

Article

The New West Japan Twins and Higher Order Multiple Births Registry

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Abstract

The new West Japan Twins and Higher Order Multiple Births Registry was established by recruiting young twins and multiple births and by referrals from public health centers in the 1990s. The participants included in the survey comprised over 7800 twins and 4241 higher order multiples, and their families. Specifically, the present registry contains one of the largest triplet samples in the world. For these twins and multiples, data on year of delivery, mode of delivery, gestational age, intrapartum complications, longitudinal physical measures, motor milestones, cerebral palsy and feeding methods were obtained from records in the Maternal and Child Health Handbooks and schools. Participating mothers were asked to indicate family structure, parental educational history, maternal sleeping time, maternal health condition, maternal and paternal age at multiple delivery, complications during pregnancy, handedness of multiples and age at menarche of multiples. However, the zygosity differed among the various collaborating public health centers according to factors such as the time of investigation. Follow-up questionnaires have been mailed out every 3–4 years for longitudinal studies. This article describes the goals of this registry, recruitment of multiples and the focus of the study. The goals of this registry are not only to conduct research on human genetics and maternal and child health, but also to contribute to providing appropriate information for families with multiples.

Keywords: Twins; triplets; multiple births; body size; development

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In Japan, multiple birth rates increased and reached a peak in 2005 because of the use of assisted reproductive technology (ART) in the management of infertility, whereas birth rates in general are decreasing. The rates of ART-related multiple births have gradually declined over the past few years (2006–2009), but remain higher than those of spontaneous multiple births, likely due to the effect of the single-embryo transfer policy for ART (Ooki, 2011).

These multiple gestations increase obstetrical complications for the mother, and prematurity and morbidity for the newborns (Santana et al., 2018). Furthermore, death is much more common in multiple births than in singletons, especially in the perinatal period (Imaizumi, 2003; Imaizumi & Hayakawa, 2013). If the newborns are in good condition, a specific feature associated with families with multiples is that rearing two or three children of the same age at the same time has been found to overburden parents — especially the mother — physically, mentally and socially (Denton, 2005). However, there are few studies on maternal and child health for families with multiples.

Meanwhile, studies on monozygotic and dizygotic twins have been widely used to elucidate overall variations based on genetic and environmental differences between individuals. Environmental factors shared by co-twins include gestational age, total placental weight and maternal factors, such as maternal body size and smoking history. Individual placental characteristics, such as placental function, including nutrient capacity, anatomy and perinatal injury, can lead to differences in birth size between co-twins and are thus part

of the environment unique to each twin. We are also interested in using this approach to analyze genetic and environmental contributions to individual differences in body size and development.

The goals of this registry are, therefore, not only to conduct research on human genetics and maternal and child health, but also to contribute to providing appropriate information for families with multiples.

Recruitment of Twins and Higher Order Multiple Births

Twins, triplets, quadruplets, quintuplets and their families in the West Japan Twins and Higher Order Multiple Births Registry (Yokoyama, 2002b, 2012; Yokoyama et al., 2012, 2005, 2008) have been recruited from several sources since the 1990s, including mothers responding to magazine articles featuring nursing guidance for families with multiple births, the Japanese Mothers' Organization for Twins and Higher Order Multiple Births, and referrals from several public health centers in west Japan including Osaka City.

Osaka City is a metropolis with a population of approximately 2,700,000. The number of births per year is about 23,000. We have been collaborating with public health centers in Osaka City to provide appropriate childcare information for families with multiples based on evidence accumulated since 2008. Expectant mothers and fathers with multiples who live in the city have been offered childcare information for families with multiples based on several articles.

Table 1 presents a summary of the number of families with twins and higher order multiple births in this registry who participated in at least one survey: 3900 pairs of twins, 1385 sets of triplets, 18 sets of quadruplets, and 3 sets of quintuplets, and their families.

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Table 1. Major characteristics

Location	Twins			
	All over Japan	Triplets	Quadruplets	Quintuplets
Number of pairs	3900 pairs	1385 sets	18 sets*	3 sets
Age	Born after 1977	Born after 1978	Born after 1990	Born after 1993
Sex				
Boys	3860 (49.5%)	2048 (49.3%)	38 (53.5%)	9 (60.0%)
Girls	3940 (50.5%)	1986 (47.8%)	33 (46.5%)	6 (40.0%)
Unknown	0 (0.0%)	121 (2.9%)	—	—
Zygosity screening	Questionnaire	Questionnaire	No	No
Number of multiple by zygosity	The zygosity differed among the various collaborating public health centers according to factors such as the time of investigation.			
Open to all types of collaboration	Yes			
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Note: *71 quadruplets excluding 1 infant death.

Zygosity Determination

Information on zygosity was based on validated questions on physical appearance to which mothers of twins responded (Ooki & Asaka, 2004). The zygosity of each same-sex twin-pair was initially diagnosed using a three-item questionnaire based on physical resemblance when the twins were around 1 year of age. The items were ‘Were they like two peas in a pod?’, ‘Were they mistaken one for the other?’ and ‘If so, who mistook them?’ According to the degree of similarity, the first question was scored from 1 (*like two peas in a pod*) to 3 (*quite different*), the second question from 1 (*very often*) to 3 (*never*) and the third from 1 (*parent*) to 4 (*nobody*). In accordance with the cut-off point established for this scale, those with a total score of 6 to 10 were considered monozygotic twins and those with a score of 13 to 19 as dizygotic twins. Those with a total score of 11 or 12 were judged as indeterminate. The zygosity differed among the various collaborating public health centers according to factors such as the time of investigation (Table 1).

Health Checkups and Measurements

In Japan, the postnatal health monitoring system changes as the child ages. Birth weight, length, head circumference and chest circumference were measured at hospitals and recorded with information on gestational age. Until 6 years of age, routine health checkups are administered by the Ministry of Health, Labor and Welfare under the Maternal and Child Health Law. All information on physical and motor development of each child is recorded in the Maternal and Child Health Handbooks provided to expectant mothers by the authorities upon notification of the pregnancy. This handbook was established by the Maternal and Child Health Law. The purpose of this handbook is the maintenance of maternal and child health, and it includes information on health checkups during pregnancy, the condition of the newborn, the progress of infant growth, periodic medical checkups for the infant and vaccinations as recorded by obstetricians or pediatricians. After 6 years of age, Japanese children receive health checkups

administered by the Ministry of Education, Culture, Sports, Science and Technology under the School Health Law. The physical measures from these school-based health checkups are routinely recorded in the school records and made available to each family.

Mothers participating in this study were offered childcare information for families with multiples based on several articles (Yokoyama, 2002a, 2002b; Yokoyama & Ooki, 2004; Yokoyama et al., 2006, 2008, 2009) published as a result of data from this registry and included birth weight of twins or multiples, maternal sleeping time after delivery, maternal health condition, coping methods, method of simultaneous feeding, and so on. Mothers were advised to refer to their records when completing the questionnaire. Tables 2 and 3 show the variables and physical measures. Follow-up questionnaires have been mailed out every 3–4 years for the purpose of longitudinal surveys.

Focus of the Study

One of the major focuses of this study has been to investigate physical growth and development features of twins and triplets in childhood (Yokoyama, 2012; Yokoyama et al., 2005, 2012, 2013; Yokoyama, Sugimoto, Pitkaniemi et al., 2011; Yokoyama et al., 2008, 2009; Yokoyama, Sugimoto, Sono et al., 2011). We analyzed the genetic architecture of the growth process (Silventoinen et al., 2010; Silventoinen, Karvonen et al., 2011; Silventoinen, Kaprio et al., 2011) and participated in the CODATwins project (Yokoyama et al., 2016, 2018). In addition, the present dataset is the largest triplet sample in the world to provide longitudinal data. The weight and height deficit of triplets compared to the general population of Japan was found to remain between 10% and 17% for weight and between 2% and 5% for height until 12 years of age. In addition, our study of triplets found that left-handedness is associated with lower birth weight when fully controlling for gestational age (Heikkilä et al., 2018). Left-handers also had significantly delayed motor development and smaller infant head circumference compared to right-handers (Heikkilä et al., 2018).

Table 2. Variables list of twins and multiples

		Twin	Triplet	Quadruple/ Quintuplet
Family and parents	Family structure	○	○	○
	Age, sex and sib order	○	○	○
	Parental educational history	○	○	
	Child-rearing burden	○	○	○
	Maternal sleeping time	○	○	○
	Maternal health condition	○	○	○
	Maternal menstrual cycle	○	○	
	Maternal job	○	○	○
	Cooperation from other family members or relatives with child-rearing	○	○	○
	Advisers for child-rearing	○	○	○
	Parental age at multiple delivery	○	○	○
	Family history of disease	○	○	○
	Obstetrical history	Information of infertility treatment	○	○
Morning sickness		○	○	○
Pregnancy toxemia		○	○	○
Threatened premature labor		○	○	○
Maternal weight gain during multiple pregnancy		○	○	○
Maternal abdominal circumference		○	○	○
Blood pressure during pregnancy		○	○	○
Fundal height		○	○	○
Maternal smoking/drinking during pregnancy		○	○	
Twin–twin transfusion syndrome		○	○	
Twin delivery, newborn twins and multiple	Parity	○	○	○
	Year of delivery			
	Mode of delivery	○	○	○
	Gestational age	○	○	○
	Respiratory distress syndrome	○	○	○
	Apparent death	○	○	○
Jaundice	○	○	○	

Note: Circles indicate there is data available.

Several other studies on maternal and child health for families with multiples have also been conducted (Yokoyama, 2002a, 2002b, 2003; Yokoyama & Ooki, 2004; Yokoyama & Shimizu, 1999, 2001). We previously reported that triplet pregnancies showed significantly higher fundal heights compared with twin pregnancies; at 36 weeks of gestational age, those of triplet and twin pregnancies were 47 and 40 cm, respectively. We also noted that the prevalence of cerebral palsy in triplets and quadruplets was higher than that in twins. Lower gestational age was associated with a greater risk of cerebral palsy (Yokoyama et al., 1995). Meanwhile, according to a

Table 3. Variables list of body and physical aspect for twin and multiples

		Twin	Triplet	Quadruple/ Quintuplet
Body and physical aspect	Longitudinal physical measures weight, height, chest circumference, head circumference	○	○	○
	Motor milestones	○	○	○
	Feeding methods (breastfeeding, bottle- feeding)	○	○	○
	Age at menarche and secondary sexual characteristic	○	○	
	Cerebral palsy and other disability	○	○	○
	Asthma	○	○	
	Atopic dermatitis and other allergies	○	○	
	ADHD	○	○	
	Asperger disorder	○	○	
	Handedness	○	○	

Note: Circles indicate there is data available.

population-based study, the risk of child maltreatment is higher in multiple births. However, findings from our study showed that multiple birth was not associated with increased risk of child maltreatment (Yokoyama et al., 2015). Compared with singletons, multiples had a significantly higher rate of risk factors for child maltreatment including low birth weight, disorders of the nervous system, and poor maternal health. Using another population-based study, the rate of exclusive breastfeeding among twins or triplets at 4 months of age was significantly lower than among singletons, 4.1% among twins and triplets compared with 44.7% among singletons. Moreover, twins and triplets were independently associated with a higher rate of bottle-feeding; the odds ratio indicated that mothers who had twins or triplets were 2.44 times more likely to choose bottle-feeding with formula milk only than those who had singletons (Yokoyama et al., 2006).

Future Directions

The nurturing of multiples entails a higher burden on the mother physically, mentally and economically than that of singletons (Yokoyama et al., 2002a, 2002b; Yokoyama & Shimizu, 2001; Yokoyama et al., 2005). This registry, therefore, aims not only to conduct research on human genetics and maternal and child health, but also to contribute to providing appropriate information for families with multiples. Follow-up questionnaires will be mailed out every 3–4 years for longitudinal studies. We will also continue to collaborate with public health centers in Osaka City and other municipalities to help provide information to families with multiples and to conduct population-based studies of twins and multiples in the future.

Collaborations are welcomed. Potential collaborations with investigators using similar measures and who are interested in pooling resources are especially encouraged.

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