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Impact of advanced maternal age on adverse infant outcomes: A Japanese population-based study

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ABSTRACT

Objective: The number of births among women of higher age has been rapidly increasing in many countries for several decades. While recent epidemiological studies on the impact of maternal age on infant outcomes in developed countries have evaluated the outcomes of singleton infants, few population-based studies have investigated all deliveries including multiple births. Thus, we aimed to assess the impact of maternal age on adverse infant outcomes using data from all birth certificates, including multiple births, in Shiga prefecture, Japan.
Study design: The data from all birth certificates in Shiga Prefecture from 2013 to 2014 (23,294 births from 23,048 mothers) were obtained. We evaluated the impact of maternal age on adverse infant outcomes, including small for gestational age (SGA), low birth weight (LBW), and preterm birth (PTB). A multivariable logistic regression analysis was performed to determine adjusted odds ratios (aORs) for infant outcomes with various maternal factors, including multiple pregnancies. Statistical analysis for trend was performed using the Jonckheere-Terpstra test.
Results: The incidence rates of adverse infant outcomes began to increase at a maternal age of 30 years. A maternal age of ≥35 years was associated with significantly increased risks of adverse infant outcomes, including SGA (adjusted odds ratio [aOR]: 1.15, 95% confidence interval [95% CI]: 1.03–1.29), LBW (aOR: 1.29, 95% CI: 1.16–1.43), and PTB (aOR: 1.17, 95%CI: 1.04–1.33).
Conclusions: The risk of adverse infant outcomes was significantly increased in women older than 35 years of age. These data would be useful for younger women to decide family-planning in advance.

Introduction

Over the past four decades, there has been an increasing trend for women in high-income countries to delay childbearing [1–3]. This trend is due to several changes, including the pursuit-by women-of higher education and career advancement, fertility control through contraception methods, and financial problems [4,5]. There rate of delayed childbearing is remarkably high in Japan, where the average of maternal age at first birth is the 5th highest among OECD countries, after South Korea, Italy, Spain, and Switzerland [6]. While the total number of births in Japan has decreased by approximately 20% over the past 20 years, both the number and proportion of the births from women of advanced maternal age (AMA), defined as ≥35 years of age, have rapidly increased for several decades; there were 118,553 (9.8%) births to women of AMA in 1996 and 278,162 (28.5%) in 2016 [7]. Thus, the evaluation of Japanese data may be useful to study the impact of AMA on perinatal issues.

AMA has been reported to be associated with various adverse perinatal outcomes, including fetal growth restriction, preterm birth (PTB), placental abruption, and preeclampsia [8]. As small for gestational age (SGA) infants, low birth weight (LBW), and PTB, are considered to be associated with a high risk of neonatal mortality and morbidity [9–11], it is important to study the impact of maternal age on infant outcomes. Recent epidemiological studies on the impact of maternal age on infant outcomes have evaluated the outcomes of singleton infants [4,12–14]; however, few population-based studies in developed countries have investigated

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all deliveries, including multiple births. Accounting for approximately 3% of total births in developed countries [15,16], multiple birth is associated with a higher risk of adverse infant outcomes, including PTB, LBW, and SGA, in comparison to singleton birth [17]. Enrolling all deliveries in a target region, including multiple births, is essential for the accurate assessment of the impact of maternal age.

Thus, we studied the impact of maternal age, investigating all birth certificates in one prefecture of Japan, Shiga. In Shiga, there are approximately 13,000 annual births and no specific of obstetric issues. The results of a population-based study in Shiga may represent the general data of Japan, and reflect the problems associated with AMA birth throughout the world.

Materials and methods

Study design

This population-based cross-sectional study was performed in Shiga Prefecture, Japan from 2013 to 2014.

Data collection

There are approximately 13,000 annual births in 30 primary obstetric clinics and 11 hospitals in Shiga Prefecture. Information from all birth certificates in Shiga prefecture between January 2013 and December 2014 was obtained with permission from the Ministry of Health, Labor and Welfare, Japan. We obtained maternal data (maternal age and gestational age [GA] at delivery, parity, and plurality), and infant data (weight and height at birth, and sex).

Infant outcomes

Low birth weight (LBW) was defined as a birth weight of <2500 g. Preterm birth (PTB) was defined as GA < 37 weeks. SGA was defined as birth weight below the 10th percentile of the Japanese neonatal anthropometric chart for GA at birth [18].

Population

This study included 26,524 births during the 2-year study period. We excluded 3230 births from the analyses for the following reasons: birth took place outside of Shiga (n = 3009), insufficient data (n = 190), and GA ≥ 42 weeks (n = 31). Previous studies in Japan only included singleton births [19,20]. In contrast, the present population-based study included both multiple births and singleton births. Thus, a total of 23,294 births from 23,048 mothers were included in the present study.

Statistical analyses

The incidence rates of the abovementioned infant outcomes were estimated by the number of outcomes divided by the total number of births in each age group. The P value for trend was estimated using the Jonckheere-Terpstra test. We also estimated impact of AMA on the incidence of adverse infant outcomes using multivariable logistic regression models, the results of which were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CIs). The multivariable models included maternal age, plurality, and parity as covariates. P values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the IBM SPSS software program, (ver.22 IBM Japan, Tokyo, Japan) (Fig. 1).

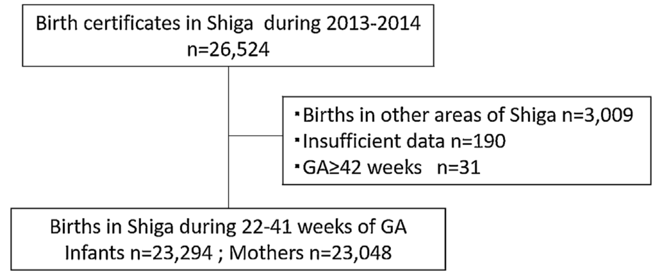

Fig. 1. Outline of this survey GA, gestational age.

Results

Characteristics

The characteristics of the study population are shown in Table 1. Among 23,048 mothers, the average maternal age was 31 years and the average gestational age at delivery was 38 weeks. Five thousand eight hundred eighty-seven (26%) women were classified as AMA (≥35 years of age at delivery). Forty-four percent of the women were primiparous and 1% of the women had multiple pregnancies. Among 23,294 infants, the average birth weight was 2999 g. The incidence rates of PTB (GA < 37 weeks) and LBW (<2500 g) were 6.2% and 9.5%, respectively. There were 503 multiple-birth infants (2.2%) and 1725 (7.4%) SGA infants.

Incidence of adverse infant outcomes according to maternal age

Fig.2 shows the incidence of adverse infant outcomes, including SGA, LBW, and PTB, according to the maternal age. The incidence of these outcomes gradually increased according to the maternal age with a rapid increase from 30 to 35 years. The incidence rates of each outcome in women of 30–34 years of age, 35–39 years of age, and ≥40 years of age, were as follows: SGA, 7.2%, 8.0%, and 9.0%, respectively; LBW, 9.1%, 10.9%, and 13.3%; and PTB, 6.0%, 7.1%, and 8.5%. The P values for trend for SGA, LBW, and PTB were 0.01, <0.001 and <0.001, respectively.

Maternal factors associated with adverse infant outcomes

In comparison to women of <35 years of age, those of ≥35 years of age hernal age. The incidence of these outcomes gradually increased according to the maternal age with a rapid increase from 30 to 35 years. The incidence rates of each outcome in women of 30–34 years of age, 35–39 years of age, and ≥40 years of age, were as follows: SGA, 7.2%, 8.0%, and 9.0%, respectively; LBW, 9.1%, 10.9%,

Table 1
Profile of the perinatal factors analyzed in this study.

Characteristics of this study	n (%)
Mother n = 23,048	
Maternal age at delivery (years)	31.0 ± 0.03
Advanced maternal age (≥ 35years)	5887 [25]
Gestational age at birth (weeks)	38.7 ± 0.01
Parity (Multiparous/Primiparous)	12,859 (56)/10,189 (44)
Plurality (Singleton/Multiple)	22,791 (99)/257 (1)
Infants (n = 23,294)	
Birth weight (g)	2999 ± 432
Gender (male/female)	12,022 (52)/11,272 (48)
Preterm birth (<37 weeks)	1451 (6.2)
Low birth weight infants (<2500 g)	2217 (9.5)
Multiple births	503 (2.2)
Small for gestational age (BW < 10 percentile)	1725 (7.4)

Data represent the mean ± standard deviation or n (%).

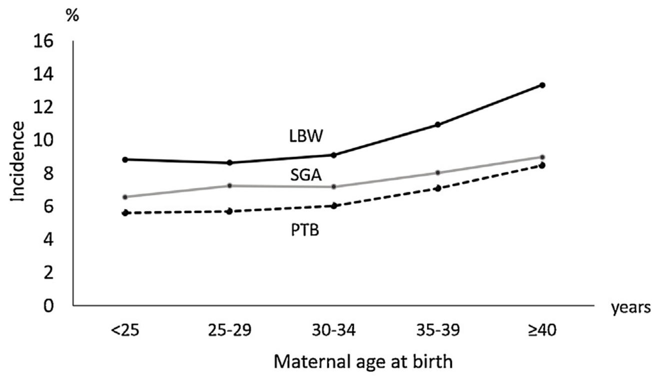

Fig. 2. Incidence of adverse infant outcomes according to maternal age Bold line, incidence of LBW; gray line, SGA; dotted line, PTB;LBW, low birth weight; SGA, small for gestational age; PTB, preterm birth.

and 13.3%; and PTB, 6.0%, 7.1%, and 8.5%. The P values for trend for SGA, LBW, and PTB were 0.01, <0.001 and <0.001, respectively.

Maternal factors associated with adverse infant outcomes

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Maternal factors associated with adverse infant outcomes

In comparison to women of <35 years of age, those of ≥35 years of age had significantly higher risks of adverse infant outcomes, even after adjustment for plurality and parity (SGA: aOR, 1.15; 95% CI, 1.03–1.29; p = 0.013, LBW: aOR, 1.29; 95% CI, 1.16–1.43; p < 0.001, and PTB: aOR, 1.17; 95% CI, 1.04–1.33; p = 0.012) (Table 2).

Comment

Our analysis of all birth certificate data from a two-year period in Shiga Prefecture, Japan revealed that women of AMA had a significantly higher incidence of adverse infant outcomes, including SGA, LBW, and PTB. Additionally, we showed that a maternal age of >30 years was associated with an increased risk of adverse infant outcomes.

First, women of AMA had a significantly higher incidence of adverse neonatal outcomes. The finding that AMA was associated with adverse infant outcomes such as SGA, LBW, and PTB, was consistent with a recent meta-analysis of AMA births in many countries [8]. While previous epidemiological studies in developed countries targeted only singleton infants [4,12–14], we enrolled all deliveries, including multiple births, and evaluated the impact of maternal age by a multivariable logistic regression analysis of maternal factors, including multiple pregnancies. To our knowledge, this is the first current population-based study in a developed country to evaluate the impact of AMA on adverse infant outcomes, including SGA, LBW, and PTB, and include all regional deliveries including multiple births based on birth certificates.

In addition, our finding was also consistent with recent Japanese population-based

studies [19,20], which had limitations with respect to the target population. The study by Ogawa et al. only included data from deliveries in tertiary perinatal centers in Japan and did not include data from non-tertiary centers, such as general hospitals and primary obstetric clinics [19]. As approximately 40% of Japanese deliveries take place in primary obstetric clinics, the study potentially included a target population bias. In contrast, our study covered deliveries in all obstetric institutions in our region, primary obstetric clinics, general hospitals, and tertiary centers in our region. Another recent population-based study by Kyozuka et al. in Japan showed that higher maternal age (≥30 years) at the first childbirth was associated with adverse infant outcomes, including LBW, PTB, and SGA [20]; however, the study population was limited to primiparous women whereas our study included both multiparous and primiparous women. In the present study the combination of primiparous delivery and AMA was not identified as an independent risk factor for adverse infant outcomes (data not shown). Our results indicated that, in comparison to pregnancies in younger women, AMA birth was associated with a high risk of adverse infant outcomes in both multiparous and primiparous women.

Next, our finding that a maternal age of ≥30 years was associated with an increased risk of adverse infant outcomes, including SGA, is consistent with a previous study [20]. Although placental dysfunction is a major cause of fetal growth restriction (FGR), which is used as a proxy for SGA, the relationship between maternal aging and the placental function is not completely understood [21]. Another cause of FGR is the compromised oocyte quality in older women [22]. In addition to compromised genetic quality, some studies using mouse models have indicated that oocyte aging is associated with epigenetic changes [23,24]. One possible explanation for the increased risks of PTB and LBW at higher maternal age is a significant increase in the rate of both

Table 2
Maternal factors associated with adverse infant outcomes.

	Small for gestational age			Low birth weight			Preterm birth		
	n (%)	aOR (95% CI)	*p*	n (%)	aOR (95% CI)	*p*	n (%)	aOR (95% CI)	*p*
Maternal age									
<35	1236 (72)	Reference		1541 (70)	Reference		1014 (70)	Reference	
≥35	489 (28)	1.15 (1.03–1.29)	0.013	676 (30)	1.29 (1.16–1.43)	<0.001	437 (30)	1.17 (1.04–1.33)	0.012
Plurality									
Singleton	1593 (92)	Reference		1851 (84)	Reference		1180 (81)	Reference	
Multiple births	132 (8)	4.62 (3.77–5.68)	<0.001	366 (17)	29.3 (24.0-35.9)	<0.001	271 (19)	21.2 (17.6–25.5)	<0.001
Parity									
Primiparous	813 (47)	1.13 (1.02–1.25)	0.015	1109 (50)	1.30 (1.18–1.42)	<0.001	648 (45)	0.97 (0.87–1.09)	0.654
Multiparous	912 (53)	Reference		1108 (50)	Reference		803 (55)	Reference	

The multivariable logistic regression analysis of maternal factors associated with adverse infant outcomes.
aOR, adjusted odds ratio; CI, confidential interval.

elective and emergency caesarean delivery in women of >30 years of age [12]. As births certificates in Japan do not include data on the mode of delivery, we could not evaluate the association between the rate of caesarean delivery and maternal age.

We have several limitations in this study. First, we were unable to assess maternal perinatal information, such as the method of conception, which could significantly affect infant outcomes because we used data from birth certificates, which contain limited information. Some reports have indicated that conception using assisted reproductive technology (ART) is associated with a higher rate of adverse infant outcomes in comparison to pregnancies achieved without ART [5,19,25]. As older women can be expected to undergo fertility treatment (including ART) more frequently than younger women, the analysis of maternal age in our study possibly includes the influence of fertility treatments. Second, we could not evaluate neonatal medical data, such as the pH of the umbilical cord artery or Apgar score, which have a significant impact on the neurodevelopmental outcomes of infants, because birth certificates lack these data. As almost all Japanese deliveries occur in obstetric clinics or hospitals in which obstetricians/pediatricians/midwives attend and routinely check their Apgar scores, it would be possible to include the Apgar score on birth certificates.

In conclusion, women of advanced maternal age have a significantly higher incidence of adverse infant outcomes, including SGA, LBW, and PTB. Our data would be useful for helping younger women determine the optimal time for child-bearing.

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Author's contribution

SK, TM, and KT conceived the idea for the study. SK, and TF performed the data collection for the original studies. HA and YI performed statistical analyses. SK wrote the first draft. All authors revised the article, and approved the final version.

Declaration of Competing Interest

The authors declare no conflicts of interest in association with the present study.

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