The effect of advanced maternal age on pregnancy outcomes: A prospective study

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Abstract

Background: Women who are 35 years of age or older at the anticipated date of delivery are considered to have advanced maternal age (AMA). This cutoff age was chosen in light of decreasing fertility data and growing concerns about the increased likelihood of genetic defects in the progeny of pregnant women over 35. An increased risk of perinatal deaths, spontaneous abortions, pregnancy complications like diabetes mellitus (DM) and hypertension (HTN), interventions like cesarean deliveries (CS), and foetal adverse events like preterm birth (PTB), low birth weights (LBW), congenital anomalies, and NICU admission is linked to older mothers.

Objective: Evaluation of the impact of advanced maternal age on maternal, obstetric, fetal, and perinatal outcomes was the main objective of the study.

Patients and methods: This study was a prospective cohort study at the Obstetrics and Gynecology Department at Mansoura University Hospitals. This study was conducted on a total of 82 primigravida women who were divided into 2 groups. The study group included 41 women aged 35 years or more. The control group included 41 women aged 20 years to 34 years.

Results: there was a significant difference between both groups about cesarean (CS) deliveries, preterm birth, high mean arterial pressure, and high Rate Pressure Product.

Conclusion: advanced maternal age is accompanied by a higher rate of preterm birth, cesarean delivery, high mean arterial pressure, and rate pressure product more than younger age women.

Keywords: advanced maternal age, obstetric, maternal, fetal, perinatal outcomes, cesarean delivery, preterm birth.

Introduction

A woman is deemed to have an advanced maternal age (AMA) if she is 35 years of age or older at the beginning of her pregnancy or at the time of delivery. There's a tendency in rich countries where older primigravida women decide not to have children out of choice or due to underlying

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infertility, but multiparous women are also choosing to continue having children [1].

Very AMA (VAMA) could be described as women over 40, while extremely AMA (EAMA) is utilized to characterize females over 45. These subcategories of advanced maternal age have also been established [2]. The selection of this age threshold was motivated by dwindling fertility data and growing apprehension over the likelihood of genetic defects in children born to pregnant mothers over 35 [3].

In wealthy countries, ladies in their advanced maternal age are probably primiparous. Unlike underdeveloped nations, where poverty, the cultural predilection for large kids, and inefficient family planning measures make childbirth at AMA the most likely among multiparous women [4].

Preeclampsia (PE), stillbirth, and foetal growth restriction (FGR) are among the pregnancy complications linked to advanced maternal age. These complications can be caused by endothelial damage, which ages with the mother, decreased maternal hemodynamic adaptation during pregnancy, and decreased uterine blood vessel compliance [5].

The older the mother, the higher the chance of premature delivery. Placental pathology explains this and might also explain why preeclampsia is more common in AMA. This adds to the list of iatrogenic factors contributing to premature labor induction [6]. Age significantly raises the risk for CD, whether it is an emergency or elective procedure. Fetal malposition, anomalies during delivery, underlying medical co-morbidities, and even mother requests are some of the factors that explain this [7].

As a mother's age rises, there is a greater chance of spontaneous abortion during the first 14 weeks of pregnancy [8]. Pregnancy at an advanced mother age is strongly linked to unfavorable newborn outcomes, which include preterm delivery, early infant mortality, LBW, and admission to the neonatal intensive care unit (NICU) [9]. The unfavorable consequences stem from insufficient cardiovascular adaptation during gestation, impeding the hemodynamic adjustments necessary to sustain the fetus [10].

Aim of the work

Analyzing the effects of advanced mother age on perinatal, obstetric, fetal, and maternal outcomes throughout pregnancy was the aim of this study.

Study design

This study was a prospective cohort study conducted at Obstetrics and Gynecology Department at Mansoura University Hospitals, from June 2021 to June 2022.

This study included primigravida women aged 20 years or more after the exclusion of the patients who refused to be included in this study, patients aged less than 20 years, and patients with medical disorders such as (pre-existing DM, chronic HTN, or autoimmune diseases).

Study population

The studies cases consisted of 82 primigravida women who were divided into 2 groups. The study group consisted of 41 pregnant women aged 35 years or more. Forty-one pregnant women, ages 20 to 34, made up the control group.

Additionally, the research group was partitioned into two subgroups: the very advanced age group, which included those older than 40, and the advanced age group, which included those between 35 and 40.

Methods

- After getting written consent from all participants. We documented personal, menstrual, obstetric, and history of surgical operation.

- Every prenatal appointment included a general examination to rule out chronic hypertension, monitor blood pressure to diagnose hypertensive diseases of pregnancy after 20 weeks of gestation and assess the mother's body mass index to identify obesity. When necessary, local and abdominal exams were performed.
- Between 24 and 28 weeks of gestation, all pregnant females were evaluated for gestational DM (GDM) using an oral glucose challenge test weighing 50 grams. A three-hour oral glucose tolerance test with a 100g oral glucose load was administered to females who had abnormal glucose challenge test results (140 mg/dL). When blood glucose levels are above 95 mg/dL during fasting, 130–140mg/dL one hour after eating, and 120mg/dL two hours after eating, GDM is diagnosed.
- Pregnancy-induced hypertension, gestational diabetes mellitus (GDM), preeclampsia, early pregnancy bleeding, antepartum hemorrhage, oligohydramnios or polyhydramnios, ICU hospitalization, sepsis, and postpartum hemorrhage were among the obstetric outcomes that were documented.
- Premature rupture of membranes, miscarriage, PTB, and CS or vaginal delivery were among the maternal outcomes that were documented.
- Congenital defects, intrauterine growth limitation, intrauterine fetal mortality, and stillbirth were among the fetal outcomes that were documented.
- The NICU hospitalization, early neonatal mortality, LBW (less than 2500g), very LBW (less than 1500g), and macrosomia (more than 4000g) are the categories into which perinatal outcomes were categorized.

Outcomes

The primary outcome was to detect the difference between the advanced age group and the younger age group about maternal, obstetric, fetal, and perinatal outcomes. The secondary outcome was to detect the difference between the advanced age group and the very advanced age group concerning maternal, obstetric, fetal, and perinatal outcomes.

Ethical consideration

The study protocol was approved by the Institutional Review Board (IRB), code no MS.21.06.1542, Date: 07/07/2021, Faculty of Medicine, Mansoura University.

Every patient received an explanation of the procedure's specifics. At every stage of the study, participants gave their informed written agreement regarding confidentiality and personal privacy. The current study was the only use of the data that was gathered.

Statistical Analysis

IBM Corp., 2020 provided the IBM-SPSS software, which was used for data entry and analysis. Armonk, NY: for Windows, Version 27.0.

The notation for qualitative data was N (%). Shapiro-Wilk's test was first used to determine if quantitative data was regularly distributed. If $p>0.050$, the data was considered normally distributed. Boxplots were examined to see whether any significant outliers (extreme values) were present. The interquartile range (Q1, or 25th percentile, to Q3, or 75th percentile) and median for quantitative data were reported as non-normally distributed.

To compare qualitative data between groups, the chi-square, Fisher's exact, or Fisher-Freeman-Halton exact tests were utilized. The quantitative data between the two groups was compared by utilizing the non-parametric Mann-Whitney U-test. The impact of predictor factors on the probability of an event, such as a mother or newborn being admitted to the ICU or NICU, was

determined using binary logistic regression.

If the p-value is less than 0.050, the results of any test that is employed will be deemed statistically significant.

Results

This study had 82 primigravida and was divided into two groups; study group (A) included 41 pregnant women aged 35 years or more. Control group (B) included 41 pregnant women aged 20 years to 34 years.

No statistically significant difference was detected between both groups concerning residence, educational level, type of conception, abnormal OGTT, DBP, Heart Rate (HR), Hemoglobin level, and platelet count. There was a statistically significant difference in previous relevant surgery such (p =.043), systolic blood pressure (SBP) (p=.019), mean arterial pressure (p=.033), Rate Pressure Product (RPP) = (SBP × heart rate) (p=.018), and body mass index (<.001) (Table 1).

Table (1): Comparisons of baseline characteristics of older age (A) vs. younger age groups (B).

Characteristic	Group A		Group B		Total		p-value
Categorical	N	%	N	%	N	%	
Residence Rural Urban	 28 13	 68.3 31.7	 28 13	 68.3 31.7	 56 26	 68.3 31.7	1.00
Education level Low Middle High	 4 25 12	 9.8 61 29.3	 2 17 22	 4.9 41.5 53.7	 6 42 34	 7.3 51.2 41.5	.076
Type of conception ART Natural	 5 36	 12.2 87.8	 4 37	 9.8 90.2	 9 73	 11 89	1.00
Previous relevant surgery	8	19.5	2	4.9	10	12.2	**.043**
Abnormal OGTT	4/37	10.8	1/38	2.6	5/75	6.7	.200
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
SBP (mmHg)	120	115-150	110	110-140	120	110-140	**.019**
DBP (mmHg)	80	75-90	80	70-90	80	70-90	.072
MAP (mmHg)	93.3	88.3-113.3	90	83.3-106.7	93.3	83.3-107.5	**.033**
Heart rate (beats/ minute)	88	80-90	84	80-90	87	80-90	.824
RPP	10920	9350-13350	9680	8800-11760	10480	9000-12390	**.018**
BMI (kg/m^2)	30	28-32.5	25	22-30	29.5	24-31.3	**<.001**
Hemoglobin level (g/dl)	10.9	10.4-11.6	10.6	9.6-11.1	10.9	10-11.3	.099
Platelet count $\times 10^9/L$	280	187-300	240	192-294.5	273	189.8-300	.192

There was a significant difference between the studied groups regarding delivery by cesarean section either elective or urgent (p=.028) being significantly higher in the advanced age group as compared to the younger age group (89.2% vs. 68.4%, respectively) and preterm birth (p=.001) being significantly higher at advanced age group as compared to younger age group (29.3% vs. 2.4%, respectively) and there was not a statistically significant difference as regards to the risk of miscarriage and PROM (Table 2).

Table (2): Comparisons of maternal outcomes in older age group (A) vs. younger age group (B).

	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Maternal outcomes							
Mode of delivery Vaginal delivery CS [elective, urgent]	4 33 [12, 21]	10.8 89.2	12 26 [7,19]	31.6 68.4	16 59 [19, 40]	21.3 78.7	**.028**
Miscarriage	4	9.8	3	7.3	7	8.5	1.00
PROM	3	7.3	6	14.6	9	11	.482
Preterm birth	12	29.3	1	2.4	13	15.9	**.001**

There was no statistically significant difference between both groups concerning obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 3).

Table (3): Comparisons of obstetric outcomes in older age group (A) vs. younger age group (B).

Obstetric outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Bleeding APH PPH Bleeding of early pregnancy	8 2 2 4	19.5 4.9 4.9 9.8	8 1 4 3	19.5 2.4 9.8 7.3	16 3 6 7	19.5 3.7 7.3 8.5	1.00 1.00 .678 1.00
Sepsis	1	2.4	0	0	1	1.2	1.00
Oligohydramnios	4	9.8	7	17.1	11	13.4	.331
Polyhydramnios	3	7.3	1	2.4	4	4.9	.616
GDM	4	9.8	1	2.4	5	6.1	.359
PET	10	24.4	8	19.5	18	22	.594
HELLP syndrome	2	4.9	1	2.4	3	3.7	1.00
PIH	5	12.2	3	7.3	8	9.8	.712
ICU admission	6	14.6	2	4.9	8	9.8	.264

There was no statistically significant difference between the studied groups about fetal and perinatal outcomes (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 4).

Table (4): Comparisons of fetal and perinatal outcomes in older age group (A) vs. younger age group (B).

Fetal and perinatal outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
$$$Birth weight	38		37		75		.666
Very low	3	7.9	4	10.8	7	9.3	
Low	7	18.4	3	8.1	10	13.3	
Normal	28	73.7	30	81.1	58	77.3	
NICU admission	15	38.5	10	24.4	25	31.3	.175
IUGR	3	7.3	4	9.8	7	8.5	1.00
Early neonatal death	4	9.8	1	2.4	5	6.1	.359
Congenital anomaly	3	7.3	1	2.4	4	4.9	.616
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
*Birth weight (g)	3200	2300-3500	3500	2800-3500	3500	2500-3500	.388

There was no statistically significant difference between the advanced age group and very advanced age group concerning type of conception, or mode of delivery "although 100% of cases in the very advanced age group were delivered by cesarean section but with no statistical difference due to decreased number of cases at this group", miscarriage, PROM, and preterm birth (Table 5).

Table (5): Comparisons of maternal outcomes in advanced vs. very advanced age groups.

Maternal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Type of conception							.563
ART	5	15.2	0	0	5	12.2	
Natural	28	84.8	8	100	36	87.8	
Mode of delivery							.556
vaginal delivery	4	13.8	0	0	4	10.8	
cesarean delivery	25	86.2	8	100	33	89.2	
[elective, urgent]	[9,16]		[3,5]		[12,21]		
Miscarriage	4	12.1	0	0	4	9.8	.569
PROM	3	9.1	0	0	3	7.3	1.00
Preterm birth	9	27.3	3	37.5	12	29.3	.672

There was no statistically significant difference between the advanced age group and the very advanced age group about obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 6).

Table (6): Comparisons of obstetric outcomes in advanced vs. very advanced age groups.

Obstetric outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Bleeding	8	24.2	0	0	8	19.5	.318
Placenta previa	2	6.1	0	0	2	4.9	1.00
PPH	2	6.1	0	0	2	4.9	1.00
Bleeding of early pregnancy	4	12.1	0	0	4	9.8	.569
Sepsis	1	3	0	0	1	2.4	1.00
Oligohydramnios	4	12.1	0	0	4	9.8	.569
Polyhydramnios	3	9.1	0	0	3	7.3	1.00
GDM	4	12.1	0	0	4	9.8	.569
PET	7	21.2	3	37.5	10	24.4	.672
HELLP syndrome	2	6.1	0	0	2	4.9	1.00
PIH	5	15.2	0	0	5	12.2	.563
ICU admission	5	15.2	1	12.5	6	14.6	1.00

There was no statistically significant difference between the advanced age group and the very advanced age group regarding fetal and perinatal outcomes including (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 7).

Table (7): Comparisons of fetal and perinatal outcomes in advanced vs. very advanced age groups.

Fetal and perinatal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Birth weight	30		8		38		.088
Very low	1	3.3	2	25	3	7.9	
Low	5	16.7	2	25	70	18.4	
Normal	24	80	4	50	28	73.7	
NICU admission	12	38.7	3	37.5	15	38.5	1.00
IUGR	2	6.1	1	12.5	3	7.3	.488
Early neonatal death	2	6.1	2	25	4	9.8	.165
Congenital anomaly	3	9.1	0	0	3	7.3	1.00
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
Birth weight (g)	3400	2500-3500	2650	1125-3500	3200	2300-3500	.170

Discussion

Pregnancies in females who are 35 years of age or older at the time of conception or birth are classified as AMA. It is becoming very common in affluent nations, mostly observed in older primigravida women who choose to put off having children out of a desire to live a longer life or because of underlying infertility, however, multiparous women are also doing so (1).

It is crucial to assess if and how AMA influences pregnancy outcomes and the maternal and foetal health, given the notable increase in the proportion of older moms. While the majority of research revealed a significant correlation between age and the outcome of pregnancy, other studies yielded inconsistent findings (11).

According to our study, there was no statistically significant difference between

the studied groups' baseline characteristics—such as place of residence, level of education, and mode of conception.

Our investigation revealed a statistically significant difference in the mean arterial pressure (P=.033), systolic blood pressure (P=.019), and rate pressure product (RPP) (p=.018) between the groups under consideration.

More and more people are using the double (rate-pressure) product (DP) as a proxy for cardiac activity and myocardial oxygen demand. It is calculated by multiplying HR by SBP. The robust correlation between left ventricular mass and DP has revealed its role in predicting the risk of acute myocardial infarction (AMI) and cardiovascular disease in hypertensive individuals (12).

In our study, the AMA group's mean RPP was 10920, whereas the younger age group's mean was 9680. This finding was consistent with research that indicated older women were predicted to have a higher incidence of AMI (13). RPP can be used to predict cardiovascular risk in women with AMA.

In terms of delivery mode, our study revealed that there was a statistically significant difference (p=0.028) between the groups under investigation; among the older group, 89.2% had an urgent or elective cesarean section, compared to 68.4% who were younger.

Although, 100% of the cases of the VAMA group were delivered by CD in comparison with 86.1% of the AMA group but with no statistically significant differences.

In accordance with the findings of Rydahi and associates, who revealed that older females had a greater possibility of CD at AMA (aOR=2.18) and VAMA (aOR=3.64). (15). The high risk of CD at AMA is explained by atherosclerosis of the uterine arteries, a decline in oxytocin receptors with age, and inadequate myometrium contractility, which results from the aged uterus's decreased ability to produce uterine contractions (14).

In our study, Preterm delivery showed statistically significantly higher incidence among older age than younger age group (29.3% versus 2.4%) (p=0.001).

Also, preterm delivery was 37.5 in the VAMA group versus 27.1% in the AMA group but of no statistically significant differences.

A significant retrospective analysis supported Waldenstrom et al.'s findings, showing that AMA and VAMA raised the odds of preterm delivery regardless of parity, both spontaneously occurring and when medically recommended. From 35 to 39 years old, age-related relationships were statistically significant but less strong across all parity groups (15).

However, even after accounting for confounding variables, a major retrospective study from Canada by Fuchs et al. and his colleagues indicated that in comparison with pregnancy at 30-34 years of age, pregnancy at a VAMA increased the risk of PTB by 1.2. Moreover, the age-group distribution of premature labor was found to be "U" shaped, indicating that young mother age is a predisposing factor for preterm labor in addition to AMA (16).

The risk of GDM in the AMA group was 9.8% group versus 2.4% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

However, in comparison to women under 35, the GDM incidence at AMA and VAMA is 1.62 (P<0.001) and 2.1 (P<0.001) higher, respectively, according to the retrospective study conducted by Khalil et al. and colleagues (17). Increasing obesity rates in older adults, which are associated with lower insulin sensitivity, might help to explain this (18).

In our study, the risk of PET in the AMA group was 24.4% group versus 19.5% in the younger age group and 21.2% in the AMA

group versus 37.5% in the VAMA group with no statistically significant difference.

The univariate analysis of the retrospective study by Nieto and his colleagues which compared women under 30 in the AMA, VAMA, and EAMA groups to a control group, only revealed a higher risk for PET at EAMA (OR=3.32). When confounding factors (obesity, utilization of ART, tobacco smoking, chronic HTN, and parity) were adjusted for using a multivariable logistic regression, age and PET did not, however, substantially correlate (19).

Regarding the comparison of fetal and perinatal outcomes, our study revealed that; there was no significant difference between studied groups as regards birth weight, congenital anomalies, NICU admission, and early neonatal death.

The risk of miscarriage was 9.8% in the AMA group versus 7.3% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

Magnus et al., in contrast, discovered that there was a considerable variation in the probability of miscarriage with mother age. Women between the ages of 25 and 29 had the lowest miscarriage risk (9.8%), while women over the age of 45 had the greatest risk (53.6%). The absolute lowest risk was at age 27 (9.5%). The risk was 15.8% for moms under the age of twenty (8).

The risk of congenital anomalies in our study was 7.3 in the AMA group versus 2.4% in the younger group and 9.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

In line with Goetzinger et al.'s retrospective analysis of congenital anomaly prevalence in AMA pregnancies with euploid babies, they discovered that AMA was protective against congenital malformations (aOR 0.59, 95% CI 0.52–0.66). The "all or none" theory, which postulates that anatomically normal foetuses have a better survival rate at advanced oocyte age, can explain this phenomenon (20).

Nevertheless, it was shown that the rate of foetal chromosomal aberrations in spontaneous miscarriages at VAMA was substantially more than in women of a younger age (60.6% versus 33.5% in women 30-34). This Chinese study examined the connection between 497 pregnancies' spontaneous miscarriages, AMA, and chromosomal abnormalities (21).

The results of our study regarding the risk of NICU admission were 38.5% in the AMA group VS. at 24.4% in the younger group and 38.7% in the AMA group VS. 37.5% in the VAMA group with no statistically significant difference.

The AMA and VAMA groups, on the other hand, had higher rates of NICU admission; their respective AORs were 1.68 (95% CI 1.42–2.15, $P < 0.01$) and 1.52 (95% CI 1.21–1.92, $P < 0.01$) were higher. Kahveci and his colleagues assessed the effects of advanced maternal age on the perinatal and neonatal results of nulliparous singleton pregnancies in Turkey (3).

The risk of FGR in our study was 7.3% in the AMA group vs. 9.8% in the younger age group and 6.1% in the AMA group vs. 12.5% in the VAMA group with no statistically significant difference.

However, FGR was described as birth weight below the 5th percentile. Lean et al. found in a major study that women with AMA had a 1.23 (95% CI 1.01–1.52) higher risk of FGR; among women over 40, the risk increases by 1.53 (95% CI 1.07−2.20) This might be explained by incorrect placentation, which causes FGR but is unrelated to a decline in oocyte fitness (22).

The limitation of our study included the small sample size in the studied group and larger future studies are needed.

Conclusion

Advanced maternal age is accompanied by a higher rate of preterm birth, Cesarean delivery, high mean arterial pressure, and high Rate Pressure Product than younger age women.

Conflict of interest: None.

Sources of funding: Nil.

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