2 maternal mortality out of 20 pregnant women reviewed from case reports, a mortality rate of 10%.¹⁸ Another early review, however, reported similar results to ours with 21.3% preterm birth rate and 1.2% perinatal mortality.⁵

The similarity of these early reviews, however, was the low number of cases included in the review. As report by PAHO showed, pregnant women with COVID-19 was not that frequent.⁴ Thus these early reviews reported results based on under 100 cases based mostly on case reports and case series.^{5,6,18} Some of these reviews also included suspected but not confirmed COVID-19 cases in the review.⁶

Later reviews and meta-analyses involving more observed reported much lower rate of adverse event however, similar to our results. Two large reviews published in the latter half of 2020 found maternal mortality rate of 1.7% and 0.6%, similar to our findings.^{19,20} Similar lower rate for other maternal and perinatal outcomes was also reported by other later reviews.

The reasoning was that earlier case reports and case series was made in the period when many things was unknown about COVID-19, such as lack of understanding of the prevalence of asymptomatic cases. This cause many reviews to include disproportionately more symptomatic cases, increasing risk of adverse events in their cohort.²¹

Our results also imply the highest risk of adverse event was among pregnant women with symptomatic COVID-19 infection. This point to the probability that the viral infection itself was not the cause of adverse event, unlike some other viral infection.²² Instead, inflammation, its associated symptoms, and potential exacerbation was the cause for the majority of adverse outcomes such as necessity for induction or caesarean section, preterm delivery, and perinatal complications.²¹

The clinical implication from our findings was the necessity to be aware of the risk of adverse outcomes when facing cases of pregnant women with concurrent COVID-19 infection. The risk would be higher in cases of symptomatic cases. As such, due preparation should be made, such as close monitoring of maternal and fetal conditions, as well as preparation for ICU and NICU admission.

Meanwhile, our result also points to a possible public health intervention in the form of targeted screening for symptomatic women during antenatal care in places where community transmission was common. Awareness for this necessary action should be emphasized in outpatient antenatal care facility which may not have in-house laboratory. Earlier detection would allow for closer monitoring and better preparation, hopefully improving outcomes. However, more study should be conducted on the cost-effectiveness of the measure.

While this study may provide updated picture of COVID-19 infection during pregnancy, it comes with its own shortcomings. Our literature search which relied on open-access databases may causes less than comprehensive results. As such, there may be some studies fulfilling inclusion criteria that was not included in this study.

CONCLUSION

Our results showed relatively low occurrences of adverse maternal and perinatal outcomes for pregnant women with concurrent COVID-19 infection. Increased risk was observed in symptomatic infections compared to asymptomatic ones. Awareness of the potential risk should be coupled with attempts for targeted early detection during antenatal care.

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