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*Original Research*

# The Impact of Advanced Maternal Age on Neonatal Outcome in Preterm Births before 34 Weeks

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**Abstract**

**Background**: In recent years a trend towards childbearing at older maternal age is evident. Most of the current literature investigated the association between advanced maternal age and neonatal outcome at term. We aimed to study the outcomes of the mother and the neonate among preterm births of women of advanced maternal age. **Methods**: This retrospective study between 2009 to 2017, comprised 494 singleton preterm births between 24 and 34 weeks gestation, of which 116 (23%) were of 35 years old or older (advanced maternal age) and 378 (77%) were of younger women. The medical records were reviewed and the outcomes of the mother and the neonate were compared between advanced maternal age (≥35 years) and younger women. **Results**: The rate of severe intra-ventricular hemorrhage (IVH) and of composite adverse neonatal outcome was lower among advanced maternal age women compared to younger women ($p = 0.02$ and $p = 0.05$ respectively). In multivariate regression analysis, composite adverse neonatal outcome was found to be independently inversely associated only with advanced maternal age (adjusted odds ratio (aOR) 0.45 95% confidence interval (CI) 0.23–0.86). **Conclusions**: Advanced maternal age was not found to be a risk factor for adverse neonatal outcome among preterm births before 34 weeks, and might be a protective factor from early neonatal complications.

**Keywords:** advanced maternal age women; preterm birth; maternal outcome; neonatal outcome

## 1. Introduction

Advanced maternal age was historically defined as 35 years of age or older, based on the risk of fetal down syndrome. In recent decades there is a trend towards childbearing at older maternal ages, particularly in developed countries [1,2]. In the USA, first births of women aged ≥35 rose from 2000 to 2014 from 7.4% to 9.1% [3]. Advanced maternal age is a known risk factor for adverse outcomes for mother and neonate, including spontaneous abortion, gestational hypertension, gestational diabetes mellitus (GDM), pre-eclampsia, stillbirth, preterm birth, delivery of a large (LGA) or small for-gestational-age (SGA) neonate and cesarean section [4–7].

Most studies report obstetric and neonatal outcomes of advanced maternal age women who delivered at term. Data about short-term neonatal outcomes in preterm births of advanced maternal age women are scarce. Thus, in the current study we investigated the differences in obstetric and neonatal outcomes of preterm births (before 34 weeks) among advanced maternal age women (≥35 years) compared to younger women (<35 years).

## 2. Methods

### 2.1 Study Population

We performed a retrospective cohort study was performed in a tertiary hospital between 1/2009 and 7/2017. After the approval of Local Institutional Review Board, medical records of live singleton preterm births from 24–34 weeks of gestation were reviewed. Multiple births, stillbirth, neonates with known major congenital malformation and pregnancies with missing data were excluded from this study.

### 2.2 Data Collection

Data were collected from the maternal medical records: maternal age, body mass index (BMI kg/m$^2$), gravidity and parity, pre-gestational/GDM, hypertensive disorders, thrombophilia (acquired/inherited), smoking and drug abuse. Gestational age was based on 1st trimester ultrasound. The following variables were collected from the neonatal medical records: birthweight, SGA (defined as birth-weight <10% percentile) [8], Apgar score at 1, 5 minutes, steroids administration prior to birth, admission to neonatal intensive care unit (NICU), duration of NICU admission, respiratory distress syndrome, phototherapy, hypoglycemia, neonatal sepsis, blood transfusion, mechanical ventilation, periventricular leukomalacia, severe intraventricular hemorrhage (IVH grade 3–4), seizures, neonatal death.

Maternal outcomes included intrapartum fever/chorioamnionitis, postpartum fever/endometritis, manual removal of the placenta, revision of the uterine cavity, postpartum hemorrhage and need for blood transfusion in the early postpartum.

The primary outcome of the study was a composite variable of neonatal morbidity, defined as any morbidity of the following: Apgar score <8 at 5 minutes, NICU admission, phototherapy, respiratory distress syndrome, hypoglycemia, sepsis, blood transfusion, mechanical ventilation, periventricular leukomalacia, severe IVH, seizures and neonatal death.

In this study maternal and neonatal outcomes of pregnancies among advanced maternal age women were compared to women younger than 35 years.

*2.3 Data Analysis*

SPSS software (version 21.0, IBM Corp., Armonk, NY, USA) was used to analyze data. Continuous variables are presented either as mean ± standard deviation (SD) or as median and range, as appropriate. Categorical variables are expressed as a n (percentage). Student *t*-tests were used to compare continuous parameters, and $chi^2$ with Yates' corrections test or Fisher exact tests were used for categorical variables. Statistics were considered significant when the *p* value was below 0.05. A sub-analysis of preterm births between 24–28 and 28.1–32 weeks gestation was performed as well.

A multivariate regression analysis was performed to identify independent associations with composite adverse neonatal outcomes. Composite adverse neonatal outcomes served as a dependent variable. The significant factors found in the univariate analysis were added to factors which are known to have an impact on neonatal outcome-Maternal age >35 years, BMI, steroids administration before delivery, diabetes mellitus, gestational age at delivery, and birth weight, served as independent variables.

## 3. Results

The study included 494 preterm births, among them 378 (77%) were of women younger than 35 years and 116 (23%) of advanced maternal age women. The maternal and obstetric characteristics of the cohort are presented in Table 1. The BMI, gravidity and parity were significantly higher among women older than 35 years compared to younger women. The rate of pre-gestational and GDM was also higher among advance maternal age women compared to younger women. The causes of preterm labor didn't differ between the study groups.

Neonatal outcomes according to maternal age are presented in Table 2. The rates of severe IVH and of composite neonatal outcome were significantly lower among neonates born to advanced maternal age women compared to younger women (2.6% *vs.* 8.8%, $p = 0.02$; 62.1% *vs.* 71.7%, $p = 0.05$). Other neonatal outcomes were similar between women older than 35 years and younger women. In a sub-analysis of preterm births between 24 and 28 weeks of gestation, neonates delivered to mothers with advanced maternal age had significantly lower composite adverse neonatal outcomes (82.1% *vs.* 63.3%, $p = 0.04$). Regarding additional neonatal outcomes, there were no other differences between the two groups. Between 28.1–32 weeks of gestation- no differences were found in neonatal outcomes between the groups including composite adverse neonatal outcome.

Table 3 presents obstetric complications according to maternal age. No differences in the rate of obstetric complications were found between advanced maternal age and younger women.

By multivariate regression analysis presented in Table 4, after adjustment for gestational age at delivery, drug abuse, diabetes mellitus, steroids administration, hypertensive disorders, SGA and birthweight, composite adverse neonatal outcome was found to be independently inversely associated to advanced maternal age (adjusted odds ratio (aOR) 0.45 95% confidence interval (CI) 0.23–0.86).

## 4. Discussion

In our study advanced maternal age women had higher BMI, gravidity and parity, as well as higher rates of pregestational and gestational diabetes mellitus compared to younger women. The rates of severe IVH and of composite adverse neonatal outcome were significantly lower among advanced maternal age women.

In the past half-century, older women have accounted for an increasing proportion of births [9]. Nine percent of first births in the USA occurred to women older than 35 in 2014, a 23 percent rise from 2002 [3].

According to studies, mothers who are older may be at an increased risk for both maternal and newborn morbidity, especially because of higher rates of hypertension [10–12] and diabetes mellitus [13–16] and their sequelae compared to younger women. These complications are also related to increased rate of low birth-weight and preterm birth among advanced maternal age women [17–22].

Our findings are supported by a large Canadian cohort study that reported about the outcome of preterm neonates younger than 33 weeks born to advanced maternal age women. According to this study, advanced maternal age was linked to considerably higher infant survival rates without severe morbidity as well as lower rates of sepsis and necrotizing enterocolitis [23]. Our findings are also supported by a recent study that investigated the effect of advanced maternal age on the survival of preterm neonates without major morbidity at less than 35 weeks at discharge from NICU. In this study chronic lung morbidity, severe IVH, periventricular lekomalacia, severe retinopathy of the premature neonate, necrotizing enterocolitis and sepsis were found not to be influenced by older maternal age at delivery [24]. Another study from Taiwan investigated the short as well as the long-term outcomes of 209 very low birth weight (<1500 g) preterm neonates, who were born to advanced maternal age (≥35 years) mothers compared to 327 infants born to younger mothers. Similar to our findings, this study didn't find significant differences between advanced age women and younger women in terms of short-term neonatal outcomes [25].

**Table 1. Maternal and obstetric characteristics according to maternal age.**

| Characteristic | Age <35 (n = 378) | Age ≥35 (n = 116) | *p* value |
|---|---|---|---|
| Mean maternal age (years) | 28.3 ± 4.4 | 39.5 ± 7.7 | **<0.001** |
| Body Mass Index (kg/m$^2$) | 23.6 ± 5.0 | 25.2 ± 5.8 | **0.03** |
| Gravidity | 2.4 ± 1.5 | 3.2 ± 2.2 | **<0.001** |
| Parity | 0.9 ± 1.1 | 1.1 ± 1.2 | **0.04** |
| Nulliparity | 165 (43.7) | 43 (37.1) | 0.2 |
| Hypertensive disorders | 82 (21.7) | 36 (31.0) | 0.06 |
| Pre-gestational diabetes mellitus | 4 (1.1) | 9 (7.8) | **<0.001** |
| Gestational diabetes mellitus | 19 (5.0) | 18 (15.5) | **<0.001** |
| Smoking | 291 (77.0) | 79 (62.1) | 0.06 |
| Drug abuse | 8 (2.1) | 7 (6.0) | 0.06 |
| Thrombophilia (acquired/inherited) | 13 (3.4) | 5 (4.3) | 0.8 |
| | Start of labor | | |
| Elective cesarean section | 61 (19.7) | 25 (25.5) | 0.17 |
| Preterm uterine contractions | 121 (39.0) | 31 (31.6) | 0.28 |
| Rupture of membranes | 97 (31.3) | 29 (29.6) | 0.88 |
| Induction of labor | 10 (3.2) | 3 (3.1) | 0.97 |
| Antepartum hemorrhage | 21 (6.8) | 10 (10.2) | 0.23 |

Data are presented as n (%) or mean ± standard deviation (SD).

Values shown in bold were statistically significant ($p < 0.05$).

**Table 2. Neonatal outcomes according to maternal age.**

| | Age <35 (n = 378) | Age ≥35 (n = 116) | *p* value |
|---|---|---|---|
| Mean gestational age (weeks) | 30.5 ± 3 | 30.6 ± 2 | 0.3 |
| Mean birthweight (grams) | 1575 ± 563 | 1620 ± 531 | 0.4 |
| Small for gestational age | 146 (38.6) | 51 (44.0) | 0.3 |
| Apgar score at 1 minute | 7.2 ± 2.6 | 7.2 ± 2.5 | 1.0 |
| Apgar score at 5 minutes | 8.8 ± 2.1 | 8.8 ± 2.0 | 0.8 |
| Apgar score <8 at 5 minutes | 44 (11.6) | 16 (13.8) | 0.5 |
| Steroids up to 1 week prior to birth | 223 (59.0) | 48 (12.7) | 0.6 |
| Steroids 1 to 2 weeks prior to delivery | 48 (12.7) | 17 (14.7) | 0.6 |
| Admission to neonatal intensive care unit | 253 (68.4) | 68 (62.4) | 0.2 |
| Duration of admission in the neonatal intensive care unit (days) | 36 ± 31 | 36 ± 27 | 0.9 |
| Respiratory distress syndrome | 113 (30.0) | 27 (23.3) | 0.2 |
| Phototherapy | 204 (54.0) | 60 (51.7) | 0.7 |
| Hypoglycemia | 42 (11.1) | 8 (6.9) | 0.2 |
| Neonatal sepsis | 23 (6.1) | 3 (2.6) | 0.2 |
| Blood transfusion | 44 (11.6) | 11 (9.5) | 0.6 |
| Ventilation | 87 (23.0) | 24 (20.7) | 0.7 |
| Periventricular leukomalacia | 5 (1.3) | 0 (0) | 0.6 |
| Severe intraventricular hemorrhage | 32 (8.8) | 3 (2.6) | **0.02** |
| Neonatal seizures | 2 (0.6) | 0 (0) | 1.0 |
| Neonatal death | 6 (1.7) | 1 (0.9) | 1.0 |
| Composite outcome | 271 (71.7) | 72 (62.1) | **0.05** |

Data are presented as n (%) or mean ± SD. No cases of Necrotizing enterocolitis/Meconium aspiration syndrome/Hypoxic ischemic encephalopathy/Hypothermia.

Values shown in bold were statistically significant ($p < 0.05$).

Compatible with results from previous studies, we found that advanced maternal age women had higher BMI, gravidity and parity and higher rate of pre-gestational and gestational diabetes [23]. Numerous studies show that perinatal problems are much more common in diabetic women than in the general population [26]. However, we did not find in our study this association among preterm newborns of advanced maternal age women. Our findings are similar to a recent large cohort that revealed that very low birth weight neonates born to diabetic mothers were not affected by a higher morbidity except for necrotizing enterocolitis [27].

**Table 3. Obstetrics complications according to maternal age.**

| Complications | Age <35 (n = 378) | Age ≥35 (n = 116) | *p* value |
|---|---|---|---|
| Intrapartum fever/Chorioamnionitis | 31 (8.2) | 9 (7.8) | 0.8 |
| Post-partum fever/Endometritis | 1 (0.3) | 0 (0) | 0.8 |
| Revision of the uterine cavity | 16 (4.2) | 4 (3.5) | 1.0 |
| Manual removal of the placenta | 12 (3.2) | 2 (1.7) | 0.5 |
| Post-partum hemorrhage | 29 (7.7) | 5 (4.3) | 0.3 |
| Maternal blood transfusion | 10 (2.7) | 4 (3.5) | 0.7 |

Continuous variables are presented as mean ± SD and categorical variables as n (%).

**Table 4. Logistic regression analysis for composite neonatal outcome between 24.1–34.0 weeks.**

| | 95% CI | | aOR | *p* value |
|---|---|---|---|---|
| | Upper | Lower | | |
| Maternal age >35 | 0.86 | 0.23 | 0.45 | **0.01** |
| Body Mass Index | 1.07 | 0.95 | 1.01 | 0.73 |
| Steroids up to 1 week prior to delivery | 3.13 | 0.82 | 1.60 | 0.16 |
| Steroids 1 to 2 weeks prior to delivery | 6.20 | 0.83 | 2.27 | 0.11 |
| Pre-gestational diabetes mellitus | 3.06 | 0.15 | 0.69 | 0.63 |
| Gestational diabetes mellitus | 1.72 | 0.21 | 0.61 | 0.35 |
| Gestational age at delivery | 1.06 | 0.73 | 0.88 | 0.19 |
| Birth weight | 1.00 | 0.99 | 0.99 | 0.46 |

OR, odds ratio; CI, confidence interval.

Values shown in bold were statistically significant ($p < 0.05$).

The explanations for our observation of improved preterm neonatal outcomes with advanced maternal age are unknown. We assume that advanced age women are more likely to have a planned birth, and to have improved prenatal care, as high risk pregnancy surveillance is obligatory in Israel for advanced age women [28–30]. Furthermore, advanced maternal age women are more likely to have a higher socioeconomic status, healthier lifestyle and better compliance, which are associated with improved perinatal outcome [31]. Further explanations for better neonatal outcome in advanced age women, which were not examined in this study, might be a more prevalent use of aspirin during pregnancy and more prevalent performance of amniocentesis among advanced age women, which might lower the ratio of placental disorders and of genetic disorders respectively. In our study, the higher parity of advanced maternal age women may confer a protective factor from preeclampsia.

There are several strengths to our study. First, it is one of the very few studies that examined neonatal outcomes among preterm neonates of advanced maternal-age women. Second, the current study was performed in a single hospital, in which neonates and women were treated according to the same protocol before and after delivery. Third, we had the data regarding the administration of steroids, which is a known influential factor in neonatal outcomes. Finally, as opposed to similar studies, data regarding neonatal morbidity was extensive in our study. Our study has limitations. First, we have only collected short-term neonatal outcomes. Second, we know that using a composite outcome may be viewed as a limitation of this study. However, its utilization was necessary because the individual components of the composite are rare complications. The same composite neonatal outcomes were described and validated in previous publications with other pregnancy complications [32,33]. Third, our data is limited to neonates born between 24–34 weeks and can't be generalized to preterm neonates born between 34–37 weeks, however, it's known that the rate and the severity of complications of prematurity after 34 weeks of gestation are lower compared to earlier gestational age. Fourth, we do not know the rate of $MgSO_4$ (Magnesium sulfate) administration during birth for neuroprotection, which may have an effect on the newborn's neurological development. According to our departmental protocol since 2011 we administer $MgSO_4$ to every woman in labor prior to 32 weeks of gestation, so differences between the groups are not to be expected.

## 5. Conclusions

In conclusion, our study highlights the possibility of a better neonatal outcome in cases of preterm deliveries among advanced maternal age women. In these cases, it seems that advanced maternal age (≥35 years) might be a protective factor from early neonatal complications. Additional studies are necessary in order to better understand this surprising phenomenon.

## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Author Contributions

DT: collected the data, wrote the manuscript, OG: performed statistical analysis, designed the research, YI: collected the data, performed statistical analysis, JB: revised the manuscript, designed the research, EW: wrote the manuscript, performed statistical analysis, GB: wrote the manuscript, designed the research. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All 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 procedures were in accordance with the ethical standards of the institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Decision number: 0144-17-WOMC, dated: 13/08/2017. This research is of retrospective design, data was analyzed without identification details, informed consent wasn't obtained from the patients.


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## Conflict of Interest

The authors declare no conflict of interest.

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