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Original Research

Adverse Perinatal Outcomes at Advanced Pregnancy Ages: A Single Center Study

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Abstract

Background: Advanced maternal age (AMA) has been associated with various adverse obstetric, perinatal, and neonatal outcomes. This study primarily aimed to compare pregnancy outcomes in women aged 40 years and older with those aged 35–39 years, with a secondary aim to determine advanced maternal age by comparing these two age groups with those aged 20–34 years. **Methods**: This was a retrospective review of adults who gave birth between January 2020 and August 2024. All pregnant women in this study were single pregnancies and aged 20 years and older. Pregnant women using assisted reproductive technology and those with missing data were excluded from the study. This study included three groups of pregnant women: 20–34, 35–39, and 40 years and older. Perinatal outcomes of the three groups were compared. **Results**: AMA has previously been associated with various adverse obstetric outcomes. However, while there was a significant difference in birth weeks between the 20–34 years age group and the ≥40 age group (p = 0.019), the birth weeks of other age groups were similar. Moreover, there was no statistically significant difference between birth weights. Maternal ages of 35–39 and ≥40 years were associated with increased rates of cesarean delivery, pre-eclampsia, low birth weight, gestational diabetes mellitus (GDM), fetal growth restriction (FGR), preterm delivery, and low Apgar score ($p < 0.001$); however, rates of placental abruption, and preterm premature rupture of membranes (PPROMs) were similar to women aged <35 years. Gestational hypertension (GHT) (adjusted odds ratio (adjOR): 6.710, 95% confidence interval (95% CI): 2.755–16.343, p = < 0.001), oligohydramnios (adjOR: 2.145, 95% CI: 1.056–4.356, p = 0.035), macrosomia (adjOR: 5.459, 95% CI: 1.164–25.609, p = 0.031), and postpartum hemorrhage (adjOR: 5.139, 95% CI: 1.021–25.872, p = 0.047) are more common in women aged ≥40 years compared to both the reference group and the <35 age group. **Conclusions**: Adverse perinatal outcomes are more common in pregnant women aged 35 and over. These adverse outcomes are more common in the ≥40 years age group. To prevent these negative outcomes as well as potential maternal and fetal mortality and morbidity, we believe it is crucial to monitor these pregnant women closely during the prenatal period.

Keywords: advanced maternal age; adverse obstetric outcomes; adverse perinatal outcomes

1. Introduction

Since the percentage of women giving birth after the age of 35 has increased over time, especially in high-income countries, concerns have simultaneously recently arisen regarding the effects of advanced maternal age (AMA) on pregnancy outcomes [1,2]. Meanwhile, AMA has been linked to a variety of unfavorable obstetric, perinatal, and neonatal outcomes [3]. Data from some studies have shown that AMA is associated with numerous adverse pregnancy outcomes, including abortus, chromosomal abnormalities, stillbirth, fetal growth restriction (FGR), preterm birth, pre-eclampsia, gestational diabetes mellitus (GDM), and higher rates of cesarean (CS) delivery [4–8]. According to previous study the primary reason for poor perinatal outcomes in AMA is insufficient uterine vascularity, which is linked to lower fetal oxygenation and an elevated risk of hypertension [9]. The impact of maternal age on perinatal outcomes is debatable, as another study has revealed that older and younger women had comparable perinatal results [10]. Although 35 years is considered to be an advanced age, this circumstance has recently started to be addressed, with some studies suggesting that 40 years is a better cutoff point for identifying high-risk pregnancies [11,12].

Therefore, this study primarily aimed to compare pregnancy complications and pregnancy outcomes in women aged 40 years and older with those aged 35–39 years, with a secondary aim to determine advanced maternal age by comparing these age groups with those aged 20–34 years.

2. Material and Methods

This study was conducted at Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital between January 2020 and August 2024. This study was approved by the local Medical Ethics Committee of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, department of Obstetrics and Gynecology, Istanbul, Turkey (grant no: E-46059653-050.04-259020152). Adults who gave birth at the research center between January 2020 and August 2024 were reviewed retrospectively. All pregnant

Table 1. Adverse maternal and perinatal outcomes.

Outcome	Definition
Iron deficiency	Hemoglobin value less than 11.0 g/dL in women who gave birth [13].
Gestational diabetes mellitus (GDM)	An absence of any threshold value: fasting glucose ≥92 mg/dL, 1-hour postprandial glucose ≥180 mg/dL, or 2-hour postprandial glucose ≥153 mg/dL on a 75-gram oral glucose tolerance test [14].
Pre-eclampsia	High blood pressure (systolic ≥140 mmHg or diastolic ≥90 mmHg) and proteinuria (≥300 mg in a 24-hour urine collection or protein/creatinine ratio ≥0.3) after the 20th week of gestation [15].
Eclampsia	Seizures in the context of pre-eclampsia [15].
HELLP syndrome	Hemolysis, elevated liver enzymes, and low platelet counts [15].
Placental abruption	Premature detachment of the placenta before delivery [13].
Postpartum hemorrhage	Total blood loss ≥1000 mL after delivery or blood loss with clinical signs and symptoms of hypovolemia within 24 hours after birth [16,17].
Preterm delivery	Delivery before 37 weeks of gestation.
Preterm premature rupture of membranes (PPROMs)	Rupture of membranes before the onset of labor and before 37 weeks of gestation [20].
Oligohydramnios	Amniotic fluid index <5 cm or the single deepest vertical pool <2 cm on ultrasound [18].
Fetal growth restriction (FGR)	Estimated fetal weight or abdominal circumference <10th percentile, combined with abnormal Doppler indices (e.g., umbilical artery pulsatility index >95th percentile) [19].
Macrosomia	Birth weight ≥4500 g.
Low birth weight	Birth weight <2500 g.
Stillbirth	Fetal death after 20 weeks of gestation, with a birth weight of ≥500 g [21].
Low Apgar score	1st-minute Apgar <7 and 5th-minute Apgar <7.

women included in this study were single pregnancies and at least 20 years old. The study included three groups of pregnant women: 20–34, 35–39, and 40 years and older. Women with multiple pregnancies, those who became pregnant with assisted reproductive technology, and pregnant women with missing data were not included in this study.

Hospital data were used to gather information on age, body mass index (BMI), obstetric history, obstetric outcomes, and chronic diseases, which included pregestational diabetes mellitus, chronic hypertension, hypothyroidism/hyperthyroidism, migraine, asthma, and epilepsy. Additionally, information on delivery mode, low birth weight (birth weight <2500 g), macrosomia (birth weight ≥4500 g), low activity pulse, grimace, appearance, respiration (Apgar) score (Apgar score <7) were noted. Data were also recorded for postpartum blood transfusions and intravenous iron therapy.

Iron deficiency, GDM, placental abruption, pre-eclampsia, eclampsia and hemolysis, elevated liver enzymes, low platelet levels syndrome (HELLP syndrome), and postpartum hemorrhage were all considered adverse maternal outcomes. A hemoglobin level below 11.0 g/dL in postpartum women was considered anemia [13]. GDM diagnoses were made following a minimum fasting value higher than 92 mg/dL, a 1-hour satiety value of 180 mg/dL, or a 2-hour satiety value of 153 mg/dL in the 75-gram oral glucose tolerance test [14]. Pre-eclampsia was diagnosed if blood pressure was high (systolic ≥140 mmHg or diastolic ≥90 mmHg), proteinuria (300 mg in a 24-hour urine collection or protein/creatinine ≥0.3 in a random urine sample or dipstick measurement ±1) and/or liver, kidney, nerve and/or blood function deterioration occurred after the 20th week of gestation. The emergence of seizures in the context of pre-eclampsia was the hallmark of eclampsia. Hemolysis, high liver enzymes, and low platelet counts were used to diagnose HELLP syndrome [15]. Indicators of early postpartum hemorrhage were total blood loss ≥1000 mL following delivery or blood loss that occurred within 24 hours of delivery and was accompanied by clinical signs and symptoms of hypovolemia [16,17].

Preterm premature rupture of membranes (PPROMs), preterm delivery, oligohydramnios, FGR, low birth weight, fetal macrosomia, and stillbirth were all considered adverse perinatal outcomes. Obstetric ultrasound measurements were defined as oligohydramnios when the amniotic fluid index was less than 5 cm, or the single deepest vertical pool of amniotic fluid was less than 2 cm [18]. Indicators of FGR included an umbilical artery pulsatility index (PI) above the 95th percentile or a cerebroplacental ratio (CPR) below the 5th percentile, along with an abdominal circumference (AC) or estimated fetal weight (EFW) below the 3rd percentile or EFW or/and AC below the 10th percentile [19]. Delivery after 24 weeks but before 37 weeks were considered preterm. Similarly, PPROMs oc-

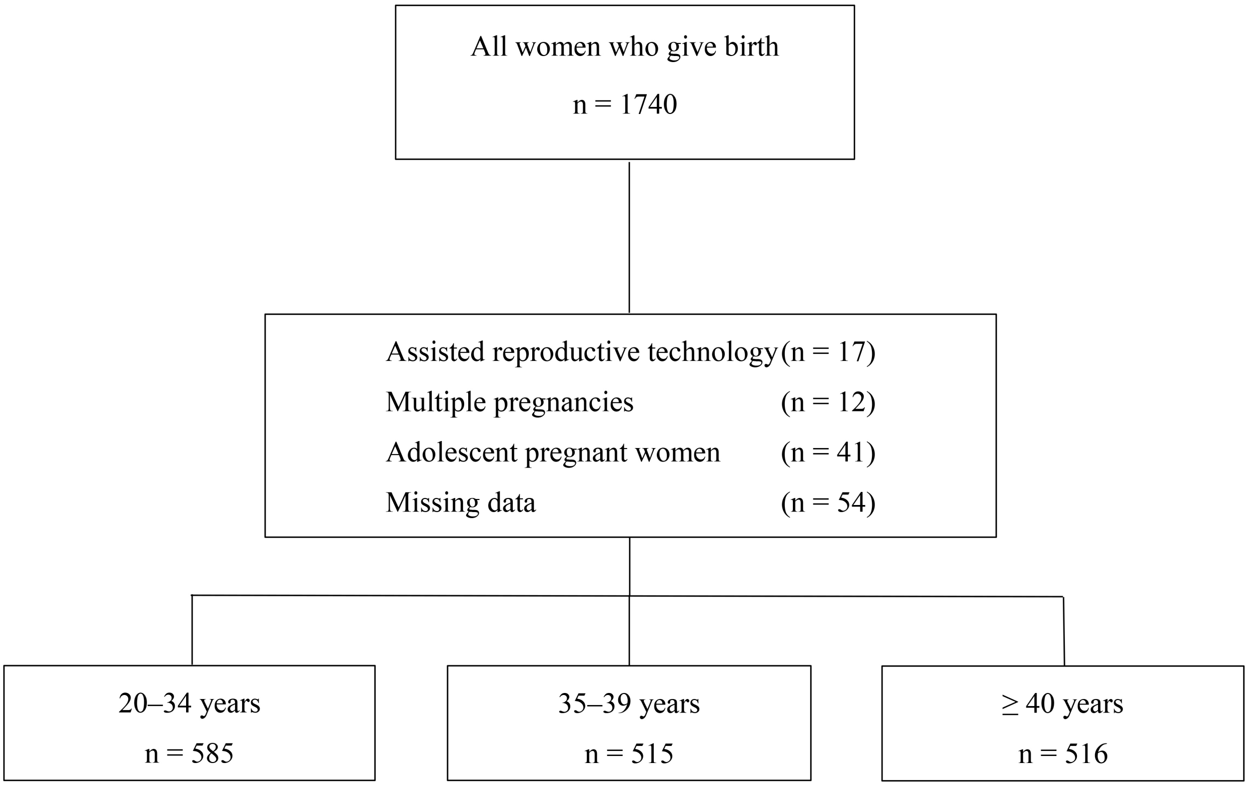

Fig. 1. Flow diagram showing the distribution of study participants according to age groups and exclusion criteria.

cur when the chorioamniotic membranes rupture between 24 and 36 weeks and 6 days [20]. Stillbirth occurs when a fetus weighs 500 grams or more and dies in utero after the 20th week of pregnancy [21]. Definitions of adverse maternal and perinatal outcomes are summarized in Table 1 (Ref. [13–21]).

Statistical analysis was conducted to assess the impact of AMA on particular pregnancy outcomes, which were considered independently. The SPSS 20 software package (SPSS Inc., Chicago, IL, USA) was used for all analyses. First, descriptive statistics were created for each of the three groups and all patients for each pregnancy outcome and any confounding factor. For nonparametric and continuous confounders, Kruskal-Wallis test/pairwise comparisons of the group (significance values were adjusted using Bonferroni correction for multiple tests) and Chi-square tests were applied for categorical variables. The reference group comprised mothers under 35 years old on the anticipated delivery date. Multivariable logistic regression was then used to determine the crude and adjusted effects of the AMA on each of the unfavorable pregnancy outcomes. Confounders for the adjusted models included parity, BMI, history of miscarriage, pregestational diabetes mellitus, chronic hypertension, and chronic disease. When 95 % confidence intervals (95% CIs) and adjusted odds ratios (adjORs) were calculated, $p < 0.05$ was considered statistically significant, indicating a difference in risk between age groups. In this study, the proportion of missing data was less than 5% for all variables. Considering the low proportion of missing data and to ensure the robustness of the analyses, cases with missing values were excluded using a complete-case analysis (listwise deletion) approach. This method is appropriate when the proportion of missing data is minimal and assumed to be missing completely at random (MCAR).

3. Results

A total of 1616 patients meeting the study criteria were included. The flow diagram is shown in Fig. 1. The patients were divided into three age groups; the first consisted of 585 (36.2%) patients aged 20–34, the second consisted of 515 (31.9%) patients aged 35–39, and the third comprised 516 (31.9%) patients aged 40 and over. The third group included eight patients aged 50 and over. Table 2 summarizes the demographic characteristics, obstetric history, and patient characteristics of the three groups according to maternal age. When patient characteristics were compared according to maternal age group, there was no significant difference in maternal anemia and chronic hypertension; however, there was a significant difference between other parameters. While the rates of gravida, parity, and chronic disease were significantly different in all age groups ($p < 0.001$), there was a significant difference in pre-gestational diabetes in the 20–34 age group and the ≥40 age group ($p = 0.006$).

Table 2. Patient characteristics by maternal age.

	20–34 years	35–39 years	≥40 years	20–34 *vs.* 35–39 years	20–34 *vs.* ≥40 years	35–39 *vs.* ≥40 years	Overall *p*-value
	n = 585	n = 515	n = 516	*p*-value	*p*-value	*p*-value	
Age (years) median (IQR)	25.0 (6)	37.0 (2)	41.0 (2)	<0.001[1a]	<0.001[1a]	<0.001[1a]	<0.001[1]
Body mass index (BMI) median (IQR)	23.8 (9.2)	24.2 (8.3)	25.8 (8.5)	0.049[1a]	<0.001[1a]	0.009[1a]	<0.001[1]
Gravidity median (IQR)	2.0 (2)	3.0 (2)	2.0 (1)	<0.001[1a]	<0.001[1a]	<0.001[1a]	<0.001[1]
Parity median (IQR)	1.0 (2)	2.0 (1)	1.0 (1)	<0.001[1a]	<0.001[1a]	<0.001[1a]	<0.001[1]
Gestational week median (IQR)	38.0 (2)	39.0 (1)	39.0 (3)	0.057[1a]	0.019[1a]	1.0[1a]	0.012[1]
Birth weight (grams) median (IQR)	3300 (508)	3365 (730)	3415 (818)				0.065[1]
History of miscarriage (%)	35 (27.3%)	58 (45.3%)	35 (27.3%)	0.002[2a]	0.195[2a]	<0.036[2a]	0.003[2]
History of previous cesarean section (%)	22 (3.8%)	191 (37.1%)	131 (25.4%)	<0.001[2a]	<0.001[2a]	<0.001[2a]	<0.001[2]
Maternal anemia (%)	199 (34.0%)	178 (34.6%)	164 (31.8%)	0.283[2a]	0.143[2a]	0.114[2a]	0.602[2]
Pregestational diabetes mellitus (%)	2 (0.3%)	4 (0.8%)	9 (1.7%)	0.109[2a]	0.006[2a]	0.054[2a]	0.049[2]
Chronic hypertension (%)	2 (0.3%)	5 (1.0%)	8 (1.6%)	0.063[2a]	0.011[2a]	0.134[2a]	0.113[2]
Chronic disease (%)	12 (2.1%)	65 (12.6%)	111 (21.5%)	<0.001[2a]	<0.001[2a]	<0.001[2a]	<0.001[2]

IQR, interquartile range. [1] Kruskal-Wallis test. [1a] Kruskal-Wallis test/pairwise group comparisons (significance values have been adjusted using the Bonferroni correction for multiple tests). [2] Chi-square test. [2a] Chi-square test (significance values have been adjusted using the Bonferroni correction for multiple tests).

Table 3. Obstetric complications by maternal age: adjusted models*.

Outcome	20–34 years (n = 585)	35–39 years (n = 515)		≥40 years (n = 516)	
	n (%)	n (%)/adjOR (95% CI)	*p*-value	n (%)/adjOR (95% CI)	*p*-value
Vaginal delivery	559 (95.6%)	269 (52.2%)/0.045 (0.029–0.070)	<**0.001**	276 (53.5%)/0.071 (0.046–0.111)	<**0.001**
Cesarean delivery	26 (4.4%)	246 (47.8%)/22.271 (14.287–34.717)	<**0.001**	240 (46.5%)/14.016 (9.035–21.745)	<**0.001**
Gestational hypertension	6 (1.0%)	11 (2.1%)/2.080 (0.753–3.749)	0.158	40 (7.8%)/6.710 (2.755–16.343)	<**0.001**
Pre-eclampsia	3 (0.5%)	32 (6.2%)/11.265 (3.397–37.353)	<**0.001**	45 (8.7%)/12.768 (3.886–42.070)	<**0.001**
Oligohydramnios	13 (2.2%)	13 (2.5%)/1.162 (0.522–2.583)	0.713	27 (5.2%)/2.145 (1.056–4.356),	0.035
Placental abruption	1 (0.2%)	1 (0.2%)/4.540 (0.482–42.760)	0.186	2 (0.4%)/3.952 (0.421–37.083)	0.186
Preterm delivery	19 (3.2%)	60 (11.7%)/3.820 (2.222–6.567)	<**0.001**	77 (14.9%)/3.802 (2.226–6.494)	<**0.001**
Preterm premature rupture of membranes	7 (1.2%)	4 (0.8%)/0.585 (0.162–2.114)	0.413	2 (0.4%)/0.233 (0.043–1.271)	0.092
Gestational diabetes	4 (0.7%)	27 (5.2%)/8.502 (2.929–24.677)	<**0.001**	46 (8.9%)/14.246 (5.042–40.307)	<**0.001**
Fetal growth restriction	3 (0.5%)	12 (2.3%)/4.700 (1.301–16.975)	0.018	15 (2.9%)/4.991 (1.402–17.769)	0.013
Low birth weight <2500 g	15 (12.0%)	40 (40.0%)/3.931 (2.155–7.173)	<**0.001**	60 (48.0%)/3.602 (1.979–6.558)	<**0.001**
Macrosomia ≥4500 g	2 (1.8%)	4 (23.5%)/2.697 (0.485–15.007)	0.257	11 (64.7%)/5.459 (1.164–25.609)	0.031
1st-minute Apgar <7	3 (4.2%)	26 (36.1%)/10.225 (3.053–34.243)	<**0.001**	43 (59.7%)/14.006 (4.261–46.041)	<**0.001**
5th-minute Apgar <7	2 (0.3%)	8 (1.6%)/5.129 (1.069–24.617)	0.041	15 (2.9%)/5.449 (1.194–24.877)	0.029
Postpartum hemorrhage	2 (0.3%)	3 (0.6%)/2.171 (0.345–13.680)	0.409	7 (1.4%)/5.139 (1.021–25.872)	0.047
Postpartum blood transfusion	8 (1.4%)	11 (2.1%)/1.490 (0.568–3.907)	0.418	4 (0.8%)/0.463 (0.130–1.650)	0.235
Postpartum intravenous iron treatment	57 (9.7%)	28 (5.4%)/0.519 (0.316–0.852)	0.009	2 (0.4%)/0.40 (0.10–0.168)	<**0.001**

95% CI, 95% confidence interval; adjOR, adjusted odds ratio. *Adjusted models controlled for parity, body mass index, history of miscarriage, pregestational diabetes, chronic hypertension, and chronic disease. All patients under 35 years on the anticipated expected date are included in the reference group. Bold values indicate statistically significant results ($p < 0.005$).

Table 3 shows the percentage of cases affected by obstetric outcomes for each maternal age group and summarizes the adjusted ORs with 95% CIs estimating the effect of AMA for each obstetric outcome compared with the reference group of women younger than 35 years.

The median gestational age at birth was 38.0 weeks (IQR: 2) in the <35 years age group, 39.0 weeks (IQR: 1) in the 35–39 years age group, and 39.0 weeks (IQR: 3) in the ≥40 years age group. There was a significant difference between the 20–34 years age group and the ≥40 years age group (p = 0.019); however, there was no statistically significant difference between the other age groups (20–34 years *vs.* 35–39 years, p = 0.570; 35–39 years *vs.* ≥40 years, p = 1.000). The median birth weight was 3300 (508) grams in the <35 years age group, 3365 (730) grams in the 35–39 years age group, and 3415 (818) grams in the ≥40 years age group (p = 0.065) (Table 2).

AMA was also significantly associated with pre-eclampsia (adjOR: 11.265, 95% CI: 3.397–37.353; adjOR: 12.768, 95% CI: 3.886–42.070), GDM (adjOR: 8.502, 95% CI: 2.929–24.677; adjOR: 14.246, 95% CI: 5.042–40.307), and CS (adjOR: 22.271, 95% CI: 14.287–34.717; adjOR: 14.016, 95% CI: 9.035–21.745). Additionally, AMA was significantly associated with gestational hypertension (GHT) (adjOR: 6.710, 95% CI: 2.755–16.343), oligohydramnios (adjOR: 2.145, 95% CI: 1.056–4.356), macrosomia (adjOR: 5.459, 95% CI: 1.164–25.609), and postpartum hemorrhage (adjOR: 5.139, 95% CI: 1.021–25.872) in pregnant women aged ≥40 years. No statistically significant difference in placental abruption and postpartum blood transfusion was observed between the groups. Eclampsia and cholestasis during pregnancy were not seen in any of the three groups. In addition, stillbirth was not seen in the <35 years age group, while it occurred for five patients (1%) in the 35–39 years age group and four patients (0.8%) in the ≥40 years age group. The 1st and 5th-minute Apgar scores were significantly lower in patients with AMA in both groups compared to the reference group.

4. Discussion

The prevalence of women who delay childbirth for various reasons is increasing worldwide. Therefore, the impact of the decision to postpone childbirth on perinatal and maternal outcomes is becoming increasingly important since adverse perinatal outcomes are becoming increasingly common in older patients [22]. Our study found that AMA is associated with several adverse obstetric outcomes. There was a significant difference in the gestational week at birth between the 20–34 and ≥40 years age groups, but no statistically significant difference between the other age groups. There was no significant difference in birth weights between the groups. Mothers in the 35–39 years age group and ≥40 years age group are associated with increased rates of CS, pre-eclampsia, GDM, preterm birth, low birth weight, FGR, and low Apgar score, but rates of placental abruption, and PPROMs remained similar to those women in the <35 years age group. The probability of having GHT, oligohydramnios, macrosomia, and postpartum hemorrhage in patients ≥40 years is more common than in both the reference group and the 35–39 years age group.

Pregnancies at ≥35 years of age are linked to poor perinatal outcomes, including hypertensive disorders, preterm delivery, GDM, elevated rates of cesarean sections, low Apgar scores, low birth weight, macrosomia, perinatal mortality, according to recent study examining obstetric complications in pregnancy at AMA [3]. Furthermore, these adverse outcomes are more pronounced in pregnancies at ≥40 years of age [22]. These results are parallel to some results in our study; we found an increased ratio of CS, pre-eclampsia, preterm delivery, GDM, low birth weight, and low Apgar score in both the 35–40 and ≥40 years age groups; however, this difference was more pronounced in the ≥40 years age group. We also found that the risk of GHT, oligohydramnios, and macrosomia increased only in the ≥40 age group. A previous study identified a higher CS rate in the 35–39 years age group, which suggested that this situation may be related to increased pregnancy complications, such as pre-eclampsia, GDM, and bleeding [3]. Moreover, this study noted a higher CS rate in the 35–39 years age group than in the <35 and ≥40 years age groups, potentially due to the lower parity rate in both groups compared to the 35–39 years age group.

Maternal age has been suggested as an independent predictor of GDM [21]. Similarly, a previous study found that the prevalence of GDM in women over 40 years of age was 12.5 times higher than in controls [23]. A recent study reported that GDM was more common in both women aged over 35 and those over 40 years of age [24]. Meanwhile, our study identified the 35–39 years and the ≥40 years age groups as high risk for GDM, with GDM being the highest perinatal risk in the ≥40 age group. In addition, the fact that the incidence of both GDM and pregestational diabetes mellitus was significantly higher in the ≥40 age group in our study can be interpreted as the reason why macrosomia, a complication of maternal diabetes, was also more common in this group.

In a study conducted for pre-eclampsia, AMA was claimed to be a risk factor for pre-eclampsia, and it was reported that the risk of pre-eclampsia increased by 4.56 times compared to pregnancies in mothers under 35 years of age [25]. Similarly, another study reported that the risk of pre-eclampsia increased by 3.4 times in pregnancies over 40 years of age [24]. Our research found that the prevalence of pre-eclampsia was higher in both the 35–39 and the over 40 age groups.

In our study, FGR rates were statistically higher in the 35–39 years and ≥40 age groups compared to the reference group. This may be due to the increase in chronic diseases and chronic hypertension with age. Similarly, in a different study, FGR rates were higher in mothers aged 40 years and over [26]. Study has been published that indicate stillbirth rates increase with maternal age [3]. In our research, stillbirth rates increased with age in the 35–39 years and the ≥40 age groups, although not to levels of statistical significance compared to the reference group. Furthermore, oligohydramnios complicates pregnancies with FGR, and amniotic fluid content falls as fetal circumstances worsen [27]. This is associated with increased perinatal mortality and low Apgar score, low birth weight, and preterm birth [28]. Our study observed low Apgar scores and preterm birth rates more frequently in the older age groups than the reference group, with the oligohydramnios rate significantly more common in the ≥40-year-old age group. We believe that this is because FGR is commonly associated with oligohydramnios, which in turn causes preterm birth and low birth weight.

Our study presents some strengths and weaknesses. The main strength of our study is the sample size, which allows for multivariate data analysis. The limitations of our study include the fact that it is a retrospective study and that data from a single center reflect the outcomes of pregnancies in a limited geographic area. Furthermore, additional confounding factors such as smoking status and socioeconomic factors may also influence perinatal outcomes; the lack of availability of these data was another limitation. Randomized controlled trials involving multiple clinical centers are needed to clarify the importance of advanced age on maternal and fetal outcomes.

5. Conclusions

The prevalence of adverse prenatal outcomes increases significantly in women who become pregnant after the age of 35 years; however, these adverse outcomes are even more pronounced in women aged 40 years and over. The risks associated with AMA not only affect the course of labor but can also negatively impact the health of the fetus, the pregnancy, and the pregnant woman. We believe that close and careful prenatal monitoring of AMA pregnancies is extremely important to avoid such risks and minimize possible maternal and infant mortalities. This approach can increase the safety of the pregnancy and play a vital role in protecting the health of both mother and baby.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Both authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by OSG, and SKA. The first draft of the manuscript was written by OSG, SKA and both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All experimental procedures of this study were approved by the local Medical Ethics Committee of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, department of Obstetrics and Gynecology, Istanbul, Turkey (E-46059653-050.04-259020152), which were in complete accordance with the ethical standards and regulations of human studies of the Helsinki declaration. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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