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CLINICAL ARTICLE

Maternal age and outcome of preterm infants at discharge from the neonatal intensive care unit

Smadar Eventov-Friedman [a,*,1], Rachel Yaffa Zisk-Rony [b,1], Sophia Nosko [c], Benjamin Bar-Oz [a]

[a] Department of Neonatology, Hadassah–Hebrew University Medical Center, Jerusalem, Israel
[b] Henrietta Szold Hadassah–Hebrew University School of Nursing, Jerusalem, Israel
[c] Uppsala School of Medicine, Uppsala, Sweden

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ABSTRACT

Objective: To assess the effect of maternal age on preterm neonates' survival free from major morbidity at discharge from two neonatal intensive care units in Jerusalem, Israel. *Methods:* A retrospective chart review of two hospitals from 2009–2010 was performed. Eligible neonates were born at less than 35 weeks of gestation and survived to discharge. Major morbidity included at least one of the following: chronic lung disease, at least grade 3 intraventricular hemorrhage, periventricular leukomalacia, at least stage 3 retinopathy of prematurity, at least stage 2 necrotizing enterocolitis, or sepsis. *Results:* The analysis was performed on 380 neonates of 294 mothers. Mean maternal age was 30.5 years (range, 17–52), mean gestational age was 31.5 weeks (range, 24–34), and mean birth weight was 1705.5 g (range, 460–3150). Of the neonates, 90 (23.7%) had major morbidity, which was associated with lower mean gestational age (29.5 weeks vs 32.3 weeks, $P < 0.001$), birth weight (1326.5 vs 1822.2 g, $P < 0.001$), and the need for resuscitation at birth ($P < 0.001$) in comparison with neonates without major morbidity. A comparison of maternal age between the two outcome groups yielded a nonsignificant result. A logistic regression model revealed that maternal age does not contribute significantly to poor neonatal outcomes. *Conclusion:* Advanced maternal age was not associated with major morbidity of preterm neonates at discharge from the neonatal intensive care units.

1. Introduction

Social trends across recent decades have resulted in women delaying their first pregnancies, including to beyond 40 years of age. With the introduction of reproductive technology, women at advanced fertility ages can sustain a pregnancy, even in postmenopausal states. Therefore, increasing numbers of women of advanced age have entered the obstetric population [1] and in many high-income countries trends toward later childbearing have strongly increased [2]. In the USA, between 1990 and 2004, birth rates increased by 43% in women aged 35–39 years, by 62% in women aged 40–44 years, and by more than 150% in women aged older than 45 years. USA national statistics demonstrate that birth rates for women aged 40–44 years have continued to increase steadily by nearly 4% each year since 1981 (3.8 per 1000 deliveries) to a rate of 9.4 per 1000 deliveries in 2007 [3]. In Israel, there were 5902 live deliveries by mothers aged 40–44 years and 548 deliveries by mothers aged older than 45 years during 2010 (in total, 3.87% of the total annual birth rate) [4].

Numerous maternal and fetal complications are known to be associated with older childbearing age, including hypertension, diabetes, cardiovascular disease, fetal malformations and fetal death, preterm labor, multiple gestation, and delivery complications [5,6]. In one recent study, these risks remained high despite adjustments for parity, body mass index, and socioeconomic status [7]. Additionally, it has been well established that advanced maternal age is a significant risk factor in fetal genetic diseases [8].

Although it is important to determine whether older motherhood is linked to child health and development beyond pregnancy and labor, data are conflicting with regard to neonatal outcomes. When controlling for possible confounders, advanced maternal age was not found to be an independent risk factor for perinatal mortality [9]. Nevertheless, higher rates of preterm deliveries and low birth weights are associated with advanced maternal age; this is primarily related to multiple gestations [10]. However, no overall increased risk was found for the composite outcome of death or neurodevelopmental impairment at 2 years of age among extremely low birth-weight infants born to mothers aged older than 39 years when compared with infants of younger mothers [6].

Research has demonstrated that women of advanced maternal age were significantly more likely to be better educated, have higher incomes, be employed, and to continue working until the end of pregnancy when compared with younger pregnant women [11]. In addition,

* Corresponding author at: Department of Neonatology, Hadassah Medical Center – Ein Kerem, P.O. Box 12000, Jerusalem 91120, Israel. Tel.: +972 50 85737353; fax: +972 2 6779085.
E-mail address: smadaref@hadassah.org.il (S. Eventov-Friedman).
[1] The first and second authors contributed equally to this study.

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increased maternal age was found to be associated with increased child development and health at a later age [12].

Most of these findings are primarily related to infants born at term, and data are scarce for infants born prematurely and with increased risk for adverse outcomes. Consequently, the aim of the present study was to examine the effect of maternal age on preterm neonate survival without severe morbidity at discharge from the neonatal intensive care unit (NICU). It was hypothesized that advanced maternal age does not affect neonatal outcomes.

2. Material and methods

This retrospective study was performed in the NICUs located at two Hadassah hospital campuses in Jerusalem, Israel: Hadassah Ein Kerem and Hadassah Mt. Scopus; both are tertiary referral centers for the local city population, which is socioeconomically and religiously diverse. The average annual birth rate at these two centers is approximately 11 500.

The present study included preterm neonates delivered at gestational age of younger than 35 weeks and 6 days between January 1, 2009 and December 31, 2010. Maternal age and neonatal gestational age were collected from the hospital computerized database. Gestational age was based on early ultrasound information, obstetric history, and clinical neonatal evaluation, in that order. Gestational age, in weeks and days, was used for the calculation. Maternal pregnancy and delivery, and the neonatal variables were collected from medical records. The exclusion criteria included neonatal death at delivery, chromosomal anomalies, and major congenital anomalies. All data were collected anonymously. The study was a chart review and was approved by the Hadassah Hospital Institutional Review Board, which both campuses are affiliated with. It was determined that no informed consent was needed from the patients owing to the retrospective nature of the study.

The primary outcome was preterm neonates that were discharged from the NICU with no severe morbidity. Severe morbidity included at least one of the following criteria: chronic lung disease, defined as the need for any form of respiratory support (oxygen or positive pressure support) at 36 weeks of corrected gestational age [13]; intraventricular hemorrhage grade 3 and above (unilateral or bilateral), according to the criteria of Papile et al. [14]; periventricular echogenicity or periventricular leukomalacia, detected using ultrasound findings after 3 weeks of age [15]; retinopathy of prematurity stage 3 and above (one or both eyes), according to the international classification [16]; necrotizing enterocolitis stage 2 and higher (pneumatosis intestinalis on abdominal X-ray), defined according to Bell's criteria [17]; and sepsis during hospital stay (early, defined as positive blood cultures at 72 hours of age and younger, and late, defined as positive blood cultures at 3 days of age and older).

Maternal variables included age, number of gestations and parity, method of conception, prenatal care, smoking, use of alcohol or drugs during pregnancy, multiple pregnancy, other chronic diseases, hypertension, pre-eclampsia, diabetes, cervical incompetence, premature uterine contractions, prenatal corticosteroids (partial or complete course), premature rupture of fetal membranes, chorioamnionitis, fetal heart rate anomalies, delivery complications (including placental abruption/previa, cord prolapse, and antibiotic treatment during labor), and method of delivery.

All study variables were examined using descriptive statistics. The study variables were examined for normality to determine whether to use parametric or nonparametric tests to examine the data. To examine associations between poor outcomes and possible risk factors, χ^2 and Fisher exact tests were employed, and Mann–Whitney tests were utilized to compare variables with continuous outcomes. Owing to the hierarchical structure of the data, the necessity of employing a mixed-model logistic regression was investigated (where the mother was considered the random factor). A log-likelihood regression was compared with a logistic regression, demonstrating no significant difference between the two tests. Consequently, the effect of maternal age on poor outcome was examined using a logistic regression.

The statistical analysis was conducted using R, version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 15 (SPSS Inc, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

3. Results

During the study period, 330 mothers delivered 416 preterm neonates at younger than 35 weeks of gestational age. Of these 416, 15 (3.6%) neonates were excluded from the study; 5 died in the delivery room (maternal age range: 18–37 years) and 10 had severe congenital anomalies (including brain anomalies, chromosome 22q11.2 deletion requiring gastrostomy, tetralogy of Fallot requiring surgical repair, trisomy 21, hypoplastic left heart syndrome, and trisomy 18). For the neonates with the major congenital anomalies, maternal age was 20 − 35 years, except for two women who were 39 years of age and delivered neonates with trisomy 21. Consequently, the study population comprised 315 mothers who delivered 401 neonates (Fig. 1). Of the 401 preterm neonates, 21 (5.2%) died after admission to the NICU. Of these 21 neonates, 16 were delivered at less than 27 weeks of gestation. Within 1 week of delivery, 18 neonates died owing to lung immaturity, severe intraventricular hemorrhage, or sepsis. Chronic lung disease or complications of necrotizing enterocolitis resulted in the deaths of three neonates at later ages. The mothers of three of the neonates that died in the NICU were older than 35 years (37, 40, and 41 years). Additionally, two of the mothers of neonates that died in the NICU were younger than 20 years old. The ages of all mothers of neonates who died in the NICU, ranged between 20 and 35 years. These outcomes were not included in the analysis because the primary outcome was based on surviving neonates at discharge.

As shown in Table 1, the mean maternal age at delivery was 30.5 ± 6.8 years (range, 17–52 years). Most mothers (n = 242; 82.3%) conceived naturally and one woman was a surrogate mother. Approximately one-third (n = 100; 34.0%) of individuals delivered vaginally and 194 (66.0%) underwent cesarean delivery.

The mean neonatal birth weight was 1705.5 ± 506.6 g (Table 1). The mean gestational age at delivery was 31.5 ± 2.8 weeks (range, 24–34 weeks). The number of neonatal admission days in the NICU ranged between 1 and 88, with a mean of 30.6 ± 24.4 days. Of the 380 neonates, 203 (53.4%) were male and 26 (6.8%) were small for gestational age (birth weight <10th percentile for age). When analyzing and categorizing the surviving neonates' outcome data according to the study definition of a poor outcome, 19 (5.0%) had chronic lung disease (requiring oxygen or respiratory support at 36 weeks corrected age), 30 (7.9%) had intraventricular hemorrhage grade 3 and above, 11 (2.9%) had periventricular leukomalacia, 69 (18.2%) had early or late sepsis, 22 (5.8%) had retinopathy of prematurity stage 3 and above, and 12 (3.2%) had necrotizing enterocolitis stage 2 or above.

According to these results, 90 of the 380 (23.7%) neonates were defined as having poor outcomes upon discharge from the NICU. Among the 294 mothers, 84 (28.6%) had at least one neonate with a poor outcome. Of the 294, 78 (26.5%) mothers had one neonate with poor outcome, and 6 (2.0%) had at least two infants with poor outcomes when discharged home.

It was of interest to explore the causes of the poor outcomes of the infants and, specifically, to examine the effect of maternal age. Consequently, all maternal variables (presented in the methods section) were examined using χ^2 or Mann–Whitney tests; none were found to be significantly associated with poor infant outcome at discharge. There were two variables that approached statistical significance, cesarean delivery ($P = 0.063$) and multiple pregnancies ($P = 0.078$).

The age of the mothers was also compared between the two outcome groups. A mother with at least one poor-outcome neonate was defined as a "poor-outcome mother." Using a Mann–Whitney test to compare age between the two groups yielded a nonsignificant finding ($P = 0.201$). Surprisingly, mothers with poor-outcome neonates were found to be slightly younger than those with good-outcome neonates.

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