

A Literature Review of Advanced Maternal Age in Pregnant Women with COVID-19

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Abstract

Background: During pregnancy, the risk of severe manifestation of COVID-19 with a worse maternal outcome can become higher because of the alteration in the immune system and physiological function. In COVID-19 infection, several studies also stated the increased risk of severe disease in advanced maternal age (AMA). Considering that the death and severe case rates in advanced-aged pregnant women with COVID-19 were high, special attention should be focused on this matter. There was still little study that focused on the outcome of COVID-19 in pregnant women with advanced age as well. Therefore, this study aims to evaluate the risks and the outcomes of advanced maternal age-pregnancy with COVID-19.

Method: The method used in this paper is the Literature Review which aspires to analyze the risk and the outcome of COVID-19 in advanced maternal-age pregnancy. The databases used in the source search are PubMed, Google Scholar, JAMA, and AJOG. The keywords for the search were advanced maternal age, COVID-19, and pregnancy.

Results: The mortality and morbidity of AMA who had COVID-19 were higher than non-AMA pregnant women. Severe conditions of COVID-19 were increased in AMA patients. They were at risk of having ICU admission and intubation. Advanced-aged mothers were more likely to have comorbidity including obesity. They also had a higher risk of adverse pregnancy outcomes.

Conclusion: The adverse maternal aged-pregnant women with COVID-19 had higher risks of having comorbidities, severe conditions of COVID-19, adverse pregnancy outcomes, and mortality. Therefore, early risk identification needs to be done to identify the special management for the patients.

Keywords: Advanced Maternal Age, pregnancy, COVID-19, obesity, preeclampsia

1. Introduction

Coronavirus Disease 2019 (COVID-19) is an acute and highly infectious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that was first discovered in Wuhan, Hubei province, China, in December 2019 (Singhal, 2020). Although COVID-19 cases have massively decreased since three years ago, the cases rose again in November 2022 accompanied by the emergence of new variant of Omicron which was XBB sub-group (ONS, 2022; Satgas COVID-19, 2022)

Pregnant women are a potential group vulnerable to COVID-19 infection (Kotlyar et al., 2021). As of May 10th, 2021, in the United States, there have been 90.099 pregnant women with COVID-19 and 101 maternity deaths (CDC, 2021). During pregnancy, the risk of severe manifestation of COVID-19 with a worse maternal outcome can become higher because of the alteration in the immune system and physiological function (Wastnedge et al., 2021). According to the Royal College of Obstetricians & Gynaecologist (2021), pregnant women with symptomatic COVID-19 requiring hospitalization have worse maternal outcomes.

In COVID-19 infection, several studies also stated the increased risk of severe disease in advanced maternal age (AMA). Advanced maternal age (AMA) is defined as the age of pregnant women at or after 35 years during delivery. Over the past ten years, the trend of delaying childbearing has become more prevalent, particularly in developed nations (Mills & Lavender, 2011). According to the Indonesia Demographic Health Survey (IDHS), this circumstance also occurred in Indonesia in 2013 (BKKBN, BPS, KEMENKES., 2013). AMA can increase the risk of adverse maternal outcomes such as stillbirth, preeclampsia, preterm birth, and fetal distress (Cavazos-Rehg et al., 2015). A study by Menezes et al (2020) reported the increased risk of mortality, admission to the ICU, or mechanical ventilation in AMA with COVID-19. Considering that the death and severe case rates in advanced-aged pregnant women with COVID-19 were high, special attention should be focused on this matter. There was still little study that focused on the outcome of COVID-19 in pregnant women with advanced age as well. Therefore, this study aims to evaluate the risks and outcomes of advanced maternal age-pregnant women with COVID-19.

2. Methods

The method used in this paper is the Literature Review which aims to explore the outcome of COVID-19 in advanced maternal age pregnancy. The review process begins by identifying journal articles that are relevant to the research topic. The databases used in the source search are Google Scholar, PubMed, JAMA, and AJOG. The search for articles was carried out by collecting themes around the discussion of the. The keywords for the search were advanced maternal age, COVID-19, pregnancy. The criteria for the articles included in the review are as follows: cohort study, case study, review, and observational. After conducting a thorough search and assessment, 12 high-quality articles that were relevant to the subject were found, from which the findings for this literature review study were derived. Figure 1 displays the chart of data retrieval.

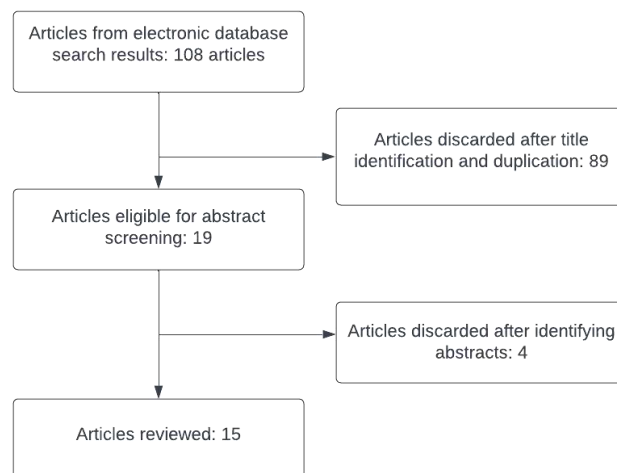


Fig. 1. Data Retrieval Charts

3. Results

This study identified 12 articles through an electronic database search. The total number of advanced maternal-age pregnant women with COVID-19 from all articles is 3468. Table 1 Is the summary of the articles reviewed. There were six among twelve articles that discussed the condition of COVID-19 disease in pregnancy with AMA. Most of them found that severe conditions were increased in AMA patients. Only two studies reported no increase in severe conditions in advanced-aged patients (Vouga et al., 2021; Shoji et al., 2022). D'Antonio et al (2021) and Torres et al (2021) found a higher number of ICU admission in the AMA group. There was one article that mentioned the increased risk of intubation and severe pneumonia (D'Antonio et al., 2021)

Three studies mentioned the comorbidities found in patients. Almost all of the pregnant women aged >35 years had comorbidity (Djusad et al., 2021; Kurniawati et al., 2022; Shams et al., 2022). The most common comorbidity found was obesity. Several studies also reported the bad outcomes of pregnancy in AMA cases. A study by Shams et al (2022) discovered AMA women had a higher rate of Abortion, Preterm delivery, and lower mean gestational age at delivery (Shams et al., 2022). Most of the studies reported most AMA mothers had cesarean section delivery except one study by Martínez-Perez et al (2020). Most pregnant women aged >35 delivered their babies via the vagina.

The number of maternal deaths in AMA was recorded by many studies. There was an increase in mortality in the AMA group compared with the non-AMA group. Two studies found that almost all maternal death in advanced-age mothers were complicated by preeclampsia (Djusad et al., 2021; Kurniawati et al., 2022).

Table 1. Summary of Articles Reviewed

Reference	Country	Research Design	Pregnant women with COVID-19	Advanced Maternal Age (AMA) case	Finding
Djusad et al., 2021	Indonesia	Case study	4 maternal death	2 AMA cases	Two among four death were pregnant women with AMA. Both of them had preeclampsia, obesity, and experienced dyspnea before admission.
Kurniawati et al., 2022	Indonesia	Retrospective study	15 maternal death	3 AMA cases	Pregnant women with AMA were found in three among fifteen maternal death. Two of them had obesity. One case had severe preeclampsia. All of them experienced ARDS.
D'Antonio et al., 2021	Multiple countries (Argentina, Australia, Belgium, Brazil,	prospective cohort study	887 pregnant women	235 AMA cases	When compared to the non-AMA group, the incidence of nulliparity and high-risk pregnancies was higher in the AMA group.

	Bulgaria, Colombia, Czech Republic, Chile, Finland, Germany, Greece, Equatorial Guinea, India, Israel, Italy, Mexico, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and The United States)				Women in the AMA group were more likely to exhibit symptoms of infection, be hospitalized, and be admitted to the intensive care unit. Women with AMA were more likely to experience a composite adverse maternal outcome.
Hantoushzadeh et al., 2020	Iran	Case study	9 pregnant women	3AMA cases	The prevalence of advanced maternal age (≥ 40 years) was 40% among all maternal mortalities.
Minisha et al., 2022	Qatar	Retrospective study	500 pregnant women	279 AMA cases	a higher proportion of older women were found and were more likely to have symptomatic disease.
Babic et al., 2022	Saudi Arabia	retrospective cohort study	209 pregnant women	90 AMA cases	60% of symptomatic patients were aged >35 years. COVID-19 infection was more common among women at an advanced age.
Shams et al., 2022	Saudi Arabia	cross- sectional study	394 pregnant women	148 AMA cases	Women who were symptomatic had a higher likelihood of

					being older mothers (45 versus 33%). Higher BMI, gravidity, and parity were more prevalent in women who had reached an advanced maternal age. Compared to older women, pregnant women under the age of 35 had lower median ARI scores (0 versus 0, $p = 0.03$). In comparison to younger women, AMA women experienced higher rates of abortion, preterm birth, and lower mean gestational ages at delivery (36 versus 38.4 weeks). Neonatal deaths were more frequent in the AMA.
Torres et al., 2021	Mexico	prospective cohort study	13062 pregnant women	2257 AMA cases	Maternal age was linked to maternal mortality; women between the ages of 35 and 39 had a higher mortality risk than those under 35. Additionally, ICU admission, severe pneumonia, and intubation rates were all higher in people with AMA.
Shoji et al., 2022	Japan	retrospective cohort study	254 pregnant women	65 AMA cases	23.3% patients who had moderate-severe conditions were AMA.
Chaichian., 2021	Iran	Case study	14 pregnant women	6 AMA cases	Six out of the fourteen patients were AMA patients. Only one of them gave birth vaginally. She developed dyspnea and fetal distress a day after being admitted to the hospital, so a normal vaginal delivery (NVD)

					was carried out. Up until three months after delivery, the mother and the child were both still alive. AMA was a patient who passed away. No patient had comorbid conditions. Two patients were admitted to the ICU, and they were all AMAs. One of the two infants admitted to the NICU was born to an AMA mother.
Vouga et al., 2021	Swiss	case control study	926 pregnant women	272 AMA cases	AMA didn't increase the risk of severe disease (30%).
Martínez-Perez et al., 2020	Spain	Retrospective cohort study	82 pregnant women	41 AMA cases	Fifty percents of severe patients were AMA. Most of pregnant women aged >35 were delivered their baby via vagina.
Du et al, 2021	China	Retrospective analysis	7699 pregnant women	495 AMA cases	The percentage of women with AMA is higher during COVID-19 pandemic compared with the pre-COVID-19 pandemic era.
Karimi et al, 2021	Multiple countries (United Kingdom, Iraq, Jordan, Peru, China, United States, Italy, Turkey, Switzerland, France, Sweden, India, Portugal, Netherland	Systematic review and meta-analysis	12 pregnant women	4 AMA cases	From all total cases, there are 136 cases of maternal death caused by COVID-19, and 4 of the women were having AMA pregnancy.

	s, Ireland, Venezuela, Spain, Iran, Canada, Australia, Thailand, Brazil, Honduras.				
Brant et al., 2021	United States	Matched case-control study	61 pregnant women	17 AMA cases	Most of the patients (n=54) had a mild disease while 7 patients had a severe to critical level of COVID-19 disease

4. Discussion

Based on most articles gathered, the percentage of AMA cases in pregnancy with COVID-19 was still lower than the younger pregnant women. In the United Kingdom, among 427 pregnant women confirmed positive for COVID-19, most of them were 20 – 34 years old (Knight, 2020). Another study in Cameroon reported 64% of pregnant women with COVID-19 were 25– 35 years old (Dingom et al., 2020). On the contrary, out of 12 articles in this study, two stated the higher portion of COVID-19 cases in pregnancy was in the AMA group (Babic et al., 2022; Minisha et al., 2022). This might be explained by social factors, such as the likelihood that older women will encounter sick older relatives and children who are left in their care at home (Minisha et al., 2022). Despite the fact that COVID-19 had a lower percentage of AMA cases, the mortality and morbidity risks were higher compared with the younger aged pregnant women. Pregnancy with AMA resulted in more severe conditions of COVID-19. According to studies, the case fatality rate of COVID-19 infection doubles every ten years between the ages of 20 and 491. The ACE2 receptor, which is upregulated during a typical pregnancy, is where SARS-CoV-2 enters human cells and binds. Additionally, increased expression of ACE2 receptors is linked to advancing age, which may contribute to the disease's worsening severity (Martinez-Portilla et al., 2020).

Factors contributing to the severity of COVID-19 were comorbidity and other coexisting disease found at AMA. Women with advanced maternal age were more likely to have higher BMI, Gravidity, and parity (Shams et al., 2022). The comorbidities found in another study were diabetes (31.1%), obesity (21.9%), cardiovascular disease (14.1%), and asthma (9.1%) (Karimi et al., 2021). Obesity during pregnancy is correlated with adverse maternal outcomes such as preeclampsia, preterm birth, gestational diabetes, and cesarean delivery (Smith, Hulsey, and Goodnight., 2008). Aging is often accompanied by progressive loss of muscle mass and strength (i.e., sarcopenia) and an increase in fat mass, even in individuals with relatively stable BMI (Oreopoulos et al., 2009). Interpregnancy interval is the period between the delivery of the previous infant and conception of the present pregnancy. Short spacing may also increase the risk of maternal obesity due to the weight changes during the interval resulting from weight retained from pregnancy or gained postpartum (Hanley et al., 2017).

Another finding shows that the percentage of women with AMA is increasing during the COVID-19 pandemic compared with the pre-COVID-19 pandemic era. It was approximately 15.53% vs 13.30% respectively. Other significant different between the pre-pandemic and pandemic era was the prevalence of caesarean sections and premature membrane ruptures. The results show that these aspects were higher during the COVID-19 pandemic which is 48.16% for the caesarean section and 33.59% for the premature membrane

rupture incident. Compared with the pre-pandemic period which are only 45.80% and 30.72%, respectively. The risk of premature membrane rupture during the pandemic period was increased by 11% compared with women in pre-pandemic period (Du et al, 2021). The increasing number of premature membrane rupture incident may be associated with the increasing of maternal anxiety during the COVID-19 pandemic (Berthelot et al., 2021; Hessami et al., 2020). Due to the decreased levels of choline and creatinine (Wu et al., 2020) as well as the altered diurnal system of cortisol (Nabi et al., 2020; Gilles et al., 2018) that happened in women with maternal depression and anxiety were associated with premature membrane rupture (Khanghah et al., 2020).

From all the four maternal death cases caused by COVID-19, they were all planned to undergo an emergency cesarean section. These happened due to many reasons such as fetal distress, preeclampsia, and dystocia (Djusad et al, 2021). It is said that AMA was an independent risk factor for prelabor cesarean section in private and public services (Martinelli et al., 2021). Some negative maternal and perinatal outcomes that have been linked with AMA include preeclampsia, congenital anomalies, gestational diabetes, placental abruption, placenta previa, preterm birth, perinatal mortality, and low birth weight (Ludford et al., 2012; Wu et al., 2019; Martinelli et al., 2018). Unfortunately, the number of women with AMA has increased in low-, middle-, and even high-income countries, compared to the previous years (Laopaiboon et al., 2014). It was found that 13,6% out of 15,071 women with AMA gave birth in public while 28,4% out of 15,071 women who gave birth in private practice were AMA (Martinelli et al., 2021).

A research conducted by Brant et al (2021) found that women with Advanced Maternal Age were more likely to get a severe to critical level of COVID-19 disease. Other factors that may influence the incidence of severe disease such as obesity, have a medical comorbidity, black and Hispanic. They also found an increased risk of preterm labour among women with severe or critical COVID-19. It is stated that COVID-19 incidence during pregnancy is linked with an increased risk of adverse neonatal and maternal outcomes. Some comorbidities that they found includes diabetes (n=7), chronic hypertension (n=2), renal disorder (n=1), asthma (n=2), anemia (n=2), and immunocompromised (n=2). 50 of the patients do not have a medical history. Excessive amounts of adipose tissues in obese women secrete interleukin 6 (IL6) and modulate the production of C-reactive protein (CRP) (Poirier et al., 2006). During pregnancy, this pro-inflammatory state is linked with an increased risk of adverse maternal outcomes, including preeclampsia and preterm birth (Smith, Hulsey, and Goodnight, 2008). Pregnant women who are obese are more prone to develop complications from viral infections such as influenza virus, cytomegalovirus, and SARS-CoV-1, as well as associated disorders such as ARDS (Poulakou, Pérez, and Rello, 2012; Bonmarin et al., 2015). Several studies also suggested a higher risk of severe manifestation of SARS-CoV-2 infection in pregnancies complicated by high BMI or obesity. A study in Italy reported severe cases of COVID-19 in obese pregnant women (Savasi et al., 2020). While another study from 12 medical centers in the United States included 64 pregnant women hospitalized due to COVID-19 reported the average BMI of 64 women with severe or critical COVID-19 disease was 33.5 kg/m² (Pierce-Williams et al., 2020).

According to Kurniawati et al (2022), the CFR of maternal deaths caused by COVID-19 is 3.49%, and it is expected to rise as people get older. According to a study, CFR was 0.2% in the 20–29 age group, 1.3% in the 50–59 age group, and 15.6% in the 80 and above age group (Kurniawati et al., 2022). Two studies found that almost all maternal death in advanced-age mothers were complicated by preeclampsia (Djusad et al., 2021; Kurniawati et al., 2022). Hypertension is known to be more likely in people who are older since endothelial damage gets worse with age. Therefore, it is reasonable to anticipate that women of AMA will have higher rates of chronic HTN as well as a higher incidence of gestational HTN and preeclampsia (Glick et al., 2021). The increased prevalence of preeclampsia has been linked to AMA in several ways, including reduced maternal hemodynamic adaptation during pregnancy, loss of uterine blood vessel compliance, and comorbid disease (Tessema et al., 2015).

Mothers with advanced maternal age require extra attention since the risk of having worse pregnancy outcomes and severe conditions of COVID-19 were high. Therefore, early risk identification is essential to

identify a subset of women who may benefit from individualized management, including extended surveillance or elective hospitalization (D'Antonio et al., 2021). According to a research conducted by Titaley et al (2010), there are some factors that can influence mother's decision to attend antenatal care including pragmatic and economic reasons, minimum knowledge regarding maternal and child health, also difficult access to the health care institution. During this COVID-19 pandemic era, minimum knowledge also economical factors might be the important causes of why these pregnant women did not seek a medical care unless there is an emergency situation (Djusad et al., 2021).

Conclusion

The adverse maternal aged-pregnant women with COVID-19 had higher risks of having comorbidities, severe conditions of COVID-19, adverse pregnancy outcomes and mortality. Therefore, early risk identification need to be done to identify the special management for the patients.

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