

# The West Japan Twins and Higher Order Multiple Births Registry

Yoshie Yokoyama

*Department of Public Health Nursing, Osaka City University, Osaka, Japan*

The West Japan Twins and Higher Order Multiple Births Registry was established in the 1990s by recruiting young twins and multiples and through referrals from public health centers. To date, over 7,000 twins and 4,300 higher order multiple births and their families have been registered in the survey, and it includes one of the largest triplet samples in the world. Follow-up questionnaires are also mailed every 2 to 3 years as part of longitudinal survey studies. This article describes the goals of the registry, the recruitment of multiples, and the overall focus of the study. The goals of the registry are not only to provide data for research on human genetics and maternal and child health, but also to provide appropriate information for families with multiples.

■ **Keywords:** Japan, twins, triplets

Despite an overall decrease in the birth rate in Japan, the rate of multiple births has increased, reaching a peak in 2005, as a result of infertility treatments. From 2006 to 2009, the multiple birth rate has shown a gradual decrease, but remains higher than the spontaneous multiple birth rate, probably due to the single-embryo transfer policy of assisted reproductive technologies (Ooki, 2011). Despite this increase and subsequent need for appropriate parental support, few studies have documented maternal and child health specific to families with multiples in Japan. The West Japan Twins and Higher Order Multiple Births Registry was therefore established to not only to collect data for research on human genetics and maternal and child health, but also to provide appropriate information for families with multiples.

## Recruitment of Twins and Higher Order Multiple Births

The Registry was previously known as the Kinki University Twins and Higher Order Multiple Births Registry (Yokoyama et al., 1995a, 1995b). Since the 1990s, twins, triplets, quadruplets, quintuplets, and their families have been recruited for the registry from several sources, including mothers who responded to magazine articles on nursing guidance for families of multiples, the various Japanese Mothers' Organizations for Twins and Higher Order Multiple Births, and referrals from public health centers in west Japan (Yokoyama, 2002b; Yokoyama et al., 2005, 2011b).

Nishinomiya city, a residential area with a population of approximately 460,000 is included within the catchment area. The number of births per year in this area is about 4,700, with an increase in multiple births being observed from 2000 onwards. The current number of multiple births per year is between 110 and 170. The public health centers in Nishinomiya city collaborate with the author to provide appropriate childcare information for families with multiples, based on evidence obtained since 2002 (Sugimoto et al., 2008; Yokoyama et al., 2004, 2006, 2007, 2011a). Expectant mothers and fathers of multiples living in the city participate in childbirth classes for multiple births and are now offered childcare information based on the findings, including optimal maternal weight gain and gestational periods in twin and triplet pregnancies, physical growth and development features of twins and triplets in childhood, child-rearing problems, and measures in mothers with multiple children and so on (Yokoyama, 2002a, 2002b; Yokoyama & Ooki, 2004; Yokoyama & Shimizu, 1999, 2001; Yokoyama et al., 1995a, 1995e, 1997, 2004, 2006, 2007, 2011a). In addition,

RECEIVED 19 June 2012; ACCEPTED 13 July 2012. First published online 29 October 2012.

ADDRESS FOR CORRESPONDENCE: Yoshie Yokoyama, Department of Public Health Nursing, Osaka City University, 1-5-17 Asahi-machi, Abeno-ku, Osaka 545-0051, Japan. E-mail: yyokoyama@nurs.osaka-cu.ac.jp

**TABLE 1**  
The West Japan Twins and Higher Order Multiple Births Registry

	Twins	Triplets	Quadruplets	Quintuplets
Location	All over Japan			
Number of pairs	3536 pairs	1,385 sets	39 sets	6 sets
Age	Born after 1977	Born after 1978	Born after 1990	Born after 1993
Zygoty screening	Questionnaire	Questionnaire	No	No
Open to all types of collaboration	Yes			
Institution	Osaka City University			
Address	1-5-17 Asahi-machi, Abeno-ku, Osaka 545-0051, Japan			
E-mail	yyokoyama@nurs.osaka-cu.ac.jp			
Fax	+816-6645-3536			

the public health centers in Osaka city have also started to collaborate with the author. Osaka city is an urban area with a population of approximately 2,665,000, and the number of births per year is about 23,000. Table 1 provides a summary of the number of families with twins and higher order multiples included in the registry and those who participated in at least one survey, namely 3,536 pairs of twins, 1,385 sets of triplets, 39 sets of quadruplets, 6 sets of quintuplets, and their families.

### Determining Zygoty

Zygoty of the same-sex twin pairs was initially diagnosed using a three-item questionnaire (Ooki & Asaka, 2004) based on physical resemblance rated by mothers of twins when twins are around 1 year of age. The three items used were: 'Are they like two peas in a pod?', 'Are they often confused for each other?', and 'If so, by whom?' 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 (*no-one*). In accordance with the cut-off point established, those with a total score of 6 to 10 were determined to be monozygotic (MZ) and those with a score of 13 to 19 as dizygotic (DZ). Those with a total score of 11 or 12 were judged as unidentified.

### Health Check-Ups and Measurements

In Japan, the postnatal health monitoring system changes according to the child's age. Birth weight, body length, head circumference, and chest circumference are measured at hospitals and recorded along with information on gestational age. Until 6 years of age, routine health check-ups are administered by the Ministry of Health, Labor and Welfare under the Maternal and Child Health Law. Information on physical and motor development is recorded in the Maternal and Child Health Handbooks provided to expectant mothers by local authorities upon notification of the pregnancy. This handbook was established under the Maternal and Child Health Law. The purpose of the handbook is to maintain a record of maternal and child health. It includes information on health check-ups during preg-

nancy, the condition of the newborn, progression of infant growth, and periodic medical infant check-ups and vaccination recorded by obstetricians or pediatricians. After 6 years of age, Japanese children receive health check-ups administered by the Ministry of Education, Culture, Sports, Science and Technology under the School Health Law. The physical measures performed during these school-based health check-ups are routinely recorded in the school records and made available to each family.

Mothers participating in this study were offered childcare information specific to families of multiples based on several articles written by authors who also cooperated with this study (Yokoyama, 2002a, 2002b; Yokoyama & Ooki, 2004; Yokoyama & Shimizu, 1999; Yokoyama et al., 1995e, 2008, 2009). Mothers were advised to refer to these records when completing the questionnaire. Table 2 shows the information obtained in the questionnaires and physical measures study. Follow-up questionnaires are being mailed every 2 to 3 years as part of longitudinal survey studies.

### Focus of the Study

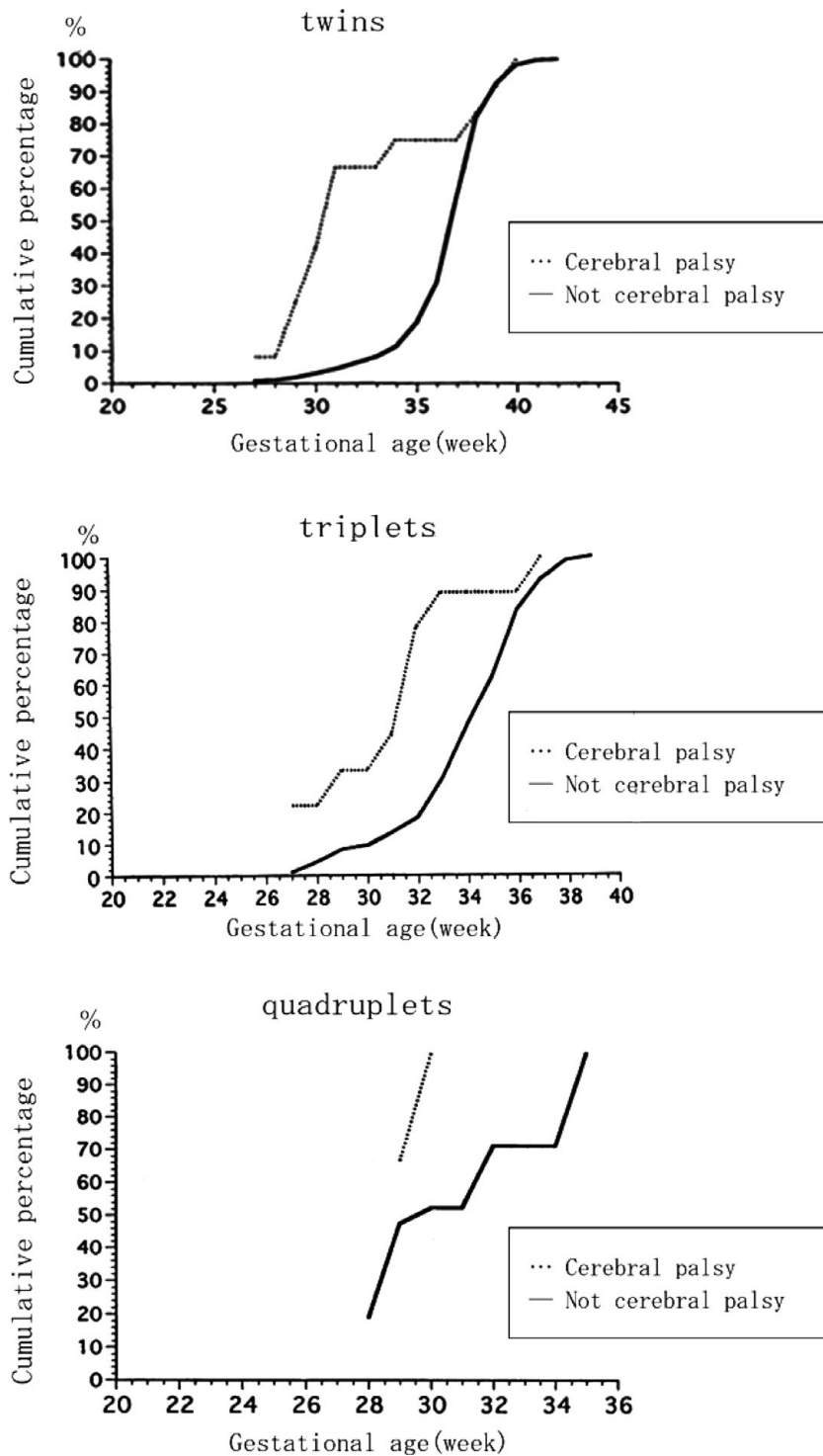
One of the major focuses of this study has been to investigate the degree of risk of disabilities in twins, triplets, and quadruplets, and to identify factors associated with the increased risk. Figure 1 shows the prevalence rates of cerebral palsy in twins, triplets, and quadruplets by gestational age at birth (Yokoyama et al., 1995a). Children with cerebral palsy tend to have a lower gestational age compared to those without cerebral palsy among twins, triplets, and quadruplets. Moreover, the risk of at least one child being disabled was found to be approximately 1 in 13 pairs of twins (7.4%), one in four to five sets of triplets (21.6%), and one in two sets of quadruplets and quintuplets (50.0%). There was also a significantly higher clustering tendency of disabilities in twins and triplets compared with the expected frequency calculated from the incidence rate of disabilities (Yokoyama et al., 1995b, 1995c).

Physical growth and development features of twins and triplets in childhood were also extensively analyzed as part of the study (Yokoyama et al., 1995d, 2005, 2008, 2009, 2011a, 2011b, 2012). The present dataset represents the

**TABLE 2**  
Information in the Questionnaire and Physical Measures for Multiples

	Twin	Triplet	Quadruplet	Quintuplet
Focus of work	Perinatal history Cerebral palsy and other disability <sup>1,2,3</sup> Longitudinal physical measures <sup>4,18-20</sup>	Perinatal history Cerebral palsy and other disability <sup>1,2,3</sup> Longitudinal physical measures <sup>4,7,10,13,14,16,17</sup>	Perinatal history Cerebral palsy and other disability <sup>2</sup> Longitudinal physical measures	Perinatal history Cerebral palsy and other disability <sup>2</sup> Longitudinal physical measures
	weight, height, chest circumference head circumference	weight, height, chest circumference head circumference	weight, height, chest circumference head circumference	weight, height, chest circumference head circumference
	Motor milestones <sup>12</sup> Feeding methods <sup>9,11</sup> breast-feeding and so on	Motor milestones <sup>15</sup> Feeding methods <sup>9,11</sup> breast-feeding and so on	Motor milestones Feeding methods <sup>9</sup> breast-feeding and so on	Motor milestones Feeding methods <sup>9</sup> breast-feeding and so on
	Asthma Atopic dermatitis and other allergosis ADHD Asperger disorder and so on Information of infertility treatment <sup>8</sup>	Asthma Atopic dermatitis and other allergosis ADHD Asperger disorder and so on Information of infertility treatment <sup>8</sup>	Asthma Atopic dermatitis and other allergosis ADHD Asperger disorder and so on Information of infertility treatment	Asthma Atopic dermatitis and other allergosis ADHD Asperger disorder and so on Information of infertility treatment
	Maternal physical variation during pregnancy <sup>5,6</sup> weight, BP, fundal height	Maternal physical variation during pregnancy <sup>5,6</sup> weight, BP, fundal height	Maternal physical variation during pregnancy weight, BP, and so on	Maternal physical variation during pregnancy weight, BP, and so on
	Family members Family history of disease	Family members Family history of disease	Family members Family history of disease	Family members Family history of disease

Note: <sup>1</sup>Yokoyama et al. (1995a); <sup>2</sup>Yokoyama et al. (1995b); <sup>3</sup>Yokoyama et al. (1995c); <sup>4</sup>Yokoyama et al. (1995d); <sup>5</sup>Yokoyama & Shimizu (1999); <sup>6</sup>Yokoyama (2002b); <sup>7</sup>Yokoyama (2003); <sup>8</sup>Yokoyama et al. (2003); <sup>9</sup>Yokoyama & Ooki (2004); <sup>10</sup>Yokoyama et al. (2005); <sup>11</sup>Yokoyama et al. (2006); <sup>12</sup>Yokoyama et al. (2007); <sup>13</sup>Yokoyama et al. (2008); <sup>14</sup>Yokoyama et al. (2009); <sup>15</sup>Yokoyama et al. (2011a); <sup>16</sup>Yokoyama et al. (2011b); <sup>17</sup>Yokoyama et al. (2012); <sup>18</sup>Silventoinen et al. (2010); <sup>19</sup>Silventoinen et al. (2011a); <sup>20</sup>Silventoinen et al. (2011b).



**FIGURE 1**  
Cerebral palsy and gestational age of twins, triplets, and quadruplets.

largest triplet sample in the world for which accurate data on age after birth are available. The weight and height deficits of triplets compared to the general population of Japan were found to be between 10% and 17% for weight and between 2% and 5% for height until 12 years of age. We

also analyzed the genetic architecture of the growth process (Silventoinen et al., 2010, 2011a, 2011b). Our results suggested that the genetic architecture of BMI development in the Japanese population is generally similar to that found in previous twin studies in Caucasian populations. More-

over, head circumference (HC) was found to be strongly genetically regulated. Several other studies have examined maternal and child health of families with multiples (Yokoyama, 2002a, 2002b; Yokoyama & Shimizu, 1999, 2001; Yokoyama et al., 1995e; 1997; Yokoyama, 2003; Yokoyama et al., 2003, 2004).

## Future Directions

Raising multiples entails a higher physical, mental, and economic burden than raising singletons (Yokoyama, 2003; Yokoyama & Shimizu, 2001; Yokoyama et al., 1995e, 1997, 2002a, 2005). This registry therefore aims not only to provide data for research on human genetics and maternal and child health, but also to provide appropriate information for families with multiples. Expectant mothers and fathers of multiples living in Nishinomiya city and Osaka city that collaborate with the author are offered childcare information based on the findings through childbirth classes for multiple births and so on.

Collaboration is welcomed, especially with investigators currently employing similar measuring tools and who are interested in pooling resources.

## Acknowledgments

The author would like to thank Kenka Lee for helping with data analysis and mothers of multiples. This research was supported by the Ministry of Education, Science, Sports and Culture of Japan through a Grant-in-Aid for Scientific Research (C), 1998–1999; Scientific Research (B), 2000–2002; Challenging Exploratory Research, 2000–2002; Scientific Research (B), 2004–2007; Challenging Exploratory Research, 2005–2007; and Scientific Research (B), 2008–2012.

## References

- Ooki, S. (2011). Effect of maternal age and fertility treatment on the increase in multiple births in Japan: Vital statistics, 1974–2009. *Journal of Epidemiology*, *21*, 507–511.
- Ooki, S., & Asaka, A. (2004). Zygosity diagnosis in young twins by questionnaire for twins' mothers and twins' self-reports. *Twin Research*, *7*, 5–12.
- Silventoinen, K., Kaprio, J., & Yokoyama, Y. (2010). Genetic regulation of pre-pubertal development of body mass index: A longitudinal study of Japanese twin boys and girls. *Behavior Genetics*, *41*, 234–241.
- Silventoinen, K., Kaprio, J., & Yokoyama, Y. (2011b). Genetics of pre-pubertal growth: A longitudinal study of Japanese twins. *Annals of Human Biology*, *38*, 608–614.
- Silventoinen, K., Karvonen, M., Sugimoto, M., Kaprio, J., Dunkel, L., & Yokoyama, Y. (2011a). Genetics of head circumference in infancy: A longitudinal study of Japanese twins. *American Journal of Human Biology*, *23*, 630–634.
- Sugimoto, M., Yokoyama, Y., Wada, S., Matsubara, M., Saito, M., & Sono, J. (2008). Anxiety and associated factors in mothers of twins or triplets as compared with mothers of singleton children. *Japanese Journal of Public Health*, *55*, 213–220.
- Yokoyama, Y. (2002a). Childcare problems in mothers with twins as compared children born singly. *Japanese Journal of Public Health*, *49*, 7–12.
- Yokoyama, Y. (2002b). Fundal height as a predictor of early triplet delivery. *Twin Research*, *5*, 71–74.
- Yokoyama, Y. (2003). Comparison of child-rearing problems between mothers with multiple children who conceived after infertility treatment and mothers with multiple children who conceived spontaneously. *Twin Research*, *6*, 89–96.
- Yokoyama, Y., Nakahara, Y., Matsubara, S., Sugimoto, M., Koyama, H., & Mitsutsuji, R. (2004). Comparison of child-rearing problems and necessary community welfare and health services between mother with twins or triplets of mothers with singleton children. *Japanese Journal of Public Health*, *51*, 94–102.
- Yokoyama, Y., & Ooki, S. (2004). Breast-feeding and bottle-feeding of twins, triplets and higher order multiple births. *Japanese Journal of Public Health*, *51*, 969–974.
- Yokoyama, Y., Pitkaniemi, J., Kaprio, J., & Silventoinen, K. (2012). Weight growth of triplet infants from birth to twelve years of age. *Twin Research and Human Genetics*, *15*, 672–679.
- Yokoyama, Y., & Shimizu, T. (1999). Optimal maternal weight gain in twin and triplet pregnancy. *Japanese Journal of Public Health*, *46*, 604–615.
- Yokoyama, Y., & Shimizu, T. (2001). Maternal partiality in attachment with multiple birth children and the related factors. *Japanese Journal of Public Health*, *48*, 85–94.
- Yokoyama, Y., Shimizu, T., & Hayakawa, K. (1995a). Prevalence of cerebral palsy in twins, triplets, and quadruplets. *International Journal of Epidemiology*, *24*, 943–948.
- Yokoyama, Y., Shimizu, T., & Hayakawa, K. (1995b). Incidence of handicaps in multiple births and associated factors. *Acta Geneticae Medicae et Gemellogiae*, *44*, 81–91.
- Yokoyama, Y., Shimizu, T., & Hayakawa, K. (1995c). Handicaps in twins and triplets. *Japanese Journal of Hygiene*, *49*, 1013–1018.
- Yokoyama, Y., Shimizu, T., & Hayakawa, K. (1995d). Antenatal complications in triplet pregnancies and birth weights of triplets compared with those of twins. *Japanese Journal of Public Health*, *42*, 113–120.
- Yokoyama, Y., Shimizu, T., & Hayakawa, K. (1995e). Childcare problems and maternal fatigue symptoms in families with twins and triplets. *Japanese Journal of Public Health*, *42*, 187–193.
- Yokoyama, Y., Shimizu, T., Yura, A., & Hayakawa, K. (1997). Actual conditions of help and support of childcare in families with multiple birth children. *Japanese Journal of Public Health*, *44*, 81–88.
- Yokoyama, Y., Sugimoto, M., & Ooki, S. (2005). Analysis of factors affecting birthweight, birth length and head circumference: Study of Japanese triplets. *Twin Research and Human Genetics*, *8*, 657–663.

- Yokoyama, Y., Sugimoto, M., Silventoinen, K., & Kaprio, J. (2008). Weight growth charts from birth to six years of age in Japanese triplets. *Twin Research and Human Genetics, 11*, 641–647.
- Yokoyama, Y., Sugimoto, M., Silventoinen, K., Pitkäniemi, J., & Kaprio, J. (2009). Growth charts of length and height from birth to six years of age in Japanese triplets. *Twin Research and Human Genetics, 12*, 320–327.
- Yokoyama, Y., Sugimoto, M., Sono, J., Kaprio, J., & Silventoinen, K. (2011a). Motor development of triplets: A Japanese prospective cohort study. *Twin Research and Human Genetics, 14*, 185–191.
- Yokoyama, Y., Sugimoto, M., Pitkäniemi, J., Kaprio, J., & Silventoinen, K. (2011b). Height growth of triplets from birth to twelve years of age in Japan. *Twin Research and Human Genetics, 14*, 468–475.
- Yokoyama, Y., Wada, S., Sugimoto, M., Katayama, M., Saito, M., & Sono, J. (2006). Breast-feeding rates among singletons, twins and triplets in Japan: A population-based Study. *Twin Research and Human Genetics, 9*, 298–302.
- Yokoyama, Y., Wada, S., Sugimoto, M., Saito, M., & Sono, J. (2007). Comparison of motor development between twins and singletons in Japan: A population-based Study. *Twin Research and Human Genetics, 10*, 379–384.
- Yokoyama, Y., Yamashiro, M., & Ooki, S. (2003). Birth weight and height characteristics of triplets. *Japanese Journal of Public Health, 50*, 216–224.
-