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Effect of Advanced Maternal Age on Pregnancy Outcome: A Retrospective Study from Three Academic Teaching Hospitals in Indonesia

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ABSTRACT

Background & Objective: Pregnancy at advanced maternal age (AMA), defined as pregnancy in women aged >35 years, has been increasing globally, including in Indonesia. AMA is associated with higher risks of adverse pregnancy outcomes, making it a significant clinical and public health concern. This study aims to evaluate the negative maternal and fetal outcomes associated with AMA pregnancies.

Materials & Methods: A retrospective cohort study was conducted at three academic teaching hospitals in West Java, Indonesia, from January 1 to December 31, 2022. Data were collected from medical records, comparing a study group of women aged >35 years with a control group of women aged <35 years. Pregnant women beyond 28 weeks of gestation, both primiparous and multiparous, were included. Maternal outcomes assessed were antepartum hemorrhage, gestational diabetes, hypertensive disorders, and cesarean delivery. Fetal outcomes included preterm labor and intrauterine fetal death (IUFD). Statistical analysis was performed using the Chi-square test with a 95% confidence interval.

Results: A total of 6763 patients were analyzed, including 1743 AMA women and 5020 younger women. AMA pregnancies showed a significantly higher incidence of antepartum hemorrhage (P<0.001; OR = 1.94 [1.55–2.42]), hypertensive pregnancy (P<0.001; OR = 1.90 [1.65–2.19]), and IUFD (P = 0.004; OR = 1.49 [1.13–1.95]).

Conclusion: AMA pregnancies are associated with increased risks of maternal and fetal complications. Significant increases in antepartum hemorrhage, hypertensive disorders, and IUFD highlight the need for enhanced prenatal monitoring and risk management in this population.

Keywords: Advanced Maternal Age (AMA), Patient Outcomes, Pregnancy Complications, Pregnancy Outcomes

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1. Introduction

Pregnancy at advanced maternal age (AMA) is defined as pregnancy in women older than 35 **(1)**. The incidence of pregnancy in older women has continued to rise over the past decade, particularly in developed nations **(2)**. The average childbearing age in Europe rose from 26.5 years in 1980-1985 to 29.4 years in 2010–2015 **(3)**. The reported prevalence of first birth in the United States, among women aged 35 years was 7.5% in 2009, and increased by 23% in 2014, accounting for 9.1% of all pregnancies **(4)**. According to the 2013 Indonesian Demographic Health Survey, there was also an increase in the number of older women who became pregnant **(5)**. Pregnancy in advanced age is of clinical and public concern, mainly because it is prone to higher rates of complications, both due to general degenerative processes and decreased reproductive function **(6)**. Most studies agree that advanced age is associated with increased adverse maternal and fetal outcomes. Adverse maternal outcomes include preeclampsia, gestational diabetes mellitus, antepartum hemorrhage, and cesarean delivery. Meanwhile, adverse fetal outcomes include intrauterine death, intrauterine growth restriction (IUGR), prematurity, preterm labor, and low APGAR scores **(6-8)**.

Overall, studies investigating the effect of AMA on maternal and child outcomes have yielded varied results. To the best of the author's knowledge, no

studies in Indonesia have investigated the effect of AMA on maternal and child outcomes. Here, we aimed to investigate the negative maternal and fetal outcomes associated with pregnancy in AMA. Maternal outcomes studied include antepartum hemorrhage, gestational diabetes, hypertension in pregnancy, and cesarean delivery. Meanwhile, infant outcomes studied include preterm labor and intrauterine fetal death (IUFD).

2. Materials and Methods

2.1. Study design

This study is a retrospective cohort study aimed at investigating the negative maternal and fetal outcomes associated with pregnancy in AMA.

2.2. Study settings

This study was a retrospective cohort study conducted in the Department of Obstetrics and Gynecology at three academic teaching hospitals in West Java, Indonesia (Hasan Sadikin General Hospital, Cikalong Wetan General Hospital, and Al-Ihsan Regional General Hospital) from January 1 to December 31, 2022.

2.3. Population and Sample

The study group consisted of pregnant women aged >35 years who delivered vaginally or by cesarean at a gestational age above 28 weeks, whereas the control group consisted of pregnant women aged 20–35 years who also delivered vaginally or by cesarean at a gestational age above 28 weeks. The investigation excluded pregnancies with major fetal defects and multiple pregnancies. This study's sample selection utilized the consecutive sampling method. Samples were chosen if they met all inclusion requirements. The selection of subjects was based on the medical records of women who gave birth in the three hospitals previously mentioned.

2.4. Variables

In this study, maternal age (age >35 and age 20–35) was the independent variable. In the meantime, the dependent variable was pregnancy outcomes, including maternal and fetal outcomes. Among the maternal outcomes examined were antepartum hemorrhage, gestational diabetes, hypertension during pregnancy, and cesarean delivery. Among the infant outcomes that were studied were preterm labor and IUFD.

2.5. Statistical Analysis

Descriptive analysis is used to determine the characteristics of research subjects who become research samples. Data analysis to see the description of the proportion of each variable that can be descriptively described in descriptive analysis and hypothesis testing. Numerical scale data such as patient age is presented with mean, standard deviation, median, and range. Then, for sample characteristic data in the form of categorical data such as patient gender, coding is given and presented as a frequency distribution and percentage. The significance test to compare the characteristics of the two research groups used statistical analysis for categorical data, namely the chi-square test. The p-value is used as the significance criterion; $p<0.05$ is significant or statistically meaningful, whereas $P>0.05$ is not significant or not statistically meaningful. The collected data were entered into a specialized form and then analyzed using SPSS version 26.0 for Windows.

3. Results

A total of 6763 patients were included in this study, which consists of 1743 (25.78%) women in the study group (age > 35 years) and 5020 (74.22%) women in the control group (age 20–35 years). Of 6763 patients included in this study, 1924 (28.4%) women were from Hasan Sadikin Hospital, 383 (5.6%) were from Cikalong Wetan General Hospital, and the remaining 4456 (65.8%) were from Al-Ihsan Regional General Hospital. Among the study group at Hasan Sadikin Hospital, hypertensive pregnancy (19.3%) was the most common adverse pregnancy outcome, followed by antepartum hemorrhage (9.8%), cesareandelivery (6.7%) preterm labor (3.1%), and intrauterine death (0.4%). Gestational diabetes was not found in this group. In a control group at Hasan Sadikin Hospital, the most common adverse pregnancy outcomes were hypertensive pregnancy (11.9%) followed by preterm labor (6.2%), antepartum hemorrhage (6.1%), cesarean delivery (4.0%), intrauterine death (0.6%), and gestational diabetes (0.07%). These findings were similar to the findings in Cikalong Wetan General Hospital, in which hypertensive pregnancy was the most common adverse pregnancy outcome in the study group (29.5%). However, in the control group, the most common adverse pregnancy outcomes were cesarean delivery (18.4%). The different findings were observed at Al-Ihsan Regional General Hospital, in which the most common adverse pregnancy outcomes were cesarean delivery, both in the study (33.2%) and control (31.9%) groups (Table 1).

Overall, among all pregnancy adverse outcomes in the study group (n = 1743), the most prevalent was cesarean delivery (439 [25.2%]), followed by hypertensive pregnancy (368 [21.1%), antepartum hemorrhage (135 [7.7%]), intrauterine death (82 [(4.7%]), preterm labor (74 [4.2%]), gestational diabetes (3 [0.2%]). A similar result was also observed in a control group, in which the most common adverse pregnancy outcomes observed were cesarean delivery (1166 [23.2%)], followed by hypertensive pregnancy (618 [12.3%]), preterm labor (243 [4.8%]), antepartum hemorrhage (208 [4.1%]), intrauterine death [161 [3.2%]], and gestational diabetes (8 [0.2%]) (Table 2).

The chi-square test revealed a statistically significant difference in adverse pregnancy outcomes consisting of incidence of antepartum hemorrhage ($P<0.001$; OR

= 1.94 [1.55–2.42]), hypertensive pregnancy (P<0.001; OR = 1.90 [1.65–2.19]), and intrauterine death (P = 0.004; OR = 1.49 [1.13–1.95]) were observed in AMA pregnancy (Table 2).

Table 1. The proportion of each pregnancy outcome in the study and control groups among three academic teaching hospitals.

Adverse pregnancy outcomes	Hasan Sadikin General Hospital (N = 1924)		Cikalong Wetan General Hospital (N = 383)		Al-Ihsan Regional General Hospital (N = 4456)	
	Study group (N = 488)	Control group (N = 1436)	Study group (N = 112)	Control group (N = 271)	Study group (N = 1143)	Control group (N = 3313)
Antepartum hemorrhage	48 (9.8%)	88 (6.1%)	1 (0.9%)	1 (0.37%)	86 (7.5%)	119 (3.6%)
Gestational diabetes	0	1 (0.07%)	1 (0.9%)	0	2 (0.17%)	7 (0.2%)
Hypertensive pregnancy	94 (19.3%)	172 (11.9%)	33 (29.5%)	46 (16.9%)	241 (21.1%)	400 (12.1%)
Cesarean delivery	33 (6.7%)	58 (4.0%)	26 (23.2%)	50 (18.4%)	380 (33.2%)	1058 (31.9%)
Preterm labor	15 (3.1%)	89 (6.2%)	17 (15.2%)	22 (8.1%)	42 (3.7%)	132 (3.9%)
IUFD	2 (0.4%)	9 (0.6%)	23 (20.5%)	29 (10.7%)	57 (4.9%)	123 (3.7%)

Table 2. The association of pregnancy outcomes and advanced maternal age

Adverse pregnancy outcomes	Study group (N = 1743)	Control group (N = 5020)	p	OR
Maternal outcomes				
Antepartum hemorrhage	135 (7.7%)	208 (4.1%)	<0.001	1.94 [1.55–2.42]
Gestational diabetes	3 (0.2%)	8 (0.2%)	0.90	1.08 [0.28 – 4.07]
Hypertension during pregnancy	368 (21.1%)	618 (12.3%)	<0.001	1.90 [1.65–2.19]
Cesarean delivery	439 (25.2%)	1166 (23.2%)	0.09	1.11 [0.98–1.26]
Fetal outcomes				
Preterm labor	74 (4.2%)	243 (4.8%)	0.31	0.87 [0.66–1.13]
IUFD	82 (4.7%)	161 (3.2%)	0.004	1.49 [1.13–1.95]

4. Discussion

Pregnancy in women beyond the age of 35, known as advanced maternal age, is considered a risk factor for negative outcomes for both the mother and the baby. Pregnancy at age 35 or older may lead to many difficulties, such as a higher likelihood of experiencing spontaneous miscarriage, premature labor, gestational diabetes mellitus, preeclampsia, stillbirth, chromosomal abnormalities, and the need for cesarean delivery. Adverse prenatal outcomes encompass conditions such as being smaller than expected for the gestational age, experiencing hindered fetal growth, having a low Apgar score, requiring admission to the neonatal intensive care unit, and being diagnosed with autism spectrum disorder **(2, 3, 8-12)**. In this study, pregnancy outcomes discussed included maternal outcomes consisting of antepartum hemorrhage, gestational diabetes, hypertension in pregnancy, and cesarean delivery. Meanwhile, the infant outcomes studied included preterm labor and IUFD. We found a statistically significant difference in adverse pregnancy outcomes consisting of antepartum hemorrhage (P<0.001; OR = 1.94 [1.55–2.42]), hypertensive pregnancy (P<0.001; OR = 1.90 [1.65–2.19]), and intrauterine death (P = 0.004; OR = 1.49 [1.13–1.95]) among AMA pregnancy.

In a comparable study conducted by Hochler et al **(13)** the objective was to examine the negative effects on both the mother and fetus during pregnancy in advanced maternal age (AMA). The study found a significant correlation between AMA and various adverse outcomes, including preterm labor, higher rates of cesarean delivery, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), gestational hypertension, gestational diabetes, very low birth weight (VLBW) infants, and intrauterine death **(13)**. A study conducted in Ethiopia compared different groups of pregnant women and found that advanced maternal age (AMA)

pregnancy was significantly associated with pregnancy-induced hypertension (AOR 4.15, 95% CI 2.272–7.575, P < 0.001), antepartum hemorrhage (AOR 2.54, 95% CI 1.32–4.91, P = 0.005), and cesarean delivery (AOR 2.722, 95% CI 1.777–4.170, P < 0.001) **(14)**. In addition, a cohort study conducted by Guarga Montori et al **(15)** discovered a statistically significant rise in the prevalence of hypertensive diseases, diabetes mellitus, induction of labor, and cesarean section among those over the age of 35. The incidence of fetal death, newborn admission, small for gestational age, placenta previa, instrument delivery, maternal ICU admission, and postpartum hemorrhage were shown to be higher in women over the age of 40 **(15)**. Lu et al **(7)** conducted a study to examine the impact of advanced maternal age (AMA) on the outcomes of preterm pregnancies. They found that AMA increased the risk of negative pregnancy outcomes such as iatrogenic preterm birth, placenta previa, preeclampsia, gestational diabetes mellitus, and postpartum hemorrhage. However, they also observed that AMA had a protective effect on multiple gestation pregnancies **(7)**.

According to the research conducted by Hu et al **(16)** advanced maternal age also influences gestational weight gain **(16)**. Omani-Samani et al **(17)** found that the prevalence of low birth weight (LBW) was 5.41%, whereas the prevalence of macrosomia was 2.18%. The prevalence of LBW in women with GWG less than the weight gain suggested by IOM was 2.13 times [95% confidence interval (CI) 1.13-4.02, P = 0.019] higher than in women with GWG equivalent to the weight gain recommended by the IOM. As a result, the prevalence of LBW among women with GWG less than the recommended weight gain by IOM was 2.13 times higher than among women with GWG equivalent to the recommended weight gain **(17)**.

The majority of authors present results comparable to our study. According to the existing literature, although most adverse outcomes can be explained by the physio pathological changes in the female reproductive apparatus that accompany aging and its inherent comorbidities, advanced maternal age can be an independent risk factor for adverse pregnancy outcomes **(18, 19)**. Advanced maternal age (AMA) is a substantial independent risk factor for poorer obstetric and perinatal outcomes in older pregnant women who do not have other health conditions such as gestational hypertension or diabetes **(20-22)**.

A study conducted by Dabiran et al **(23)** also showed that there was a notable increase in the occurrence of preeclampsia, gestational hypertension, and GDM (P < 0.05). The two groups also significantly differed in terms of the quality of prenatal treatment (P < 0.001). In terms of the method of delivery, cesareansection was more common in the group of women of advanced maternal age (AMA), whereas vaginal delivery was more frequent in the younger group (P < 0.001) **(23)**. These findings were in line with our study.

In this study, we only found three variables that were significantly associated with AMA: antepartum hemorrhage, hypertensive pregnancy, and intrauterine death. A correlation exists between advanced maternal age (AMA) and antepartum hemorrhage, which is linked to a higher occurrence of placenta previa and placental abruption in the latter stages of pregnancy (often after 20 weeks) **(11, 24)**. A cohort research involving 64,886 pregnant women examined different risk factors and observed that women aged 35 years or older (n = 12,686) had a higher occurrence of antepartum hemorrhage and placenta previa **(25)**. Furthermore, it is commonly acknowledged that hypertension is more likely to occur in individuals of advanced age, as the endothelium damage that contributes to this condition tends to escalate with increasing age **(26)**. Hence, it is logical to assert that older pregnant women are more prone to experiencing chronic hypertension, gestational hypertension, and preeclampsia. In a retrospective study conducted by Claramonte Nieto et al **(2)** different age groups were compared to a control group of women under the age of 30. The study found that only women in the severely advanced age group had an increased risk of preeclampsia, with an odds' ratio of 3.32 and a 95% confidence interval of 1.78-6.21. Nevertheless, despite employing multivariable logistic regression to account for confounding factors such as obesity, ART usage, smoking, chronic hypertension, and parity, no statistically significant correlation was discovered between age and preeclampsia **(2)**.

The association between AMA (Advanced Maternal Age) and IUFD (Intrauterine Fetal Demise) remains uncertain. Salihu et al **(27)** conducted a retrospective cohort analysis and found that pregnant women with advanced age had a two-fold increase in stillbirth compared to pregnant women aged 20–24 years (95% CI 1.7-2.4). Additionally, highly advanced pregnant women had a 3.4-fold increase in stillbirth (95% CI 2.8-4.2) compared to the same control group **(27)**. Similarly, a comprehensive meta-analysis that examined 44 studies and a total of 44,723,207 births, including 185,384 stillbirths, discovered a higher likelihood of intrauterine fetal demise (IUFD) among older pregnant women. The odds' ratio (OR) was 1.75, with a 95% confidence interval (CI) of 1.62-1.89 **(1)**.The researchers postulated that the elevated rate of stillbirths was associated with the aging of the placenta, which is caused by vascular dysfunction related to advancing age **(28, 29)**. Conversely, a comprehensive study comprising 369,516 pregnancies with just one fetus in Denmark examined the occurrence of intrauterine fetal demise (IUFD) among older pregnant women, namely those who were elderly or very elderly, and compared it to a control group of women aged 20–34 years **(30)**. The incidence of stillbirth was greater in pregnant women of advanced age (0.35% vs 0.28%, adjusted odds' ratio [aOR] 1.43 [99.8% confidence interval (CI) 1.05-1.96]), although the difference was not statistically significant in the extremely senior

group (0.43% vs 0.28%, odds ratio [OR] 1.47 [99.8% CI 0.76-2.84]) **(31)**. In this study, the highest percentage of IUFD was found in Cikalong Wetan General Hospital. This is likely due to the demographic factors of the community in this area **(32)**. Constraints in the referral process from primary health care facilities or other health care facilities to this hospital due to limited resources and abnormalities lead to a high infant mortality rate in this hospital. Therefore, improvements to health services in this region are required to reduce infant mortality **(33)**.

There are several limitations in our study. The retrospective nature of this investigation raises the possibility of random bias. Second, although our study controlled for common maternal characteristics, there is a possibility of undetermined confounding due to the absence of other sociodemographic factors (i.e., socioeconomic status) that influence perinatal outcome. Thirdly, the study only investigated the short-term effects of maternal age on fetal or neonatal complications. A comprehensive evaluation of the impact of advanced maternal age on the outcomes of preterm birth infants requires long-term neurodevelopmental status monitoring. Regardless of those limitations, this study presented a large sample, thus minimizing the chance of sampling bias.

5. Conclusion

Increasing incidences of adverse pregnancy outcomes, both maternal and fetal, were observed in the advanced-age mothers. There was a significant increase in antepartum hemorrhage, hypertensive pregnancy, and IUFD in advanced-age mothers. Therefore, healthcare providers should counsel couples who wish to have a child later in life about the dangers associated with advanced maternal age. To reduce the number of women in this age group who become pregnant, healthcare professionals must also emphasize improving the health of mothers of advanced age through the use of contraception.

6. Declarations

Acknowledgments

Not applicable.

Ethical Considerations

This study has received ethical approval from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, under approval number LB.02.01/X.6.5/155/2023. The committee has ensured that the research adheres to ethical standards, safeguarding the rights and welfare of all participants involved, and complies with the principles outlined in the Helsinki Declaration.

Authors' Contributions

All authors contributed to conceiving and designing the study. G.H. collected the data. T.D. and D.S. contributed data and analysis tools; T.D. and D.S. performed the analysis. G.H. wrote the paper. All authors have reviewed the manuscript and given their approval for publication.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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