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ORIGINAL ARTICLE

Risk of morbidity and mortality in preterm infants born to advanced maternal age pregnancies

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Abstract

Background: Little is known about the effect of advanced maternal age on preterm morbidity and mortality. This study aimed to evaluate the possible relationship between maternal age and morbidity and mortality in premature infants born at a gestational age ≤32 weeks.

Methods: Premature infants born at ≤32 weeks of gestation and admitted to the neonatal intensive care unit were divided into three groups by maternal age: <35, 35-39, and ≥40 years. Infant and maternal demographic and clinical characteristics, and preterm morbidity and mortality were compared between the groups.

Results: A total of 827 preterm infants were included. Their distribution by maternal age was as follows: 659 infants in the <35 years group, 120 in the 35-39 years group, and 48 in the ≥40 years age group. Older maternal age was associated with higher gravidity, frequency of assisted reproductive technology use, preeclampsia, gestational diabetes mellitus, and caesarean delivery (P=0.004, P<0.001, P=0.007, P=0.004, and P<0.001, respectively). Respiratory distress syndrome, patent ductus arteriosus, and necrotising enterocolitis were significantly more frequent in preterm infants aged ≥35 years (P=0.014, P=0.029, and P<0.001, respectively).

Conclusions: In addition to the maternal risks associated with pregnancy at older ages, some prematurity morbidities may also increase in frequency. Although this novel study presents important results, further studies are needed to evaluate the relationship between advanced maternal age and preterm morbidity.

Keywords: Maternal Age, Preterm Infants, Morbidity, Mortality, Aged.

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INTRODUCTION

Worldwide, the childbearing age for women extends into 30s and sometimes 40s. The Centre for Disease Control and Prevention have reported that pregnancy in women over 40 years of age is becoming more common in developed countries. The prevalence of first pregnancy at the age of >35 years was 9% in developed countries in the 2000s, but has increased to 23% in 2014 (1). The most common reason for this is that women with higher socioeconomic status and education levels tend to postpone motherhood until after their 30s. As a result, the use of assisted reproductive technology (ART) has increased (2).

Although the impact of childbirth in older mothers on maternal and perinatal outcomes has been extensively studied, there is no universal consensus on the definition of advanced maternal age (AMA). The term AMA refers to the prolongation of a woman's reproductive life in later years and is usually used for women aged ≥35 years (3,4). Additionally, the term extremely advanced maternal age (EAMA) has been used for pregnancies in women over 40 years of age (5).

Women with AMA (>35 years) are at risk of obstetric complications and serious interventions (6). The AMA increases the risk of pregnancy complications, such as ectopic pregnancy, miscarriage, fetal chromosomal abnormalities, congenital anomalies, placenta previa, placental abruption, gestational diabetes mellitus (GDM), preeclampsia, and caesarean delivery. These maternal complications may lead to preterm delivery and an increased risk of perinatal death (1). Despite this information, data regarding the clinical outcomes of preterm infants born to mothers under 35 years of age compared to those born to mothers ≥35 years of age are lacking. It is not known whether premature infants born at ≤32 weeks gestation, which is already a high-risk group in terms of preterm morbidity, have a higher risk of morbidity and mortality when born to mothers with AMA (7). We hypothesised that preterm infants born to mothers with AMA are at a greater risk of morbidity and mortality than those born to younger mothers. The present study was conducted to test this hypothesis by comparing morbidity and mortality of premature infants born at ≤32 weeks gestation to mothers with and without AMA.

MATERIALS AND METHODS

Study design and patients

This retrospective study included infants admitted to the neonatal intensive care unit (NICU) of our hospital between September 2019 and December 2021. Patient data were obtained by reviewing the medical records. Infants born at ≤32 weeks of gestation and admitted to the NICU were included in this study. Infants born after 32 weeks of gestation were excluded from this study. The study was carried out after obtaining approval from the local clinical ethics committee (Date:02.02.2022, Approval No: 2022/E2-22-1362). All the authors conducted the study in accordance with the principles of the Declaration of Helsinki. During the study period, care and feeding conditions were similar for all newborns.

Demographic and clinical characteristics

For all infants included in the study, the following data were obtained from the medical records: maternal age, gravidity, use of ART, antenatal steroid therapy, congenital anomaly, presence of preeclampsia, maternal thyroid disease, maternal chorioamnionitis, and GDM, mode of delivery, intubation in the delivery room, GA, birth weight (BW), sex, Apgar scores at 1 and 5 min, presence of severe congenital anomaly, small for gestational age (SGA), duration of mechanical ventilation (MV), non-invasive ventilation (NIV), supplemental oxygen, presence of early onset neonatal sepsis (EOS), late-onset neonatal sepsis (LOS), respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) requiring treatment, intraventricular haemorrhage (IVH; grade≥3), necrotic enterocolitis (NEC; ≥2), day of full enteral feeding, length of NICU stay, and mortality.

Definitions of morbidities of prematurity

Small for gestational age was defined as BW below the 10th percentile for GA on the Lubchenco curve (8). All significant clinical and echocardiographic PDAs were regarded as haemodynamically significant PDA (9). All preterm infants requiring >30% oxygen at a postmenstrual age of 36 weeks were classified as having moderate/severe BPD (10). The ROP was defined according to the third edition of the International Classification of Diseases (11). Intraventricular haemorrhage on cranial ultrasound was defined according to the Volpe criteria (12). Necrotic enterocolitis was defined using the Bell criteria (13). Sepsis was defined as EOS if it occurred within the first 72 h of life, and as LOS if it occurred after the first 72 h (14). The need for surfactants was determined according to the national guidelines, and infants that received surfactants were classified as having RDS (15).

The infants were divided into three groups by maternal age: mothers aged <35, 35–39, and ≥40 years. The three groups were compared in terms of infants' demographic and clinical characteristics, morbidity, and mortality.

Statistical Analysis

Data were analysed using Statistical Package for Social Sciences (SPSS) version 18 for Windows (SPSS Inc., St. Louis, MO, USA). Non-normally distributed continuous variables were compared between the groups using the t-tests. Categorical variables were analysed using the chi-squared or Fisher's exact tests. Continuous variables are presented as mean ± standard deviation (SD) and/or median (minimum-maximum). Categorical variables were expressed as frequency and percentage distributions. Analysis of variance (ANOVA) with Bonferroni correction was used for comparisons among three groups. Results with P values <0.05 were considered statistically significant in all comparisons.

Sample size

Sample size calculation was based on the morbidity variable. The power calculation was performed according to the data from a previous study which was conducted in the relationship of neonatal morbidity in advanced maternal age pregnancy (16). The total sample size of 138 (46 patients per group) will be sufficient to detect power of 80% and a significance level of 5%.

RESULTS

This study included 827 premature infants born at ≤32 weeks of gestation. When grouped by maternal age, 659 infants were in the <35 years age group, 120 were in the 35-39 years group, and 48 were in the ≥40 years age group. The mean (± SD) maternal age was 26.1 ± 4.5 years in the <35 years age group, 36.2 ± 1.2 years in the 35-39 years age group, and 41.6 ± 2.2 years in the ≥40 years age group. ANOVA method was used to compare the groups. Older maternal age was associated with higher gravidity and frequency of ART, preeclampsia, GDM, and caesarean delivery (P=0.004, P<0.001, P=0.007, P=0.004, and P<0.001, respectively. Other demographic characteristics showed no significant differences between the groups (P>0.05) (Table 1). The RDS, PDA, and NEC were significantly more frequent in preterm infants born to mothers aged ≥35 years (P=0.014, P=0.029, and P<0.001, respectively). The other infant clinical outcomes and morbidity rates were similar between the groups (P>0.05) (Table 2).

Table 1. Demographic characteristics of patients

Characteristics	Maternal Age Groups			P value			
	< 35 years (I) (n = 659)	35–39 years (II) (n = 120)	≥ 40 years (III) (n = 48)	ANOVA	I vs. II	I vs. III	II vs. III
Gravidity [a]	1 (1–4)	3 (1–6)	3 (1–6)	0.004*	0.018*	0.001*	0.107
Assisted reproductive technology [b]	34 (5.1)	19 (15.8)	10 (20.8)	<0.001	<0.001*	<0.001*	0.373
Antenatal steroid [b]	453 (68.7)	84 (70)	33 (98.7)	0.946	0.753	0.930	0.809
Preeclampsia [b]	123 (18.6)	26 (21.6)	18 (37.5)	0.007*	0.443	0.002*	0.035*
Maternal chorioamnionitis [b]	52 (7.8)	11 (9.1)	6 (12.5)	0.512	0.330	0.307	0.474
Maternal thyroid disease [b]	16 (2.4)	3 (2.5)	2 (4.1)	0.466	0.551	0.187	0.306
GDM [b]	21 (3.1)	10 (8.3)	6 (12.5)	0.004*	0.002*	0.001*	0.036*
Gestational age (weeks) [c]	28.1±1.2	28.0±1.1	27.7±1.2	0.385	0.487	0.199	0.464
Birth weight (g) [c]	1058±230	1065±219	1064±208	0.944	0.758	0.853	0.975
Cesarean delivery [b]	342 (51.8)	79 (65.8)	39 (81.2)	<0.001*	0.002*	<0.001*	0.021*
Male sex [b]	345 (52.3)	62 (51.6)	23 (47.9)	0.259	0.890	0.110	0.171
Apgar score at 1 min [a]	5 (1-8)	5 (1-7)	5 (1-7)	0.711	0.798	0.303	0.355
Apgar score at 5 min [a]	8 (2-10)	8 (3-9)	8 (2-9)	0.481	0.893	0.158	0.270
Intubation in the delivery room [b]	51 (7.7)	10 (8.3)	4 (8.3)	0.711	0.497	0.510	0.833
SGA [b]	47 (7.1)	11 (9.1)	6 (12.5)	0.219	0.332	0.115	0.187
Congenital anomaly [b]	5 (0.7)	2 (1.6)	1 (2)	0.212	0.105	0.067	0.153

GDM, gestational diabetes mellitus; SGA, small for gestational age.
*Statistically significant p values are highlighted.
[a] Data are given as median (minimum-maximum)
[b] Data are presented as n (%)
[c] Data are given as mean ± standard deviation.

Table 2. Clinical outcomes and morbidities

Variables	Maternal Age Groups			P value			
	< 35 years (I) (n = 659)	35–39 years (II) (n = 120)	≥ 40 years (III) (n = 48)	ANOVA	I vs. II	I vs. III	II vs. III
Duration of MV (days) [a]	3.8±3.0	4.4±2.6	3.9±2.6	0.442	0.488	0.273	0.173
Duration of NIV (days) [a]	7.6±5.6	8.3±5.4	8.2±6.1	0.762	0.515	0.679	0.941
Duration of supplemental oxygen (days) [a]	24.3±13.5	26.2±15.5	25.7±14.8	0.683	0.445	0.668	0.899
ENS [b]	14 (2)	4 (3.3)	2 (4.1)	0.830	0.586	0.872	0.807
LOS [b]	141 (21.3)	27 (22.8)	10 (20.8)	0.092	0.083	0.182	0.335
RDS [b]	398 (60.4)	86 (71.6)	35 (72.9)	0.014*	0.019*	0.005*	0.248
PDA [b]	238 (36.1)	58 (48.3)	24 (50)	0.029*	0.011*	0.008*	0.594
BPD (moderate/severe) [b]	119 (18.1)	19 (15.8)	6 (12.5)	0.561	0.614	0.319	0.525
ROP [b]	59 (8.9)	10 (8.3)	5 (10.4)	0.363	0.804	0.174	0.189
IVH (grade≥3) [b]	58 (8.8)	9 (7.5)	4 (8.3)	0.678	0.413	0.643	0.860
NEC (grade≥2) [b]	9 (1.3)	9 (7.5)	3 (6.2)	<0.001*	<0.001*	0.003*	0.067
Full enteral feeding (days) [a]	16±7.3	17.4±7.9	16.4±4.2	0.199	0.100	0.708	0.460
NICU stay (days) [a]	55.1±30.1	57.6±32.7	57.4±31.5	0.649	0.708	0.621	0.640
Mortality [b]	106 (16.1)	21 (17.5)	7 (14.5)	0.884	0.431	0.609	0.969

BPD, bronchopulmonary dysplasia; EOS, early-onset neonatal sepsis; IVH, intraventricular hemorrhage; LOS, late-onset neonatal sepsis; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NIV, non invasive ventilation; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age

*Statistically significant p values are highlighted.

[a]Data are given as mean ± SD

[b]Data are presented as n (%)

DISCUSSION

The risk of maternal morbidity and preterm birth increases at later maternal age. A higher risk of preterm birth is associated with a higher risk of perinatal morbidity and mortality. However, no previous study has investigated whether preterm babies born to mothers with AMA have an increased risk of morbidity and mortality compared to preterm infants born to younger mothers. In our study, the frequencies of ART, preeclampsia, GDM, and caesarean delivery were higher in AMA mothers than in mothers <35 years of age. Additionally, preterm infants born to mothers with AMA had significantly higher rates of RDS, PDA, and NEC than preterm infants born to mothers <35 years.

As women age, the number of pregnancies increases, but the rate of live births may decrease. Therefore, the use of ART is on the rise (1,17). Clinical studies have shown that adverse obstetric and perinatal outcomes may be more common in mothers over 35 years of age (1,18-23). Unfavorable neonatal outcomes have been demonstrated in studies on term, early term, and late preterm infants. There are insufficient data on maternal age-related outcomes in preterm infants. In this study, we observed that negative maternal outcomes and some prematurity morbidities increased in frequency in association with maternal age.

The adverse obstetric consequences of AMA may also have unfavourable effects on the foetus. Advanced maternal age mothers are known to have a four-fold higher risk of preterm delivery than younger mothers (18). A higher risk of preterm birth is associated with lower BW and GA, lower Apgar scores, greater need for resuscitation, and

higher rates of respiratory distress and NICU admission (18-20,24). More importantly, greater prematurity in infants born to mothers with AMAs increases mortality risk (18,20,23). In fact, an unfavourable maternal obstetric history associated with AMA is followed by an increase in the risk of preterm birth, and increased preterm morbidity is the last link in the chain. Numerous studies conducted in different centres have revealed maternal outcomes similar to those in our study (18-20,24). However, whether preterm infants born to older mothers have a greater morbidity and mortality risk than infants born at ≤32 weeks of gestation to mothers <35 years of age has not been investigated.

Previous studies have evaluated infants born to mothers with AMA in terms of short-term clinical outcomes, such as in the delivery room and indications for NICU admission (1,18-20,24). Our study is the first to evaluate the possible relationship between morbidity in preterm infants and their mothers by maternal age. The results of our study indicated that RDS, PDA, and NEC were more common among infants born at ≤32 weeks of gestation when the maternal age was ≥35 years. Low BW and GA are the most important risk factors for RDS, PDA, and NEC (7). The BW and GA were similar among the groups in our study. This demonstrates the main finding of our study that maternal age ≥35 years was associated with a higher frequency of RDS, PDA, and NEC. Adverse intrauterine conditions in mothers with AMAs may also increase the frequency of neonatal respiratory distress. Placental factors are not only responsible for unfavourable intrauterine conditions but have also been implicated in neonatal respiratory distress (7,25). As histopathological examination of the placenta could not be performed in our study, the influence of placental factors on RDS could not be evaluated.

Our results indicate that preterm infants born to mothers with AMA have a higher rate of RDS; however, the underlying pathophysiology is not clear. The aetiology may involve impaired foetal surfactant production, resulting from unfavourable intrauterine conditions with increasing maternal age. This in turn results in greater neonatal surfactant use. A surfactant deficiency causes hypoxaemia, which improves with surfactant administration. As hypoxaemia resolves, the neonatal pulmonary arterial pressure decreases. This results in faster systemic arterial blood flow to the pulmonary artery via the PDA. All of these pathophysiological changes may cause PDA to remain open. Additionally, PDA can contribute to a reduction in gastrointestinal blood flow and NEC development (9). These pathophysiological mechanisms might explain the increased prevalence of RDS and subsequent increases in PDA and NEC observed in preterm infants born to AMA mothers in our study (7,9). The results of our study suggest that maternal age had no effect on other prematurity morbidities. A possible reason for this may be that the surfactant therapy shortened the duration of respiratory support in infants with RDS, which may explain why the groups had similar respiratory support times. The lack of significant differences between the groups in terms of morbidities, such as sepsis, BPD, ROP, IVH, and NICU stay and mortality may be related to their comparable respiratory support duration, BW, and GA (7,9-11).

Study limitations

Our study had certain limitations, owing to its single-centre and retrospective design. An investigation of placental histopathology, cord blood laboratory values, prenatal NST or umbilical cord Doppler, maternal drug use, and maternal BMI data was not possible. Therefore, our results must be evaluated based on available data.

This study showed that the prevalence of RDS, PDA, and NEC was significantly higher among preterm infants (GA≤32 weeks) born to mothers aged ≥ 35 years. Further studies, including placental histopathology and hormonal and biochemical markers, should be conducted to explain the increase in morbidity associated with AMA.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study was carried out after obtaining approval from the Ethics Committee (E2) of Ankara City Hospital (Date: 02.02.2022, Approval No: 2022/E2-22-1362).

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