Awareness of paternal age effect disorders among Japanese pregnant women: implications for prenatal genetic counseling for advanced paternal age

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Abstract

The increasing prevalence of advanced paternal age (APA) has mirrored the rise in maternal age. APA is associated with an increased risk of de novo pathogenic single-nucleotide variants, but this topic has been much less frequently discussed than advanced maternal age (AMA). To explore the awareness of pregnant women regarding paternal age effect (PAE) disorders, a self-administered questionnaire survey was conducted for pregnant women at their first prenatal visit before 17 weeks of gestation. A total of 120 valid respondents (95.2%) were included in the analyses. Of these, 63.3% of pregnant women were aware of PAE disorders. This was markedly lower than the 90.8% recognition of maternal age effect (MAE) disorders. One-third of women with awareness of MAE disorders were not aware of PAE disorders. Pregnant women who were parous, older than their male partners, with knowledge of prenatal testing prior to this pregnancy, and with experience of prenatal testing in a prior pregnancy were significantly more aware of PAE disorders than others. Awareness of PAE disorders was not associated with undergoing prenatal testing during the present pregnancy. Our results show that the prevalence of pregnant women's awareness of PAE disorders was lower than that of MAE disorders. The current study served as a preliminary baseline of information about pregnant women's awareness of PAE disorders. With the introduction of non-invasive prenatal testing, which has the potential to identify PAE disorders, these findings will help the development of a framework for comprehensive prenatal genetic counseling for APA pregnancies.

Keywords Genetic counseling · Prenatal diagnosis · Advanced paternal age · Paternal age effect disorders · Non-invasive prenatal screening · Exome sequencing

Introduction

With the increasing trend in the proportion of pregnant women with advanced maternal age (AMA) (Vital Statistics of Japan 2020), more pregnancies are being conceived with men with advanced paternal age (APA), defined as ≥ 40 years old at the time of conception (Toriello and Meck 2008; Brandt et al. 2019). In Japan, the proportion of live births to fathers ≥ 40 years old increased from 7.3% in 1997 to 15.9% in 2019 (Vital Statistics of Japan 2020).

Associations between APA and spontaneous miscarriage (du Fossé et al. 2020) and perinatal or pediatric poor outcomes (Oldereid et al. 2018) have been described. Several reports have indicated that APA is associated with an increased risk of de novo autosomal dominant (AD) pathogenic variants (Kong et al. 2012; Jonsson et al. 2017; Rahbari et al. 2016; Wong et al. 2016). Because of the large number of cell divisions during spermatogenesis, the mutation rate for base substitution is much higher in men than in women and increases with advancing paternal age (Toriello and Meck 2008). Syndromes caused by these de novo AD pathogenic single-nucleotide variants, collectively termed “paternal age effect” (PAE) disorders, present with a triad of features: bias in paternal origin of mutations, strong paternal age effect, and a high germline mutation rate (Goriely and Wilkie 2012). Examples of PAE disorders involve specific pathogenic single-nucleotide variants in *FGFR2*, *FGFR3*, *HRAS*, *KRAS*, *PTPN11*, and *RET* (Goriely

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and Wilkie 2012; Wilkie and Goriely 2017). The prevalence of PAE in the offspring of father who are ≥ 40 years old attributed to de novo autosomal-dominant pathogenic single-nucleotide variants is estimated to be 0.3 to 0.5% (Brandt et al. 2019; Friedman 1981; Glaser and Jabs 2004), which is equivalent to the maternal age-related risk of trisomy 21 at birth among 35- to 40-year-old mothers (Friedman 1981).

Regarding the reproductive risk associated with AMA, the best documented example of a strong maternal age effect (MAE) has been in fetuses with common autosomal aneuploidy (Nishiyama et al. 2015), which have historically been the focus of prenatal genetic counseling (Brandt et al. 2019). Although, in addition to face-to-face genetic counseling, most of pregnant women receive information from websites and the media, PAE has received little attention in such information sources. Recently, however, prenatal testing options for some PAE conditions have also become available to patients. With advances in sequencing techniques, such as non-invasive prenatal testing (NIPT) using circulating cell-free DNA, some PAE pathogenic single-nucleotide variants could be identified (Brandt et al. 2019). NIPT targeting de novo AD pathogenic single-nucleotide variants, including several PAE pathogenic single-nucleotide variants, is commercially available overseas with need of validation studies (Brandt et al. 2019; Wilkie and Goriely 2017). In addition, in the future, prenatal whole-exome sequencing (WES) is expected to become more feasible and would be a recognized and accepted technology (Brandt et al. 2019).

The characteristics of NIPT targeting de novo AD disorders and prenatal WES are more complicated than those of conventional prenatal testing for MAE disorders. It is required for genetic professionals to provide appropriate genetic counseling to couples prior to such testing in prenatal genetic counseling. While understanding pregnant women's awareness of PAE disorders and their awareness differences from MAE disorders would be useful information in genetic counseling for APA pregnancies, the attitudes and knowledge of pregnant women regarding PAE disorders are poorly studied. In addition, it is suspected that pregnant women's degree of knowledge concerning PAE disorders is influenced by various factors, as described in previous studies for MAE disorders (Al-Jader et al. 2000; Goel et al. 1996; Mavrou et al. 1998; Marteau et al. 1988; Mavrou et al. 1998; Schoonen et al. 2012; Sheinis et al. 2018).

In the present study, we investigated Japanese pregnant women's awareness of PAE disorders and factors that contribute to their awareness.

Methods

Participants

We conducted a prospective observational study to assess awareness regarding PAE disorders among Japanese

pregnant women at the National Center for Child Health and Development (NCCHD) in Tokyo. Pregnant women attending the general outpatient clinic were recruited at their first prenatal visit before 17 weeks of gestation from June 2019 to August 2019.

Recruited participants were asked to complete a self-administered questionnaire that assessed their awareness toward PAE disorders and the associations of this awareness with their attitudes, knowledge, and experience with prenatal testing, as well as their knowledge and experience concerning MAE disorders, such as trisomy 21. Participants with missing data were excluded from the data analysis.

All participants provided their written informed consent prior to the questionnaire survey. This study protocol was approved by the Institutional Review Board at the NCCHD on May 14, 2019 (project number 2193).

Instrumentation

We developed a self-report survey designed to address the study objectives reported here as well as those reported elsewhere (Nishiyama et al. 2021). The questionnaire consisted of 28 questions focused on experience and attitudes of prenatal testing (10 questions), preferences toward prenatal genetic counseling models (5 questions), knowledge of congenital abnormalities (including PAE and MAE disorders, 5 questions), knowledge and experiences with people with trisomy 21 (4 questions), and demographic data (including the male partner's age and socioeconomic status; 4 questions). These were presented in a multiple-choice format with a range from two to seven potential choices, with women allowed to select one of the choices. All survey questions and response options are available within the [Appendix S1](#). It is common to obtain agreement from the male partner for testing, since the agreement of the male partner is required to perform termination of pregnancy in Japan. In addition to the questionnaire, participants' mental state at their first prenatal visit was assessed using Edinburgh Postpartum Depression Scale (EPDS) as is clinical practice in the NCCHD.

Our primary outcome of interest was pregnant women's awareness of PAE disorders. As questions regarding PAE and MAE disorders, pregnant women were asked the following in questions 18/19: "Do you think disorders associated with an advanced paternal/maternal age exist?" Possible answers were "yes," "no," and "don't know." Answers of "yes" were considered to indicate that participants were aware of PAE/MAE disorders, and the "no" and "don't know" were added together and considered to indicate that participants lacked awareness of PAE disorders. This survey instrument was developed with input from maternal

fetal medicine physicians, medical geneticists, and genetic counselors at the NCCHD.

Data analyses

Maternal age, parity (nulliparous, parous), history of spontaneous abortion (yes, no), method of conception (natural conception, assisted reproductive techniques, other infertility treatment), fetal number (singleton, multiple gestation), gestational age, a history of prenatal testing in this pregnancy, and employment status (full-time, part-time, unemployed) were obtained from the medical records and treated as variables. Regarding EPDS, a positive screen was considered a total EPDS score of ≥ 13 in the present study (Usuda et al. 2017).

We assessed pregnant women's awareness regarding PAE/MAE disorders descriptively. The chi-square test was used to compare maternal demographics between pregnant women with and without awareness of PAE disorders. The influence of pregnant women's attitudes, knowledge, and experience on their awareness concerning PAE disorders were also evaluated by the chi-square test. All descriptive and statistical analyses were performed using the statistical software package, Stata SE 15 (STATA Corp, College Station, TX, USA). Statistical significance was set at ≤ 0.05 , and all statistical tests were two-tailed.

Results

Among 126 pregnant women who visited our hospital for a routine maternal checkup, 6 women with missing data (4, annual household income; 2, planned prenatal testing at questionnaire) were excluded. Thus, we conducted our analysis in the remaining 120 women.

The distribution of pregnant women's awareness toward APA/AMA risks is shown in Table 1. The proportion of pregnant women who were aware of PAE disorders (63.3%) was lower than those who recognized MAE disorders (90.8%). Responses of "don't know" were more frequent for PAE disorders (20.8%) than those for MAE disorders (6.7%). All 76 women who were aware of PAE disorders also were aware of MAE disorders. In contrast, among pregnant women with awareness of MAE disorders, 30.3% (33/109) lacked awareness of PAE disorders. None of the pregnant women lacking awareness of MAE disorders were aware of PAE disorders.

The demographic characteristics by the presence or absence of awareness of PAE disorders are shown in Table 2. The awareness of PAE disorders significantly differed according to the age difference between partners ($p=0.045$); the proportion of pregnant women who were aware of PAE

Table 1 Participant's awareness of PAE/MAE disorders

PAE disorders	MAE disorders			Total
	Aware (%)	Unaware (%)	Don't know (%)	
Aware (%)	76 (100.0)	0 (0.0)	0 (0.0)	76 (63.3)
Unaware (%)	16 (84.2)	3 (15.8)	0 (0.0)	19 (15.8)
Don't know (%)	17 (68.0)	0 (0.0)	8 (32.0)	25 (20.8)
Total	109 (90.8)	3 (2.5)	8 (6.7)	120 (100.0)

MAE maternal age effect, PAE paternal age effect

disorders was highest among the women who were older than their male partners (78.9%) followed by those who were younger than their male partners (57.8%) or where there were no age differences (50.0%). Parous pregnant women were more likely to be aware of PAE disorders ($p=0.045$). The awareness of PAE disorders did not significantly differ by other demographics.

Pregnant women's awareness of PAE disorders by their attitudes, knowledge, and experiences of prenatal testing and MAE disorders, including trisomy 21, are shown in Table 3. Pregnant women who were aware of prenatal testing before they became pregnant this time and who had undergone prenatal testing in a prior pregnancy were more likely to be aware than others ($p=0.041$ and 0.026 , respectively). Awareness of PAE disorders was not associated with undergoing prenatal testing in this pregnancy ($p=0.585$) as well as other attitudes, preferences, knowledge, and experiences.

Discussion

In this study population, while 63.3% pregnant women were aware of PAE disorders, one-third with awareness of MAE disorders lacked awareness of PAE disorders. Pregnant women who were parous, older than their male partners, with knowledge of prenatal testing prior to this pregnancy, and with experience of prenatal testing in a prior pregnancy were more likely to have awareness regarding PAE disorders than others. No significant association was observed between pregnant women aware of PAE disorders and undergoing prenatal testing in this pregnancy. To our knowledge, this is the first study on pregnant women's awareness of PAE disorders.

Our findings showed that the prevalence of pregnant women's awareness of PAE disorders was lower than that of MAE disorders. This may be due to relatively little exposure to information about PAE disorders, as the reproductive risks associated with maternal age have largely been the focus in clinical practice (Brandt et al. 2019; Phillips et al. 2019). Thus, educational intervention among pregnant

Table 2 Demographic characteristics of the study participants with an awareness of PAE disorders ($n = 120$)

	$n = 120$	With an awareness of PAE disorders		p -value
	Number (%)	Yes ($n = 76$) Number (%)	No ($n = 44$) Number (%)	
Gestational age at questionnaire (weeks)				0.877
< 10	48 (40.0)	30 (62.5)	18 (37.5)	
≥ 10	72 (60.0)	46 (63.9)	26 (36.1)	
Age at questionnaire (years)				0.156
< 35	47 (39.2)	26 (55.3)	21 (44.7)	
35–39	46 (38.3)	34 (73.9)	12 (26.1)	
≥ 40	27 (22.5)	46 (59.3)	11 (40.7)	
Age of male partner at the time questionnaire was completed (years)				0.410
< 35	40 (33.3)	25 (62.5)	15 (37.5)	
35–39	41 (34.2)	29 (70.7)	12 (29.3)	
≥ 40	39 (32.5)	22 (56.4)	17 (43.6)	
Age difference between partners				0.045
Pregnant women > male partners	38 (31.7)	30 (78.9)	8 (21.1)	
Male partners > pregnant women	64 (53.3)	37 (57.8)	27 (42.1)	
No age difference	18 (15.0)	9 (50.0)	9 (50.0)	
Parity				0.045
Nulliparous	82 (68.3)	47 (57.3)	35 (42.7)	
Parous	38 (31.7)	29 (76.3)	9 (23.7)	
History of spontaneous abortion				0.306
Yes	31 (25.8)	22 (71.0)	9 (29.0)	
No	89 (74.2)	54 (60.7)	35 (39.3)	
Method of conception				0.381
Natural conception	61 (50.8)	42 (68.9)	19 (31.1)	
Assisted reproductive techniques	40 (33.3)	24 (60.0)	16 (40.0)	
Other infertility treatment	19 (15.8)	10 (52.6)	9 (47.4)	
Fetal number				0.769 (Fisher's exact)
Singleton	106 (88.3)	68 (64.2)	38 (35.8)	
Multiple	14 (11.7)	8 (57.1)	6 (42.9)	
Education				0.839
Middle school	1 (0.8)	1 (100.0)	0 (0.0)	
High school	8 (6.7)	4 (50.0)	4 (50.0)	
Junior college	24 (20.0)	16 (66.7)	8 (33.3)	
University	80 (66.7)	51 (63.8)	29 (36.2)	
Post-graduate	7 (5.8)	4 (57.1)	3 (42.9)	
Annual household income ($\times 10,000$ yen)				0.810
< 500	15 (12.5)	8 (53.3)	7 (46.7)	
500–699	22 (18.3)	13 (59.1)	9 (40.9)	
700–999	33 (27.5)	21 (63.6)	12 (36.3)	
1000–1499	31 (25.8)	22 (71.0)	9 (29.0)	
≥ 1500	19 (15.8)	12 (63.2)	7 (36.8)	
Employment				0.608
Full-time employment	76 (63.3)	49 (64.5)	27 (35.5)	
Part-time	12 (10.0)	8 (66.7)	4 (33.3)	
Unemployed	30 (25.0)	17 (56.7)	13 (43.3)	
Others	2 (1.7)	2 (100.0)	0 (0.0)	
EPDS				0.651 (Fisher's exact)
< 13	115 (95.8)	72 (62.6)	43 (37.4)	
≥ 13	5 (4.2)	4 (80.0)	1 (20.0)	

EPDS Edinburgh Postnatal Depression Scale, MAE maternal age effect, PAE paternal age effect

Table 3 Influence of the participants' attitudes, preferences, knowledge, and experience on their awareness of PAE disorders

Variables	Number (%)	With an awareness of PAE disorders		<i>p</i> -value
		Yes Number (%)	No Number (%)	
Attitudes				
Planned prenatal testing at questionnaire				0.334
No testing	35 (29.2)	19 (54.3)	16 (45.7)	
Undecided	35 (29.2)	22 (62.9)	13 (37.1)	
Had or will have testing	50 (41.2)	35 (70.0)	15 (30.0)	
Need for agreement from the male partner for prenatal testing				0.481
Yes	94 (78.3)	58 (61.7)	36 (38.3)	
No or neither or don't know	26 (21.7)	18 (69.2)	8 (30.8)	
Want to have GC with a male partner				0.452
Yes	107 (89.2)	69 (64.5)	38 (35.3)	
No	13 (10.8)	7 (53.9)	6 (46.1)	
Preferences				
Want to be provided with a brochure about prenatal testing at the hospital				0.348
Yes	80 (66.7)	53 (66.3)	27 (33.7)	
No or neither or don't know or no response	40 (33.3)	23 (57.5)	17 (42.5)	
Type of information materials ^a				0.098
Brochures	62 (77.5)	44 (71.0)	18 (29.0)	
Other materials ^b or don't know	18 (22.5)	9 (50.0)	9 (50.0)	
GC models				0.394
In-person (face to face)	96 (80.0)	59 (61.5)	37 (38.5)	
Other models ^c or don't know	24 (20.0)	17 (70.8)	7 (29.2)	
Knowledge				
Aware of prenatal testing before this pregnancy				0.041
Yes	103 (85.8)	69 (67.0)	34 (33.0)	
No	17 (14.2)	7 (41.2)	10 (58.8)	
Understanding of mechanism of T21				0.426
Not an inherited disease	63 (52.5)	42 (66.7)	21 (33.3)	
Inherited disease or don't know	57 (47.5)	34 (59.7)	23 (40.3)	
Understanding of average of life expectancy of T21				0.789
≥40 years old	51 (42.5)	33 (64.7)	18 (35.3)	
<40 years old or don't know	69 (57.5)	43 (62.3)	26 (37.7)	
Understanding of MAE disorders				<0.001 (Fisher's exact)
Yes	109 (90.8)	76 (69.7)	33 (30.3)	
No	11 (9.2)	0 (0.0)	11 (100.0)	
Experience				
Prenatal testing in a prior pregnancy				0.026
Yes	8 (6.7)	8 (100.0)	0 (0.0)	
No	112 (93.3)	68 (60.7)	44 (39.3)	
Underwent prenatal testing in this pregnancy				0.585
Yes	53 (44.2)	35 (66.0)	18 (34.0)	
None	67 (55.8)	41 (61.2)	26 (38.8)	
Had someone in their vicinity with T21 or talked with people of T21				0.432
Yes	41 (34.2)	24 (58.5)	17 (41.5)	
No	79 (65.8)	52 (65.8)	27 (34.2)	

MAE maternal age effect, PAE paternal age effect, GC genetic counseling, T21 trisomy 21

^aOnly participants who preferred to be provided with a brochure about prenatal testing at the hospital responded to this question (*n* = 80)^bIncludes videos (*n* = 6), smartphone app (*n* = 6), others (*n* = 2)^cIncludes classroom (*n* = 11), group (*n* = 4), telegenetics (*n* = 4)

women regarding PAE disorders during prenatal genetic counseling to raise awareness of PAE should be considered. In addition to pregnant women, their male partners should be educated as well. Although we did not assess their male partners' awareness regarding PAE disorders, it is reported that many men have inadequate awareness regarding the effect of their age on the reproductive process (Phillips et al. 2019).

While multiparity and age difference between partners correlated with knowledge of PAE disorders, other sociodemographic factors showed no such correlation. In particular, we failed to detect a significant association between socioeconomic status (SES) and knowledge about PAE disorders. Several studies from other countries have shown that women's adequate knowledge about prenatal testing for MAE disorders was significantly higher among women with a higher SES than among those with a lower SES (Al-Jader et al. 2000; Dahl et al. 2011; Goel et al. 1996; Lewis et al. 2016; Mavrou et al. 1998; Rostant et al. 2003; Schoonen et al. 2012; Suriadi et al. 2004). In Japan, there are few studies examining the association between SES and prenatal testing. Studies assessing public attitudes and the level of genomic literacy in Japan have reported that people with a higher annual income and school education have a significantly higher genomic literacy level than others (Ishiyama et al. 2008; Nakamura et al. 2017). The reason for the lack of an association between awareness regarding PAE disorders and the SES may be due to little general interest in PAE disorders compared to MAE disorders. Even among professional societies, little attention has been paid to the issue of APA pregnancies, despite their recently increasing numbers (Brandt et al. 2019; Toriello and Meck 2008; Quirin et al. 2020).

The current study suggested that women's interest in prenatal testing is associated with their awareness of PAE disorders. Being aware of the option to undergo prenatal testing before this pregnancy was significantly correlated with awareness regarding PAE disorders. The overall knowledge about conventional prenatal screening was increased among pregnant women who reported that they had heard of such testing (Goel et al. 1996). Therefore, pregnant women who were proactive in gathering information about prenatal testing for MAE disorders may have greater awareness of PAE disorders than other women.

Interestingly, while a history of undergoing prenatal testing in a prior pregnancy was significantly correlated with awareness regarding PAE disorders, undergoing prenatal testing in the present pregnancy was not significantly related. The discrepancy is speculated to be because knowledge of PAE disorders was not an influential factor affecting pregnant women's decision concerning prenatal testing in the current pregnancy. No studies have examined the association between knowledge about PAE disorders and the current use of prenatal testing options. A previous study

assessing pregnant women's knowledge about trisomy 21 and their decision to accept or decline prenatal testing found that knowledge was not a factor influencing their decision (Ternby et al. 2016). Based on our study, we are unable to answer whether or not knowledge of PAE disorders would affect the decision to undergo prenatal testing, as that would require an interventional study.

Although there are no recommended screening or diagnostic panels that target PAE disorders (American College of Obstetricians and Gynecologists 2016), with the recent rapid development of genetic testing technology, NIPT targeting single-nucleotide variants and prenatal WES in material obtained by chorionic villus sampling or amniocentesis combined with first and second trimester ultrasound examinations have the potential to screen for or identify many pathogenic PAE single-nucleotide variants. Knowledge is a prerequisite for making informed decisions about undergoing any prenatal testing (Marteau et al. 1988). Therefore, increasing pregnant women's knowledge about PAE disorders is expected to affect their decisions concerning prenatal testing. In addition to NIPT, ultrasound examinations would be applicable in screening for PAE disorders.

We acknowledged several limitations in association with our study. First, our study was conducted in a population of a fairly high SES. Despite the lack of readily accessible sources of information about PAE disorders, 63.3% of women are aware of PAE disorders. The most likely explanation is that the study participants had a relatively high educational level, 73.3% were employed, and 70% had a total income of > 7 million yen per year. Thus, further population-based studies should be conducted to confirm whether or not our results are replicable and thus generalizable. Second, this study depended on participant's self-assessed knowledge concerning PAE disorders, with possible answers of "yes," "no," and "don't know." Thus, the details of their understanding and their confidence with respect to the answers were not assessed in this study. To improve their understanding of PAE disorders, further studies including multiple questions, such as how subjects gained their awareness and what exactly they know about these entities, are needed. Furthermore, our study was not designed to explore the understanding of PAE disorders among male partners. Further studies are therefore needed to clarify the gap in awareness about PAE disorders between partners and the influence of any differences between them.

We reported that the prevalence of pregnant women's awareness of PAE disorders was lower than that of MAE disorders among Japanese women. With the introduction of NIPT, which has the potential to identify PAE disorders, these findings will develop a framework for performing comprehensive prenatal genetic counseling for APA

pregnancies, along with further large-scale studies on pregnant women, their male partners, and genetic counseling providers.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12687-021-00555-y>.

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Author contribution MN substantially contributed to the conception and design of this study, data collection and analysis, and drafting of this work and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KO substantially contributed to the conception and design of this study, data analysis, and interpretation of the data for the work and helped revise the work critically for important intellectual content. FH, AS, RA, and SW substantially contributed to the conception and design of this study. HS substantially contributed to the interpretation of the data for the work, aided in revising the work critically for important intellectual content, and provided final approval of the version to be published.

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

Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study. This article does not contain any studies with human or animal subjects performed by the any of the authors. This study was approved by Institutional Review Board at the NCCHD on May 14, 2019 (project number 2193).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publication Not applicable.

Conflict of interest The authors declare no competing interests.

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