ORIGINAL ARTICLE

Factors affecting parental decisions to terminate pregnancy in the presence of chromosome abnormalities: a Japanese multicenter study†

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ABSTRACT

Objective To investigate the rates of termination of pregnancy (TOP) for fetal chromosomal abnormalities and factors related to such parental decision in Japan.

Methods A multicenter retrospective cohort study of chromosomal abnormalities diagnosed before 22 weeks of gestation between April 2008 and March 2015. The pregnancy outcomes and parental decisions were investigated.

Results Among 931 fetuses with chromosome abnormalities, the total TOP rate was 75.1% (699/931). TOP rates were 89.3% (585/655) in autosomal aneuploidies and 40.8% (51/125) in sex chromosome aneuploidies. Trisomy 21 showed the highest TOP rate (93.8% [390/416]) followed by trisomy 18 (84.5% [163/193]) and trisomy 13 (71.9% [23/32]). Indications for karyotyping were related to a parental decision for TOP ($p < 0.01$): in cases of autosomal aneuploidy, with fetal abnormal ultrasound findings as the reference value, diagnoses made following positive results at non-invasive prenatal testing (adjusted odds ratio [OR]: 13.7, 95% confidence interval [CI] 4.07–45.9) and those because of advanced maternal age (adj. OR 2.91, 95% CI 1.15–7.35) were significantly more frequent.

Conclusions In Japan, pregnancies with fetal trisomy 21 are more likely to result in TOP when diagnosed *in utero* than any other chromosome anomaly. The indications for prenatal karyotyping strongly affect the decision to TOP. © 2016 John Wiley & Sons, Ltd.

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INTRODUCTION

Fetal karyotyping allows the prenatal diagnosis of fetal chromosome abnormality prior to delivery. In recent years, the proportion of pregnant women ≥35 years of age in Japan has been increasing against decreasing birth rates, leading to an annual increase in the number of fetal karyotyping cases.[1]

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The most frequent indication for fetal karyotyping in Japan, where prenatal screening policies have not yet been universally adopted, is advanced maternal age (AMA) defined as age ≥35 years at the expected date of delivery, which accounts for over half of indications.[2] While only 2% of pregnant women choose maternal serum screening (MSS)[1] in Japan, positive results on MSS account for 18% of the indications.[2] In April 2013, non-invasive prenatal testing (NIPT) was introduced in Japan as part of a nationwide clinical research for the detection of trisomy 21, trisomy 18 and trisomy 13.[3] The number of pregnant Japanese women who underwent NIPT has been increasing since then, and about 1% of pregnant women have undergone this testing.[3] However, previous studies have suggested that increased detection rates of fetuses with chromosomal abnormalities by NIPT may lead to an increase in rates of termination of pregnancy (TOP).[4–6]

When fetal chromosome abnormalities are diagnosed by karyotyping, parents become concerned with TOP. Parental decisions to continue or terminate a pregnancy affected with a chromosome abnormality are complicated by the influence of various factors. Previous studies have shown that the TOP rates in cases of chromosomal abnormalities vary greatly by country and ethnicity.[7–10] While recent TOP rates and the factors affecting parental decision for TOP are useful information in the genetic counseling of parents of fetuses with chromosome abnormalities, data for the Japanese population are scarce.

We investigated the TOP rates and factors that contribute to parental decisions regarding a pregnancy after a diagnosis of chromosomal abnormalities before 22 weeks of gestation, which is the legal limit for TOP in Japan.

METHODS

We conducted a multicenter retrospective cohort study at 17 hospitals on pregnant women who underwent fetal karyotyping between April 2008 and March 2015. Of these 17 hospitals, 6 were located in Tokyo and 2 in Osaka; the other 9 hospitals were located in the following cities (1 each): Fukuoka, Isehara, Nagasaki, Nagoya, Nishinomiya, Moroyama, Sapporo, Sendai and Yokohama. Pregnant women with fetuses showing chromosome abnormalities on chorionic villi sampling (CVS) or amniocentesis before 22 weeks of gestations were enrolled and reviewed based on the medical records at each institution. Variants that were common polymorphisms of no known significance were excluded. The legal limit of gestational age for TOP is 22 weeks of gestation in Japan. All of the enrolled women were offered genetic counseling provided by genetic specialists before and after testing. This study was approved by the institutional ethics committee of each institution.

The pregnancy outcomes (TOP, fetal death or live birth) and clinical characteristics, including maternal age, parity, method of conception, number of fetuses, type of diagnostic procedure (amniocentesis or CVS), referral indications for fetal karyotyping and fetal karyotype, were all extracted from medical records at each institution. The indications for karyotyping were classified into five groups: fetal abnormal findings by ultrasound, AMA, increased nuchal translucency (NT) and/or positive result of MSS, positive result of NIPT and others. Because prenatal aneuploidy screening policy is not widely accepted in Japan, NT measurement and/or MSS or amniocentesis for AMA are performed at the request of the parents who chose prenatal screening. NIPT for the detection of trisomy 21, trisomy 18 or trisomy 13 was available for pregnant women at high risk for fetal aneuploidy after April 2013 by request at the patient's expense.[3] In contrast, an ultrasound examination was routinely performed in all pregnant women at each prenatal check-up, with the expenses covered by local governments in most cases. Fetal abnormalities at ultrasound examinations were another major indications for fetal karyotyping. In cases with several indications, the primary indication, that is, the one deemed most influential for the decision, for fetal karyotyping was used for the analysis.

We conducted a descriptive analysis of pregnancy outcomes by fetal karyotype. We also conducted a descriptive analysis of the decision for TOP by autosomal aneuploidy or sex chromosome aneuploidy. Univariate and multivariate logistic regression analyses valuated the association between indications for invasive diagnostic genetic testing and the decision for TOP using abnormal fetal findings by ultrasound as reference group. All multivariate analyses were adjusted for maternal age, parity and method of conception. Statistical analyses were separately performed for autosomal and sex chromosomal aneuploidies. All descriptive and statistical analyses were performed using the STATA version 13 software program (STATA Corp, College Station, TX, USA).

RESULTS

During the 7-year study period, 12,395 pregnant women underwent fetal karyotyping that included 640 (5.2%) cases of CVS and 11,755 (94.8%) cases of amniocentesis before 22 weeks of gestation (Figure 1). Among 978 fetuses (7.9%) diagnosed with chromosome abnormalities, 47 with no pregnancy outcomes were excluded, leaving 931 cases (95.2%) for the analysis.

Table 1 shows the demographics of the pregnant women with a fetal chromosome abnormality. Approximately 75% of these women were ≥35 years old, and over 80% of cases of fetal chromosome abnormalities were diagnosed by amniocentesis. The most frequent indication was increased NT and/or a positive result on MSS (28.8%) and abnormal fetal findings on

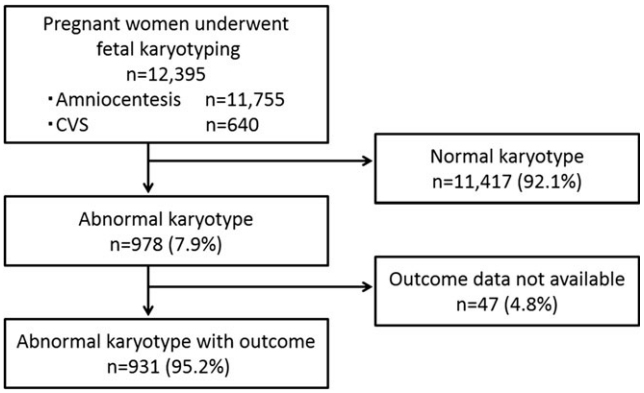

Figure 1 Study subjects between April 2008 and March 2015 in Japan. Among 12,395 pregnant women who underwent fetal karyotyping, 931 with fetuses with abnormal karyotypes were enrolled in the present study

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Table 1 Characteristics of pregnant women with a fetal chromosome abnormality

	Number	% of all ($n=931$)
Maternal age, years[a]		
<30	85	9.1%
30–34	143	15.4%
35–39	359	38.6%
≥40	344	36.9%
Having children		
Yes	448	48.1%
No	431	46.3%
Unknown	52	5.6%
Method of conception		
Natural conception	739	79.4%
Assisted reproductive techniques	127	13.6%
Other infertility treatment	47	5.1%
Unknown	18	1.9%
Fetal number		
Singleton	918	98.6%
Twins	13	1.4%
Diagnostic test		
Amniocentesis	786	84.4%
CVS	145	15.6%
Indication for karyotype		
Increased NT and/or positive results on MSS	268	28.8%
Abnormal fetal findings on ultrasound	268	28.8%
Positive result on NIPT	168	18.0%
AMA	158	17.0%
Others[b]	69	7.4%

AMA, advanced maternal age; CVS, chorionic villus sampling; MSS, maternal serum screening; NIPT, non-invasive prenatal testing; NT, nuchal translucency.
[a]Maternal age at the expected date of delivery.
[b]Including carrier of structural chromosome abnormality (39 cases), history of a prior pregnancy with aneuploidy (13 cases), parental anxiety (7 cases), family history of single-gene disorders (8 cases) and history of a prior pregnancy with structural abnormality (2 cases).

ultrasound (28.8%) followed by a positive result on NIPT (18.0%) and AMA (17.0%). Abnormal fetal findings on ultrasound included cystic hygroma, hydrops, cardiac defect, omphalocele, musculoskeletal abnormality, brain abnormality, fetal growth restriction, urogenital abnormality, oligohydramnios, polyhydramnios, facial abnormality and diaphragmatic hernia, in order of frequency. Approximately 80% of pregnancies were achieved by natural conception. Almost half of these women had at least one child already.

The overall distributions of all fetal chromosomal abnormalities and pregnancy outcomes are shown in Table 2. About 70% of the cases were autosomal aneuploidies, including trisomy 21 (44.7%), trisomy 18 (20.7%) and trisomy 13 (3.4%). The TOP rate was 89.3% for autosomal aneuploidy. The highest TOP rate among the autosomal aneuploidies was for trisomy 21 (93.8%), followed by trisomy 18 (84.5%) and trisomy 13 (71.9%). The fetal death and live birth rates for autosomal aneuploidies were 7.3% and 3.4%, respectively. The highest live birth rate among autosomal aneuploidies was for trisomy 13 (9.4%), followed by trisomy 18 (3.6%) and trisomy 21 (2.6%). A univariate analysis showed that trisomy 21 was associated with higher TOP rates than other autosomal aneuploidies ($p<0.01$).

Over half of sex chromosomal aneuploidies were 45,X. For sex chromosomal aneuploidies, the TOP and live birth rates were the same (40.8%). The highest TOP rate among sex chromosomal aneuploidies was for 45,X (47.9%) followed by 47, XYY (42.9%).

Parental decisions for TOP by clinical characteristics are shown in Table 3. The TOP rates varied significantly by indications for karyotyping ($p<0.01$). There were no significant associations among other variables. In cases of autosomal aneuploidies, significantly higher rates of TOP were found for positive results on NIPT (97.6%), AMA (92.9%) and increased NT and/or positive results on MSS (90.0%) ($p<0.01$).

The crude and adjusted odds ratio (aOR) for TOP among indications for karyotyping are shown in Table 4. Regarding the association between indications for karyotyping and decision for TOP of autosomal aneuploidy, with fetal abnormal findings by ultrasound as the reference value, the aOR of positive results on NIPT was 13.7 (95% confidence interval [CI] 4.07–45.9, $p<0.01$), that of AMA was 2.91 (95% CI 1.15–7.35, $p<0.01$) and that of increased NT and/or positive results on MSS was 2.45 (95% CI 1.33–4.50, $p=0.02$). In contrast, regarding the association between indications for karyotyping and decision for TOP of sex chromosome aneuploidy, the aOR of AMA was 0.31 (95% CI 0.09–1.04, $p=0.06$), and that of increased NT and/or positive results on MSS was 0.37 (95% CI 0.14–0.97, $p=0.04$).

DISCUSSION

We presented an analysis of the parental decisions after a prenatal diagnosis of chromosome abnormalities before 22 weeks of gestation in Japan. In our study population, the TOP rate in cases of autosomal aneuploidy was 89.3%, which was consistent with previously published reports in the United States[7,10] and the Netherlands.[11] When compared with the ethnic groups in the United States,[7,10] the TOP rate in the Japanese population in this study was comparable to those of Caucasians and Asians, but higher than those of Hispanics and Filipinos. Such differences may reflect religious and personal preferences in the study populations. The TOP rate for trisomy 21 (93.8%) in the current study was similar to that in other recent population-based or multicenter studies in Australia, China, England and Wales, and Netherlands (92%–94%),[12–15] although it was higher than that in the population-based studies reported from Canada and the United States (67%).[16,17] Among cases of prenatally diagnosed trisomy 21 before 22 weeks of gestation, the live birth rate was only 2.6%. This finding suggests that fetuses with trisomy 21 mostly result in TOP when diagnosed *in utero* during the period in which TOP is allowed.

There are few population-based or multicenter studies examining the TOP rates of trisomy 13 and trisomy 18 in the same study population as trisomy 21. A network of population-based registries in Europe reported that TOP was

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Table 2 **Pregnancy outcomes of fetal chromosome abnormality diagnosed before 22 weeks of gestation**

		TOP		Fetal deaths		Live births	
Chromosome abnormality	Number	*n*	%	*n*	%	*n*	%
Autosomal aneuploidy	655	585	89.3%	48	7.3%	22	3.4%
Trisomy 21[a]	416	390	93.8%	15	3.6%	11	2.6%
Trisomy 18[b]	193	163	84.5%	23	11.9%	7	3.6%
Trisomy 13[c]	32	23	71.9%	6	18.7%	3	9.4%
Other trisomy[d]	14	9	64.3%	4	28.6%	1	7.1%
Sex chromosome aneuploidy	125	51	40.8%	23	18.4%	51	40.8%
45,X[e]	73	35	47.9%	21	28.8%	17	23.3%
47,XXY[f]	23	9	39.1%	0	0.0%	14	60.9%
47,XXX[g]	14	1	7.1%	1	7.1%	12	85.7%
47,XYY	7	3	42.9%	0	0.0%	4	57.1%
Other sex chromosome aneuploidy[h]	8	3	37.5%	1	12.5%	4	50.0%
Unbalanced structural rearrangement	74	53	71.6%	4	5.4%	17	23.0%
Balanced structural rearrangement	66	2[i]	3.0%	0	0.0%	64	97.0%
Others[j]	11	8	72.7%	1	9.1%	2	18.2%
Total	931	699	75.1%	76	8.1%	156	14.8%

TOP, termination of the pregnancy.
[a]Includes 4 cases with variant, 3 cases of Robertsonian trisomy 21, 5 cases with balanced structural rearrangement and 1 case of mosaicism.
[b]Includes 2 cases with variant and 2 cases of mosaicism.
[c]Includes 2 cases of mosaicism and 1 case of Robertsonian trisomy 13.
[d]Includes 3 cases of trisomy 9, 2 cases of trisomy 22, 2 cases of mosaicism of trisomy 22, 5 cases of mosaicism of other trisomy and 2 cases of mosaicism of trisomy and double trisomy. Nine cases were diagnosed by amniocentesis, and other 5 cases were diagnosed by CVS.
[e]Includes 16 cases of mosaicism.
[f]Includes 1 case of mosaicism.
[g]Includes 1 case of mosaicism.
[h]Includes 3 cases of XX/XY, 2 cases of XXYY, 2 cases of 45,X/47,XXX and 1 case of XYYY/XYY.
[i]Includes only *de novo* cases.
[j]Includes 7 cases of aneuploidy and structural rearrangement, 2 cases of double trisomy (trisomy 18, XXY) and 2 unknown cases.

more common for trisomy 18 and trisomy 13 than trisomy 21.[9] In our study, however, the TOP rate was highest for trisomy 21. Our study was not designed to explore the variables underlying the parental choices. We hypothesize that viable chromosome abnormalities associated with mental retardation are less acceptable to Japanese parents than those with poorer survival.[18] Another possible explanation is that women may have concerns about ensuring the care of such children after the parents' death and putting a burden on their other children,[19] as the average life expectancy for trisomy 21 individuals has increased to around 60 years.[20] Finally, women may be less familiar with the features of trisomy 13 and trisomy 18, because trisomy 13 and 18 are relatively rare compared with trisomy 21, which is more frequently seen in daily life.

The TOP rate in sex chromosomal aneuploidies was 40.8%. Among sex chromosomal aneuploidies, 45,X led to the highest TOP rate (47.9%), which was in line with the findings of a systematic review of the subject.[21] However, the TOP rates in our study were lower than those in that review, except for those of 47,XYY. This difference may be attributed to the information parents received after the prenatal diagnosis of sex chromosomal aneuploidies. In this study, all of the sessions of genetic counseling before the invasive procedure and after testing with the results of karyotyping were provided by genetic specialists. Some previous studies have included cases that were offered genetic counseling sessions by non-genetic specialists.[21] As reported in the systematic review,[21] genetic counseling by specialists might lead to the continuation of sex chromosomal aneuploidy-affected pregnancies more often than counseling given by non-specialists.

The current study showed that the referral indications for fetal karyotyping contributed to the parental decisions for TOP. Ultrasound examinations are routinely performed in pregnant women at almost every prenatal visit in Japan. As such, for pregnant women referred because of fetal abnormalities found on ultrasound, fetal karyotyping is an unexpected event: such women had declined genetic screening tests. In contrast, parents who choose invasive genetic testing following abnormal results at genetic screening tests may already have a positive attitude towards invasive prenatal testing and possible TOP of the affected pregnancy. Previous studies have shown that the decision to terminate the affected pregnancy was significantly associated with accepting prenatal screening[22] and fetal karyotyping.[23] Our findings suggest that requesting a prenatal genetic screening is more likely to result in a decision for TOP of fetuses with autosomal aneuploidy. In particular, the highest likelihood for TOP was observed in pregnant women referred because of positive results on NIPT.

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Table 3 **Parental decision for TOP by clinical characteristics**

	Autosomal aneuploidy			Sex chromosome aneuploidy		
	Terminated			Terminated		
Variables	*n*	(%)	*p*-value	*n*	(%)	*p*-value
Maternal age, years						
<35	93/110	(84.5)		30/63	(47.6)	
≥35	492/545	(90.3)	0.08	21/62	(33.9)	0.12
Having children[a]						
No	265/293	(90.4)		31/75	(41.3)	
Yes	294/333	(88.3)	0.39	20/45	(44.4)	0.74
Method of conception[b]						
Natural conception	463/514	(90.1)		42/103	(40.8)	
Pregnancy after infertility treatment	110/126	(87.3)	0.36	8/21	(38.1)	0.82
Diagnostic test						
CVS	85/99	(85.9)		14/24	(58.3)	
Amniocentesis	500/556	(89.9)	0.23	37/101	(36.6)	0.06
Indication for karyotyping						
Increased NT and/or positive results on MSS	180/200	(90.0)		10/32	(31.2)	
Abnormal fetal findings on ultrasound	152/192	(79.2)		28/51	(54.9)	
AMA	78/84	(92.9)		8/33	(24.2)	
Positive results on NIPT	161/165	(97.6)		1/1[c]	(100)	
Others	14/14	(100)	<0.01	4/8	(50.0)	0.02

AMA, advanced maternal age; CVS, chorionic villus sampling; MSS, maternal serum screening; NIPT, non-invasive prenatal testing; NT, nuchal translucency; TOP, termination of the pregnancy.
[a]No data available for 29 cases of autosomal aneuploidy including 26 terminated cases, and 5 cases of sex chromosome aneuploidy.
[b]No data available for 15 cases of autosomal aneuploidy including 12 terminated cases, and 1 case of terminated sex chromosome aneuploidy.
[c]Positive result of trisomy 18.

NIPT allows for the detection of autosomal aneuploidy at an early gestational age, which may be a reason for the termination of affected pregnancies. However, no significant differences were noted in the TOP rate because of autosomal aneuploidy detected with CVS (earlier detection) versus amniocentesis (later detection) (Table 3). This finding suggests that factors other than early detection may underlie the extremely high rates of TOP among pregnant women with positive results on NIPT.

In cases of sex chromosome aneuploidy, however, pregnant women referred because of AMA and increased NT and/or positive results on MSS were less likely to terminate the affected pregnancy than those referred because of abnormal ultrasound findings. This opposite trend in the decisions

Table 4 **The crude and adjusted odds ratios for TOP among indications for karyotyping**

	Autosomal aneuploidy			Sex chromosome aneuploidy		
Indications	Crude OR (95% CI)	aOR[a] (95% CI)	*p*-value	Crude OR (95% CI)	aOR[a] (95% CI)	*p*-value
Abnormal fetal findings on ultrasound	Ref	Ref		Ref	Ref	
Increased NT and/or positive result on MSS	2.37 (1.33–4.22)	2.45 (1.33–4.50)	0.02	0.37 (0.15–0.95)	0.37 (0.14–0.97)	0.04
AMA	3.42 (1.39–8.42)	2.91 (1.15–7.35)	<0.01	0.26 (0.10–0.69)	0.31 (0.09–1.04)	0.06
Positive result of NIPT	10.6 (3.70–30.3)	13.7 (4.07–45.9)	<0.01	—	—	

AMA, advanced maternal age; aOR, adjusted odds ratio; CI, confidence interval; MSS, maternal serum screening; NIPT, non-invasive prenatal testing; NT, nuchal translucency; OR, odds ratio; TOP, termination of the pregnancy.
[a]Adjusted for maternal age, parity, method of the conception.

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compared with autosomal aneuploidy can be explained by prior data indicating that fetal ultrasound abnormalities had a strong influence on the decision for TOP of sex chromosome aneuploidies.[24,25] Therefore, abnormal ultrasound findings may adversely influence the decision to continue the pregnancy.

Several limitations associated with the present study warrant mention. First, as our study was a retrospective review of medical records without any interviews, we were unable to assess the individual and complex psychological factors that influence parental decisions. Second, all of the participating institutions are special in Japan, providing genetic counseling before and after testing by genetic specialists. Therefore, our study is unable to represent the TOP rates among institutions where non-specialists are involved in genetic counseling. Finally, we do not know how many couples with sonographic evidence of fetal anomalies chose TOP without undergoing genetic diagnostic tests.

In conclusion, the TOP rate of trisomy 21 (93.8%) was significantly higher than that of other autosomal aneuploidies. TOP rates are affected by the indication for invasive genetic testing. In particular, the highest likelihoods of TOP were observed for pregnant women referred because of elevated risk of aneuploidies based on genetic screening tests.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- The rates of termination of pregnancy (TOP) because of chromosomal abnormalities vary greatly by country and ethnicity, and the termination rate in Japan is unknown.
- Parental decisions to continue or terminate a pregnancy affected with a chromosome abnormality are influenced by various factors.

WHAT DOES THIS STUDY ADD?

- Trisomy 21 showed the highest TOP rate (93.8%), with a live birth rate of 2.6% in Japan for prenatally diagnosed cases.
- Indications for prenatal karyotyping, especially positive results at non-invasive prenatal testing, strongly contribute to TOP when a chromosomal abnormality is found.

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