

Study of Relationship Between Mode of Conception and Non-Specific Psychological Distress in Women Undergoing Noninvasive Prenatal Testing

Nobuhiro Suzumori ^{1*}, Eri Takeda ¹, Takeshi Ebara ², Kyoko Kumagai ¹, Yuki Sawada ¹, Mayumi Sugiura-Ogasawara ¹

1- Department of Obstetrics and Gynecology, Nagoya City University Hospital, Nagoya, Japan

2- Department of Occupational and Environmental Health, Nagoya City University Hospital, Nagoya, Japan

Abstract

Background: Noninvasive prenatal testing (NIPT) has been performed worldwide to detect common fetal chromosomal aneuploidies.

Methods: Pregnant women (n=3743) with advanced maternal age who visited Nagoya University for NIPT were enrolled in this study. The K6 mental stress scores, that is non-specific psychological distress scores were obtained by questionnaires which were administered pre-NIPT and postpartum. High K6 scores (≥ 10) indicate anxiety or depression. The K6 stress scores at pre-NIPT and postpartum were evaluated about the relationship between mode of conception and non-specific psychological distress using binomial logistic regression.

Results: In general, 7.5% of pre-NIPT women (179/2393) and 5.1% of postpartum women (121/n) were found with high K6 scores. They also did not differ significantly based on maternal age, previous live birth, previous miscarriage, and mode of conception, *i.e.*, natural conception, artificial insemination with husband (AIH), or assisted reproductive technology (ART). Moreover, the prenatal K6 scores were not significantly higher than those at postpartum.

Conclusion: Our present data suggest that mental distress in women undergoing NIPT during pregnancy and after birth has no statistical relationship with maternal age, previous live birth, previous miscarriage, or infertility treatment, and continuous mental care may help reduce mental distress in the postpartum period.

Keywords: ART, Depression, Infertility, NIPT, Prenatal diagnosis.

To cite this article: Suzumori N, Takeda E, Ebara T, Kumagai K, Sawada Y, Sugiura-Ogasawara M. Study of Relationship Between Mode of Conception and Non-Specific Psychological Distress in Women Undergoing Noninvasive Prenatal Testing. *J Reprod Infertil.* 2020;21(3):189-193.

* Corresponding Author:
Nobuhiro Suzumori,
Department of Obstetrics
and Gynecology, Nagoya
City University Graduate
School of Medical Sciences,
Nagoya, Japan
E-mail: og.n.suz@med.
nagoya-cu.ac.jp

Received: Sept. 25, 2019

Accepted: Feb. 23, 2020

Introduction

To detect common fetal chromosomal aneuploidies, noninvasive prenatal testing (NIPT) has been performed worldwide so far (1-3). A nationwide NIPT trial in Japan for trisomies 21, 18, and 13 has been conducted by the Japan NIPT consortium since April 2013 (4, 5). The test sensitivity and specificity of NIPT is much higher than those of conventional maternal serum screening for trisomies. Between April 2013 and March 2019, the Japan NIPT consortium has studied more than 50,000 test results in 73 medical institutions approved by the Japanese Association of Medical Sciences as clinical data.

Lately, the number of pregnancies at advanced maternal age using assisted reproductive technology (ART) has been increasing in Japan, and NIPT for fetal anomalies has raised concerns regarding the need for a more sensitive prenatal testing choice (6). In this paper, it was found that pregnant women who underwent NIPT tend to have relatively high scores for depression and anxiety (7), particularly in women (n=697) undergoing ART (8). Because the sample size of women undergoing NIPT was limited in the previous study, an attempt was made to reassess rate of fetal chromosomal abnormalities and the relationship

between maternal age, previous live birth, previous miscarriage, or mode of conception, and non-specific psychological distress by binomial logistic regression model.

Methods

Pregnant women (n=3743) with advanced maternal age who visited our university between June 2014 and December 2017 for NIPT were enrolled in this study. Their blood samples were collected and NIPT analysis was performed by massively parallel sequencing for fetal trisomies 13, 18, and 21 at Kazusa DNA Institute (Chiba, Japan) (6). The women confirmed their responses by questionnaires completed one month postpartum.

The K6 scores, which were considered representative of mental status, show how frequently the respondents experienced symptoms of non-specific psychological distress, which means feeling depressed and anxious (9). According to the Japanese validation study of K6 in the general population, performance of K6 in detecting anxiety disorders by the area under receiver operating characteristic curve (AUC) was excellent with values as high as 0.94 (95% confidence interval=0.88 to 0.99) (7). The self-administered questionnaires were assessed using a five-category scale (4=Always, 3=Often, 2=Sometimes, 1=Seldom, 0=Never), with a score range of 0–24. High K6 scores (≥ 10) indicate anxiety or depression (7, 8). The questionnaires were administered pre-NIPT (At approximately 10–12 weeks of gestation) and postpartum (One month after delivery) in women undergoing NIPT, excluding women with stillbirths.

Invasive prenatal procedures by amniocentesis were performed if the NIPT results were positive for trisomies 13, 18, or 21; all nonreportable results were confirmed by retesting or invasive testing using amniocentesis. The covariables were maternal age, previous live birth, previous miscarriage, and conception mode (*i.e.*, natural conception, artificial insemination with husband (AIH), or ART including in vitro fertilization and embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI)).

The invasive prenatal procedures by amniocentesis were performed, and the characteristics and outcome of women who underwent NIPT, including prenatal, postnatal, and neonatal data were collected at one month postpartum. Statistical significance was determined by binomial logistic regression using IBM SPSS software version 23 (Chicago, IL, USA). Significant difference was

determined at $p \leq 0.05$. This study was approved by the Research Ethics Committee of our University.

Results

In this study, 3743 pregnant women with advanced maternal age, which is usually defined as age 35 or more for the mother at the time of delivery, visited our university for NIPT using massively parallel sequencing for fetal trisomies 13, 18, and 21. Of the 3743 women undergoing NIPT, 2393 women (63.9%), who confirmed their responses with questionnaires completed after fetal birth, were enrolled in this study. The mean age of participants was 38.4 years (Range: 34–47 years).

Table 1 shows the characteristics and pregnancy outcomes. No false negative cases were found in this study. Next, 548 pregnant women (22.9%) underwent ART (IVF-ET and ICSI-ET). Totally, 7.5% of pre-NIPT women (179/2393) and 5.1% of postpartum women (121/2393) were found with high K6 scores (≥ 10) (Table 2). They also did not differ significantly based on maternal age, previous live birth, previous miscarriage, and mode of conception, *i.e.*, natural conception, AIH, or ART. In addition, the prenatal K6 scores were not significantly higher than those at postpartum. Also, fetal trisomies 13, 18, or 21 (n=37) confirmed by amniocentesis depended on the maternal age (OR of 1.38 per one year of age) (Table 2).

Discussion

The present study showed that 7.5% and 5.1% of women undergoing NIPT had high K6 score, and it is speculated that some women may have anxiety or depression during the pregnancy and postpartum periods, respectively. The high K6 score was not influenced by AIH or IVF-ET. It was also shown that fetal trisomies depended on maternal age but not the mode of conception.

Our previous study presented that even if women with NIPT did not experience mental distress before NIPT, those who conceived through ART (IVF-ET and ICSI-ET) may experience mental stress during the postpartum period (8). Stanhiser and Steiner reported that couples with infertility struggled in coping with the psychosocial aspects of ART (10). Although no relationship was found between infertility treatment and non-specific psychological distress using binomial logistic regression, information before and after NIPT must be provided to health care professionals for genetic counseling.

Several lines of evidence suggest that the nega-

Table 1. The characteristics and pregnancy outcomes in our study population

		Study population (n=2393)
Maternal age (years)	Mean±SD	38.4±2.5, (34–55)
Partner age (years)	Mean±SD	39.3±4.6, (25–65)
Marriage age (years)	Mean±SD	33.1±4.2, (18–45)
First pregnancy age (years)	Mean±SD	35.9±3.8, (18–55)
Previous live birth, n (%)	0	1266 (52.9)
	1	860 (35.9)
	2	237 (9.9)
	3	26 (1.1)
	≤4	4 (0.17)
Previous miscarriage, n (%)	0	1680 (70.20)
	1	500 (20.89)
	2	151 (6.31)
	≤3	62 (2.6)
Mode of conception, n (%)	Natural conception	1524 (63.7)
	AIH	321 (13.4)
	ART (IVF-ET and ICSI)	548 (22.9)
Maternal body mass index	Mean±SD	21.0±3.0, (14.5–42.0)
Gestational age at test (weeks)	Mean±SD	13.7±1.0, (11.0–16.4)
Trisomy, n (%)	Trisomy 21	26 (1.1)
	Trisomy 18	10 (0.4)
	Trisomy 13	1 (0.04)
Gestational age at delivery (weeks)	Mean±SD	38.8±2.3, (22.0–43.0)
Birth weight (g)	Mean±SD	2973.4±503.5, (390–5400)
Birth height (cm)	Mean±SD	49.0±3.1, (20.0–58.0)
IUFD/stillbirth, n (%)		43 (1.8)

Note: ART: Assisted reproductive technology; AIH: Artificial insemination with husband; IVF-ET: In vitro fertilization and embryo transfer; ICSI: Intracytoplasmic sperm injection; IUFD: Intrauterine fetal death

Table 2. The study of the pre-NIPT, postpartum K6 high and fetal trisomy using binomial logistic regression analysis

	Pre-K6 high (n=179)			Post-K6 high (n=121)			Fetal trisomy (n=37)		
	ORs	95% CI	p-value	ORs	95% CI	p-value	ORs	95% CI	p-value
Maternal age	0.98	0.92-1.04	0.56	0.92	0.85-0.99	0.03	1.38	1.22-1.55	0.0001*
Previous live birth (Yes/No)	1.13	0.91-1.40	0.28	0.94	0.71-1.24	0.67	0.91	0.46-1.80	0.79
	1			1			1		
Previous miscarriage (Yes/No)	0.84	0.66-1.06	0.14	0.96	0.74-1.26	0.77	1.97	0.88-4.41	0.10
	1			1			1		
Natural conception mode									
	1			1			1		
AIH	0.85	0.46-1.58	0.61	0.72	0.37-1.41	0.34	0.79	0.17-3.71	0.76
ART (IVF-ET and ICSI)	0.84	0.47, 1.50	0.55	0.64	0.34-1.21	0.17	1.16	0.27-5.05	0.84

Note: ART: Assisted reproductive technology; AIH: Artificial insemination with husband; IVF-ET: In vitro fertilization and embryo transfer; ICSI: Intracytoplasmic sperm injection

tive predictive value is almost the same between NIPT and conventional serum screening test (2, 3). In this study, no false negative cases were found, so that NIPT was assumed to be appropriate for fetal screening in women with advanced maternal age. Conventional serum screening using ultrasounds is not common in Japan because of the limited number of co-medical professional workers, however, NIPT is useful for fetal chromosomal screening in the country.

The relationship between advanced maternal age and trisomy has been identified for over 50 years and is one of the most important etiological factors associated with any human genetic disorder (11). The risk of trisomy in a conception rises from approximately 2%–3% for women in their 20s to $\geq 30\%$ for women in their 40s. Our present data also suggested that the increased risk of trisomies 13, 18, and 21 was recognized due to advanced maternal age, and the OR was 1.38 per one year of age in pregnant women.

Because NIPT can be performed at its current pace, it will provide comprehensive prenatal information (12). Although it increases patient autonomy and comfort, this revelation of fetal information may also increase patient anxiety or generate undesired outcomes including selective abortion. Our present data suggest that women, regardless of infertility treatment, after undergoing NIPT tend to have psychological distress postpartum. Couples undergoing NIPT must be continuously supported to reduce psychological distress.

NIPT is now increasingly used for screening of sex chromosome aneuploidies, microdeletions, and multiple Mendelian monogenic disorders (13, 14). Genetic counseling to postpartum women including consultations with mental healthcare professionals and psychological support must be offered (15, 16). Additional assessments may also be needed if continuous mental care helps reduce their mental distress while caring for their children.

Conclusion

Pregnant women with advanced maternal age for NIPT were enrolled, and the K6 mental stress scores were administered pre-NIPT and postpartum. High K6 scores (≥ 10) indicate anxiety or depression. In general, 7.5% of pre-NIPT women and 5.1% of postpartum women were found with high K6 scores. They did not differ significantly based on maternal age, previous live birth, previous miscarriage, and mode of conception, *i.e.*,

natural conception, AIH, or ART. Our findings suggest that mental distress in women with NIPT during pregnancy and after birth has no statistical relationship with maternal age, previous live birth, previous miscarriage, or infertility treatment.

Acknowledgement

We would like to thank Drs. Shinobu Goto, Saki Inuzuka, Ayano Ohtani, and the staff of our division at Nagoya City University Hospital.

Conflict of Interest

None of the authors had any personal or financial conflicts of interest.

References

1. Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, Brar H, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015;372(17):1589-97.
2. Bianchi DW, Chiu RWK. Sequencing of circulating cell-free DNA during pregnancy. *N Engl J Med*. 2018;379(5):464-73.
3. Abdalla O, Woods C, de Costa C. A clinical audit of combined first trimester screening and non-invasive prenatal testing offered to pregnant women in a regional Australian hospital. *Aust N Z J Obstet Gynaecol*. 2019;59(1):157-60.
4. Sago H, Sekizawa A, Japan NIPT Consortium. Nationwide demonstration project of next-generation sequencing of cell-free DNA in maternal plasma in Japan: 1-year experience. *Prenat Diagn*. 2015;35(4):331-6.
5. Samura O, Sekizawa A, Suzumori N, Sasaki A, Wada S, Hamanoue H, et al. Current status of noninvasive prenatal testing in Japan. *J Obstet Gynecol Res*. 2017;43(8):1245-55.
6. Suzumori N, Ebara T, Yamada T, Samura O, Yotsumoto J, Nishiyama M, et al. Fetal cell-free DNA fraction in maternal plasma is affected by fetal trisomy. *J Hum Genet*. 2016;61(7):647-52.
7. Suzumori N, Ebara T, Kumagai K, Goto S, Yamada Y, Kamijima M, et al. Non-specific psychological distress in woman undergoing noninvasive prenatal testing because of advanced maternal age. *Prenat Diagn*. 2014;34(11):1055-60.
8. Takeda E, Suzumori N, Ebara T, Yotsumoto J, Kumagai K, Oseto K, et al. Psychological distress in post-partum women after non-invasive prenatal testing (NIPT) in Japan. *J Obstet Gynaecol Res*. 2018;44(1):35-42.
9. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales

- to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med.* 2002;32(6):959-76.
10. Stanhiser J, Steiner AZ. Psychosocial aspects of fertility and assisted reproductive Technology. *Obstet Gynecol Clin North Am.* 2018;45(3):563-74.
 11. Hassold T, Hunt P. Maternal age and chromosomally abnormal pregnancies: what we know and what we wish we knew. *Curr Opin Pediatr.* 2009; 21(6):703-8.
 12. Allyse MA, Sayres LC, Havard M, King JS, Greely HT, Hudgins L, et al. Best ethical practices for clinicians and laboratories in the provision of non-invasive prenatal testing. *Prenat Diagn.* 2013;33 (7):656-61.
 13. Lo KK, Karampetsou E, Boustred C, McKay F, Mason S, Hill M, et al. Limited clinical utility of non-invasive prenatal testing for subchromosomal abnormalities. *Am J Hum Genet.* 2016;98(1):34-44.
 14. Zhang J, Li J, Saucier JB, Feng Y, Jiang Y, Sinson J, et al. Non-invasive prenatal sequencing for multiple Mendelian monogenic disorders using circulating cell-free fetal DNA. *Nat Med.* 2019;25(3): 439-47.
 15. Ghaedrahmati M, Kazemi A, Kheirabadi G, Bahrami M, Ebrahimi A. Examining the relationship between mothers' prenatal mental health and demographic factors with postpartum depression. *J Educ Health Promot.* 2018;7:146.
 16. Massarotti C, Gentile G, Ferreccio C, Scaruffi P, Remorgida V, Anserini P. Impact of infertility and infertility treatments on quality of life and levels of anxiety and depression in women undergoing in vitro fertilization. *Gynecol Endocrinol.* 2019;35(6): 485-9.