

The impact of advanced maternal age on the outcomes of very low birth weight preterm infants

Kai-Ti Tseng, MD, MSc^a, Chun-Chih Peng, MD^{a,b}, Jui-Hsing Chang, MD^a, Chyong-Hsin Hsu, MD^a, Chia-Ying Lin, MD^a, Wai-Tim Jim, MD, MSc^a, Hung-Yang Chang, MD^{a,b,*}

Abstract

The association between advanced maternal age and neonatal outcomes remains controversial. This study attempted to determine the short-term and long-term outcomes of very low birth weight (VLBW, <1500 g) preterm infants, born to mothers of advanced age (≥ 35 years).

In this retrospective cohort study, VLBW infants were divided into the advanced maternal age group and comparison group. We compared the pregnancy complications, demographic factors, short-term morbidities, and neurodevelopmental outcomes using the Bayley Scales of Infant Development-Third Edition, at 24 months of corrected age between the 2 groups.

The study comprised of 536 VLBW infants born to 483 mothers. Mothers of advanced age had a significantly lower rate of primiparity compared to the comparison group (45.8% vs 65.2%, $P < .001$), and were more likely to have gestational diabetes (13.7% vs 5.5%, $P = .002$) and to undergo in vitro fertilization (IVF; 18.4% vs 9.9%, $P = .01$). No significant differences were found between the 2 groups in terms of short-term outcomes. At 2 years of corrected age, advanced maternal age was associated with a higher incidence of severe speech delay (11.3% vs 5.7%, $P = .04$), neurodevelopmental impairment (NDI; 28.8% vs 18.4%, $P = .02$), and adverse composite outcome (37.4% vs 27.3%, $P = .02$). However, the differences in NDI and composite adverse outcomes were not statistically significant between the groups after adjustments for potential confounders.

Advanced maternal age was not associated with major morbidities and long-term NDI among VLBW preterm infants. The association between advanced maternal age and severe speech delay in the infant needs further investigation.

Abbreviations: aORs = adjusted odds ratios, BPD = bronchopulmonary dysplasia, BSID-III = Bayley Scales of Infant and Toddler Development-III, CCS = cognitive composite score, CIs = confidence intervals, CP = cerebral palsy, cPVL = cystic periventricular leukomalacia, IUGR = intrauterine growth restriction, IVF = in vitro fertilization, IVH = intraventricular hemorrhage, LCS = language composite score, MCS = motor composite score, NDI = neurodevelopmental impairment, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity, VLBW = very low birth weight.

Keywords: advanced maternal age, adverse outcomes, preterm, very low birth weight infants

1. Introduction

There has been a significant increase in the maternal age at childbirth in many developed countries.^[1,2] A recent study reported that 20% of live births occurred in mothers aged 35 years or above.^[3] A similar trend of higher maternal age has also been observed in very low birth weight (VLBW, birth weight <1500 g) preterm infants.^[2] Advanced maternal age considered as 35 years and above at childbirth has long been associated with numerous adverse maternal and perinatal outcomes.^[4–14]

Older women are at increased risks for hypertension, diabetes, cardiovascular diseases, caesarean section, and the need for infertility treatments and assisted reproductive technology.^[4–12] Most studies have demonstrated higher incidences of multiple gestation, preterm birth, intrauterine growth restriction (IUGR), fetal malformations, intensive care unit admission, and neonatal death among infants born to older mothers.^[5–14] Delayed childbearing has long been associated with both congenital and acquired health concerns in the child, including Down syndrome, Alzheimer disease, hypertension, and diabetes.^[15] Most of these findings are primarily seen in infants born at term, and data are scarce for infants born prematurely, who are at higher risk for adverse outcomes.^[16–18] Recent studies have yielded inconsistent conclusions. Some studies have suggested a favorable effect of advanced maternal age on the neonatal mortality and morbidities among preterm infants.^[6,16,17]

Given the rapid increase in the proportion of older motherhood and the limited evidence in literature, it is important to determine whether, and how, advanced maternal age is linked to the preterm infant's health and development beyond the neonatal stage. We hypothesized that advanced maternal age leads to adverse short-term and developmental outcomes among preterm infants. This study attempted to determine the short-term and long-term outcomes in VLBW preterm infants born to mothers with advanced age (≥ 35 years), compared to those born to younger mothers (20–34 years).

Editor: Jing Liu.

The authors have no funding and conflicts of interest to disclose.

^a Department of Neonatology, MacKay Children's Hospital, Taipei, ^b Department of Medicine, MacKay Medical College, New Taipei City, Taiwan.

* Correspondence: Hung-Yang Chang, Department of Neonatology, MacKay Children's Hospital, No 92, Sec 2, Zhongshan N Rd, Taipei City 10449, Taiwan (e-mail: 4583@mmh.org.tw).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:5(e14336)

Received: 6 November 2018 / Received in final form: 7 January 2019 /

Accepted: 9 January 2019

<http://dx.doi.org/10.1097/MD.0000000000014336>

2. Methods

2.1. General

This retrospective cohort study was performed at a single, referral level III neonatal intensive care unit of MacKay Children's Hospital (Taipei, Taiwan). The medical charts of all VLBW infants during the period between August 2010 and November 2014 were retrospectively reviewed. Infants with major congenital anomalies were excluded. All data were obtained from the prospectively collected database of the Taiwan Premature Infant Developmental Collaborative Study Group. The study was approved by MacKay Memorial Hospital's Institutional Review Board (IRB number: 16MMHIS169e), with a waiver for informed consent. However, all patient records/information were anonymized and de-identified prior to analysis.

Infants were divided into the advanced maternal age group (maternal age ≥ 35 years) and comparison group (maternal age 20–34 years), based on the maternal age at childbirth. We collected data regarding the intrapartum and demographic variables. The use of antenatal steroids was defined as any dose of betamethasone administered before delivery. Premature rupture of membranes was defined as membrane rupture more than 18 hours prior to delivery. Clinical chorioamnionitis was diagnosed if the mother had fever, uterine fundal tenderness, and foul odor of the amniotic fluid. Small for gestational age was defined as birth weight less than the 10th percentile for gestational age. Delivery room resuscitation was defined as chest compression with or without administration of medications.

2.2. Short-term outcomes

The short-term outcome variables included respiratory distress syndrome (RDS) requiring surfactant therapy, necrotizing enterocolitis (NEC) at Modified Bell's Stage \geq II, severe intraventricular hemorrhage (IVH, grade III or IV), bronchopulmonary dysplasia (BPD, oxygen use at 28 days of life and at 36 weeks of postmenstrual age), patent ductus arteriosus (PDA) which required treatment, cystic periventricular leukomalacia (cPVL), culture-proven sepsis, retinopathy of prematurity (ROP) which required treatment, and neonatal mortality. Infants were diagnosed with sepsis if they had positive blood cultures for either bacteria or fungus. Neonatal mortality was defined as infant death before hospital discharge.

2.3. Long-term outcomes

Neurologic examinations and developmental outcomes were assessed at the 24th month of corrected age, but the protocol allowed a window of 23 to 25 months. The Bayley Scales of Infant Development, Third Edition (BSID-III) was the only tool used to evaluate developmental outcomes during the study period.^[19] The assessments were performed by a single, trained psychologist. The BSID-III contains 3 individual developmental scores: a cognitive composite score (CCS), a language composite score (LCS) (with receptive and expressive subscores), and a motor composite score (MCS) (with gross and fine motor subscores). Moderate to severe cerebral palsy (CP) was diagnosed when the child had nonprogressive motor impairment, characterized by abnormal muscle tone and abnormal control of movement or posture. Neurodevelopmental impairment (NDI) was defined as the presence of any of the following: CP, hearing loss in both ears requiring amplification, blindness in both eyes, MCS $<$ 85, or CCS $<$ 85. Severe NDI was defined as the presence

of any of the following: CP, hearing loss in both ears requiring amplification, blindness in both eyes, MCS $<$ 70, or CCS $<$ 70. Composite outcomes of NDI and death were compared between the groups.

2.4. Statistical analysis

The crude risks were described as percentages. Unadjusted comparisons between categorical variables were analyzed using the Chi-squared test; continuous data were compared using the independent *t* test. Multivariate analyses were performed using the logistic regression model to estimate the relative risks of advanced maternal age on the long-term neurodevelopmental outcome of the cohort. Sociodemographic characteristics and perinatal conditions, including sex, gestational age, premature rupture of membrane, multiple births, resuscitation, antenatal steroid use, and maternal education, were included in the logistic regression models as potential confounders. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated for all outcomes if applicable. *P*-values were derived from Wald tests. All analyses were performed using Stata 15 (StataCorp, College Station, TX).

3. Results

The study comprised 536 VLBW infants born to 483 mothers, of whom 190 (39.3%) were aged more than 35 years at childbirth, during the 4-year study period (Table 1). Mothers of advanced age had a significantly lower proportion of primiparity compared to the other group (45.8% vs 65.2%, $P < .001$), and were more likely to have gestational diabetes (13.7% vs 5.5%, $P = .002$) and to undergo IVF (18.4% vs 9.9%, $P = .01$).

Table 2 shows the neonatal characteristics and morbidities among the live births, by maternal age groups. More than half of the VLBW preterm infants were born to mothers between the ages of 20 and 35 years (61%). Infants in the 2 groups were comparable on demographic parameters, except for a marginally significant difference in the need for resuscitation between infants born to advanced age mothers and the comparison group (7.2% vs 3.6%, $P = .07$). There were no differences in the neonatal short-term outcomes between the groups, including RDS, pneumothorax, BPD, sepsis, NEC, ROP, PDA, IVH, cPVL, and death. A multivariable logistic regression model, which adjusted for the confounding factors, yielded the same results.

Among all live births, 187 infants from the advanced maternal age group and 296 infants from the comparison group survived to a corrected age of 24 months. However, 27 infants in the advanced age group and 31 infants in the comparison group were lost to follow-up. The overall follow-up rate was 88%. The infants were assessed for neurodevelopment at a mean 24.4 ± 0.5 months of corrected age. Crude risk and relative risk estimates of the outcomes derived from the regression model are shown in Table 3. There were no significant differences between the study groups in nutritional status, BSID-III cognitive or motor scores, incidence of bilateral blindness, hearing loss requiring amplification, and moderate to severe CP. The incidence of NDI and adverse composite outcomes were significantly higher in the advanced maternal age group, compared to the comparison group (28.8% vs 18.4%, $P = .01$; 37.4% vs 27.3%, $P = .02$, respectively). However, the logistic regression analysis showed that after controlling for potential confounding variables, the significance was diminished. The risk of severe speech delay (LCS $<$ 70) was also significantly higher in the advanced maternal

Table 1
Maternal and prenatal characteristics of mothers by maternal age group.

	Maternal age group		P-value
	<35 yrs, n (%)	≥35 yrs, n (%)	
Total number of mothers	483		
Number of mothers	293	190	
College education and higher	188 (64.2%)	122 (64.2%)	.99
In vitro fertilization	29 (9.9%)	35 (18.4%)	.01
Low socioeconomic status	127 (46.5%)	90 (49.5%)	.54
Primiparity	191 (65.2%)	87 (45.8%)	<.001
Antenatal steroid use*	252 (86.0%)	162 (85.3%)	.82
C-section delivery	206 (70.3%)	139 (73.2%)	.50
Multiple gestation	52 (17.7%)	31 (16.3%)	.68
Preeclampsia	61 (20.8%)	49 (25.8%)	.20
Gestational DM	16 (5.5%)	26 (13.7%)	.002
Placental abruption	14 (4.8%)	9 (4.7%)	.99
Placenta previa	14 (4.8%)	11 (5.8%)	.61
Antepartum hemorrhage	64 (21.8%)	45 (23.7%)	.61
Antepartum infection	24 (8.2%)	16 (8.4%)	.91
Chorioamnionitis	9 (3.1%)	9 (4.7%)	.34
PROM	84 (25.7%)	63 (30.1%)	.24
Oligohydramnios	62 (19.0%)	39 (18.7%)	.96
IUGR	55 (16.8%)	29 (13.9%)	.38

C-section = cesarean section; DM = diabetes mellitus; IUGR = intrauterine growth restriction; PROM = premature rupture of membrane.

* Any antenatal steroid use.

Table 2
Neonatal characteristics of very low birth weight infants by maternal age group*.

	Maternal age group		P-value
	<35 yrs, n (%/SD)	≥35 yrs, n (%/SD)	
Total number of infants	536		
Number of infants	327	209	
Gestational age	28.46 (±2.97)	28.67 (±2.95)	.44
Birth weight	1063.74 (±275.12)	1075.14 (±275.88)	.64
Males	168 (51.4%)	98 (46.9%)	.31
Twins/triplets	80 (24.5%)	50 (23.9%)	.89
SGA	109 (33.3%)	72 (34.4%)	.79
Death	31 (9.5%)	22 (10.5%)	.69
Fetal distress	94 (28.7%)	65 (31.1%)	.56
Apgar score at 1 min	6.17 (±1.75)	6.14 (±1.75)	.86
Apgar score at 5 min	7.95 (±1.43)	7.79 (±1.55)	.23
Resuscitation	12 (3.7%)	15 (7.2%)	.07
Transfer from another hospital	44 (13.5%)	25 (12.0%)	.61
Pneumothorax	17 (5.2%)	16 (7.7%)	.25
Early sepsis	3 (0.9%)	0 (0.0%)	.17
Late sepsis	43 (14.2%)	29 (15.0%)	.81
Necrotizing enterocolitis	2 (0.7%)	4 (2.1%)	.16
Severe ROP	16 (5.4%)	7 (3.7%)	.39
Severe PDA†	83 (27.2%)	46 (23.6%)	.37
Surfactant	152 (46.5%)	83 (39.7%)	.12
Oxygen use at 36 wks	125 (41.9%)	81 (43.1%)	.81
Severe IVH	31 (9.5%)	15 (7.2%)	.36
Cystic PVL	23 (7.7%)	9 (4.8%)	.21

IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; SGA = small for gestational age.

* Deaths were excluded from the following variables: late sepsis, necrotizing enterocolitis, severe ROP, PDA need operation, O2 at 36 weeks, severe IVH, cystic PVL.

† Severe PDA: PDA that needs surgical operation.

age group (11.3% vs 5.7%, $P=.04$). This statistical difference remained consistent in the logistic regression analysis (aOR 2.27, 95% confidence interval [CI] 1.09–4.74, $P=.03$). To further investigate the effect of maternal age on severe speech delay in this population, the mothers were stratified into finer age groups: <35, 35–40, and >40 years. There was a trend of speech delay as the maternal age increased; however, no statistical significance was seen for the oldest maternal group (aOR for severe speech delay comparing mothers >40 to <35 years: 2.36, 95% CI 0.61–9.18, $P=.216$).

4. Discussion

Delayed childbearing has been a growing trend over the past decades in many developed countries. In this cohort of VLBW preterm infants, 40% mothers gave birth at an advanced age. This proportion was higher than in a previous report of the general population.^[3] Against our hypothesis, we found that advanced maternal age did not affect any short-term outcomes. Although we found an association between advanced maternal age and severe speech delay, the neurodevelopmental and composite outcomes at 2 years of corrected age were not affected.

Pregnant women at an older age are at a higher risk for a range of complications. There are evidences that preeclampsia, pregnancy-associated hypertension, and caesarean section occurred more frequently in older pregnant women.^[5–11] A recent study reported that fetal exposure to maternal preeclampsia might reduce the risk of BPD in relatively mature VLBW infants.^[20] However, we did not find this association in our cohort. Compatible with results from previous researches in the general neonatal population, our study also found that mothers of VLBW infants who were at an advanced age were also at an increased risk for diabetes, and were more likely to conceive through IVF.^[5,10–12] A systematic review of term babies suggested that maternal diabetes seemed to be negatively associated with the offspring's cognitive development during childhood.^[21] However, a recent large cohort study revealed that VLBW infants born to diabetic mothers did not appear to be at a higher risk of mortality or early morbidity, except for NEC.^[22,23] VLBW infants conceived by IVF also exhibited a similar risk for mortality and morbidity compared to term infants.^[24]

Among the full-term newborns born to mothers with advanced age, the incidences of multiple births, preterm birth, IUGR, congenital malformations, and neonatal death were reported to be higher.^[5–14] Many of the high risks could be explained by multiple pregnancy, preterm birth, or use of assisted conception. However, we did not find these associations in this study. On the contrary, most recent studies suggested that short-term morbidities and mortality of VLBW infants were not affected by advanced maternal age.^[16–18] One study even reported that the odds of survival improved, and the rates of mortality, NEC, and sepsis reduced as the maternal age increased.^[17] Based on evidences from the current and recent studies, advanced maternal age seems to have no significant effect on short-term outcomes in this vulnerable population.

To the best of our knowledge, this was the 1st study to report a correlation between severe speech delay, especially receptive language ability, and advanced maternal age. Speech and language impairments are common in preterm infants.^[25,26] A study by the National Institutes of Child Health and Human Development (NICHD) reported that 20% of extremely low birth weight preterm infants had severe speech delay (composite score <70).^[25] Speech and language development including

Table 3**Nutritional and neurodevelopmental outcomes of the cohort by maternal age group.**

		Unadjusted analysis			Adjusted analysis: odds ratios for advanced maternal age on the long-term outcomes*	
		Maternal age group		P-value	aOR (95% CI)	P-value
		<35 yrs, n (%/SD)	≥35 yrs, n (%/SD)			
Seen in follow-up		265	425			
			160			
Nutritional status	Underweight	111 (42.4%)	62 (39.5%)	.56		
	Stunting	64 (24.4%)	48 (30.6%)	.15		
	Small HC for age	69 (26.3%)	38 (24.2%)	.68		
Cognitive composite score	Mean overall score	93.76 (±11.31)	94.06 (±11.64)	.79		
	CCS < 85	31 (11.7%)	20 (12.5%)	.81	1.10 (0.59–2.06)	.76
	CCS < 70	10 (3.8%)	6 (3.8%)	.99	1.03 (0.35–3.00)	.96
Motor composite score	Mean overall score	88.73 (±12.77)	89.43 (±12.80)	.58		
	MCS < 85	64 (24.2%)	41 (25.6%)	.75	1.15 (0.71–1.86)	.57
	MCS < 70	21 (8.0%)	14 (8.8%)	.77	1.25 (0.60–2.62)	.56
Language composite score	Mean overall score	91.31 (±11.87)	89.91 (±14.67)	.29		
	LCS < 85	61 (23.2%)	45 (28.3%)	.24	1.35 (0.85–2.14)	.20
	LCS < 70	15 (5.7%)	18 (11.3%)	.04	2.27 (1.09–4.74)	.03
Morbidity/Mortality	Cerebral palsy	19 (7.1%)	11 (6.8%)	.91	1.05 (0.47–2.36)	.91
	Blindness	0 (0.0%)	0 (0.0%)	NA	NA	NA
	Hearing impairment	1 (0.4%)	3 (1.9%)	.12	5.64 (0.53–59.87)	.15
	NDI [†]	48 (18.4%)	46 (28.8%)	.01	1.23 (0.77–1.97)	.39
	NDI and deaths [†]	80 (27.3%)	68 (37.4%)	.02	1.26 (0.81–1.95)	.31

aOR=adjusted odds ratio; CCS=cognitive composite score; CI=confidence interval; LCS=language composite score; MCS=motor composite score; NA=not assessable. NDI=neurodevelopmental impairment; SD=standard deviation.

* All long-term outcomes were adjusted for sex, gestational age, premature rupture of membrane, multiple births, resuscitation, steroid use, and maternal education, using logistic regression model.

[†] Neurodevelopmental impairment: individuals with at least one of the followings: CCS or MCS lower than 85, cerebral palsy, hearing impairment.

expressive ability, receptive language processing, articulation, and phonologic memory are complex functions.^[26] Risk factors for preterm infants developing language impairment include low gestational age, IUGR, severe illness, and neonatal morbidities such as brain injury, feeding difficulty, duration of hospitalization, hearing capability, gender, and socioeconomic status.^[26,27] Our result was inconsistent with that of a previous study conducted among term infants, which reported that language development improved with increasing maternal age.^[28] Further research is necessary to investigate the relationship between advanced maternal age and speech delay in VLBW infants.

For long-term outcomes, few data are available regarding the influence of advanced maternal age on subsequent neurodevelopment of the offspring. Few studies on the effects of older motherhood on the health and development beyond birth and the postnatal period of term infants reported mixed results.^[15,28–30] Recent population-based cohort studies suggested that older maternal age might be beneficial for early child development.^[28–30] Contemporary older mothers tend to have a higher socioeconomic status, which might be related to higher education, higher family income, private health insurance, marital status, and are of lower parity than older mothers from earlier times. All these factors provide a more optimal environment and contribute to more favorable outcomes for children.^[6,31] However, our study result suggested that advanced maternal age did not have a significant effect on neurodevelopment and composite outcomes at 2 years of corrected age. The probable reason could be that the causes of impairment in neurodevelopment are multifactorial. Maternal age is definitely one of these factors, but its causal role in long-term impairment is limited.

Our study is limited by its retrospective nature. The data also should be interpreted with caution due to the relatively small

sample size and a single center population, which can lead to random bias. We did not have detailed information on the socioeconomic status, body mass index, placental weight, and behavioral factors such as smoking or alcohol consumption, which are known to be associated with maternal age and perinatal outcomes.^[6,31,32] Recent studies also indicated that not just maternal age, but advanced paternal age, might also affect the long-term health of the child.^[33–36] Additionally, longer follow-up might be needed in these infants since psychiatric disorders, such as poor social skills, schizophrenia, and autistic behaviors, have been linked to older parental age.^[33–36] Furthermore, our study sample was limited to VLBW infants, and the results might not apply to term infants or other populations of preterm infants.

In summary, in a VLBW preterm infant population, advanced maternal age was not associated with short-term morbidity and mortality. Long-term neurodevelopmental and composite outcomes at 2 years corrected age were also not affected by advanced maternal age. We found that maternal age was a risk factor for severe speech delay. However, from our data, we could not determine if older maternal age was the cause for severe speech delay or was merely representative of confounding. With a larger number of patients, the role of numerous confounding factors could be clarified. Future research with larger sample sizes involving multiple centers are necessary to minimize the random bias, and to determine whether the negative association is due to the advanced maternal age itself, or other older pregnancy related morbidities.

Author contributions

Conceptualization: Hung-Yang Chang, Kai-Ti Tseng, Chyong-Hsin Hsu.

Data curation: Chun-Chih Peng, Jui-Hsing Chang, Chyong-Hsin Hsu, Chia-Ying Lin.

Formal analysis: Kai-Ti Tseng, Wai-Tim Jim.

Methodology: Chun-Chih Peng, Jui-Hsing Chang, Chyong-Hsin Hsu, Chia-Ying Lin.

Resources: Hung-Yang Chang.

Validation: Hung-Yang Chang.

Writing – original draft: Hung-Yang Chang, Kai-Ti Tseng.

Writing – review & editing: Hung-Yang Chang, Kai-Ti Tseng, Wai-Tim Jim.

References

- [1] Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2015. *Natl Vital Stat Rep* 2017;66:1–70.
- [2] Su YY, Wang SH, Chou HC, et al. Morbidity and mortality of very low birth weight infants in Taiwan-Changes in 15 years: a population based study. *J Formos Med Assoc* 2016;115:1039–45.
- [3] Office for National Statistics. Frequently asked questions: births & fertility. section 1; UK births-general: 1.5. How many live births were there in specific age groups in 2010? How do these figures compare with 2008 and 2009? 2011 August, 1–31.
- [4] Lisonkova S, Potts J, Muraca GM, et al. Maternal age and severe maternal morbidity: a population-based retrospective cohort study. *PLoS Med* 2017;14:e1002307.
- [5] Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol* 2004;104:727–33.
- [6] Carolan M, Frankowska D. Advanced maternal age and adverse perinatal outcome: a review of the evidence. *Midwifery* 2011;27:793–801.
- [7] Hsieh TT, Liou JD, Hsu JJ, et al. Advanced maternal age and adverse perinatal outcomes in an Asian population. *Eur J Obstet Gynecol Reprod Biol* 2010;148:21–6.
- [8] Kenny LC, Lavender T, McNamee R, et al. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. *PLoS One* 2013;8:e56583.
- [9] Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, et al. Maternal age and risk of labor and delivery complications. *Matern Child Health J* 2015;19:1202–11.
- [10] Khalil A, Syngelaki A, Maiz N, et al. Maternal age and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol* 2013;42:634–43.
- [11] Lamminpää R, Vehviläinen-Julkunen K, Gissler M, et al. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland. *BMC Pregnancy Childbirth* 2012;12:47.
- [12] Fitzpatrick KE, Tuffnell D, Kurinczuk JJ, et al. Pregnancy at very advanced maternal age: a UK population-based cohort study. *BJOG* 2017;124:1097–106.
- [13] Salem Yaniv S, Levy A, Wiznitzer A, et al. A significant linear association exists between advanced maternal age and adverse perinatal outcome. *Arch Gynecol Obstet* 2011;283:755–9.
- [14] Hviid MM, Skovlund CW, Mørch LS, et al. Maternal age and child morbidity: a Danish national cohort study. *PLoS One* 2017;12:e0174770.
- [15] Myrskylä M, Fenelon A. Maternal age and offspring adult health: evidence from the health and retirement study. *Demography* 2012;49:1231–57.
- [16] Vohr BR, Tyson JE, Wright LL, et al. Maternal age, multiple birth, and extremely low birth weight infants. *J Pediatr* 2009;154:498–503.
- [17] Kanungo J, James A, McMillan D, et al. Advanced maternal age and the outcomes of preterm neonates: a social paradox? *Obstet Gynecol* 2011;118:872–7.
- [18] Eventov-Friedman S, Zisk-Rony RY, Nosko S, et al. Maternal age and outcome of preterm infants at discharge from the neonatal intensive care unit. *Int J Gynaecol Obstet* 2016;132:196–9.
- [19] Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment, Inc; 2006.
- [20] Yen TA, Yang HI, Hsieh WS, et al. Preeclampsia and the risk of bronchopulmonary dysplasia in VLBW infants: a population based study. *PLoS One* 2013;8:e75168.
- [21] Adane AA, Mishra GD, Tooth LR. Diabetes in pregnancy and childhood cognitive development: a systematic review. *Pediatrics* 2016;137:e20154234.
- [22] Grandi C, Tapia JL, Cardoso VC. Impact of maternal diabetes mellitus on mortality and morbidity of very low birth weight infants: a multicenter Latin America study. *J Pediatr (Rio J)* 2015;91:234–41.
- [23] Rehan VK, Moddemann D, Casiro OG. Outcome of very-low-birth-weight (<1,500 grams) infants born to mothers with diabetes. *Clin Pediatr (Phila)* 2002;41:481–91.
- [24] Schimmel MS, Hammerman C, Lusky A, et al. Very low-birth-weight-infants conceived by in vitro fertilization are not at higher risk for mortality and morbidity: a population-based study. *Fertil Steril* 2006;85:907–12.
- [25] Vohr BR, Stephens BE, Higgins RD, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr* 2012;161:222–8.
- [26] Vohr BR. Language and hearing outcomes of preterm infants. *Semin Perinatol* 2016;40:510–9.
- [27] Marchman VA, Adams KA, Loi EC, et al. Early language processing efficiency predicts later receptive vocabulary outcomes in children born preterm. *Child Neuropsychol* 2016;22:649–65.
- [28] Sutcliffe AG, Barnes J, Belsky J, et al. The health and development of children born to older mothers in the United Kingdom: observational study using longitudinal cohort data. *BMJ* 2012;345:e5116.
- [29] Barclay K, Myrskylä M. Advanced maternal age and offspring outcomes: reproductive ageing and counterbalancing period trends. *Popul Dev Rev* 2016;42:69–94.
- [30] Kato T, Yorifuji T, Yamakawa M, et al. Association of maternal age with child health: a Japanese longitudinal study. *PLoS One* 2017;12:e0172544.
- [31] Fergusson DM, Woodward LJ. Maternal age and educational and psychosocial outcomes in early adulthood. *J Child Psychol Psych* 1999;40:479–89.
- [32] de Jongh BE, Mackley A, Jain N, et al. Effects of advanced maternal age and race/ethnicity on placental weight and placental weight/birthweight ratio in very low birthweight infants. *Matern Child Health J* 2015;19:1553–8.
- [33] Zammit S, Allebeck P, Dalman C, et al. Paternal age and risk for schizophrenia. *Br J Psychiatry* 2003;183:405–8.
- [34] Croen LA, Najjar DV, Fireman B, et al. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med* 2007;161:334–40.
- [35] Ek M, Wicks S, Svensson AC, et al. Advancing paternal age and schizophrenia: the impact of delayed fatherhood. *Schizophr Bull* 2015;41:708–14.
- [36] Weiser M, Reichenberg A, Werbeloff N, et al. A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry* 2014;71:301–9.