D

Dizygotic (DZ)

Sanjay Das[1] and Akash Gautam[2]
[1]National Institute of Mental Health and Neurosciences, Bangalore, India
[2]Centre for Neural and Cognitive Sciences, School of Medical Science, University of Hyderabad, Hyderabad, India

Synonyms

Monochorionic dizygotic twins; Twins

Definition

In the course of fertilization, when two sperms fertilize two mature ova due to multiple ovulation under the control of hypothalamo-pituitary-ovarian axis promoted by different physiological, genetic, and other environmental factors, including the use of advanced reproductive technologies to maximize reproductive success.

Introduction

The word "twins" originates from old English: "*twi*" means two or "*twin*" means double. Twin babies are although less frequent but not rare in parallel with the single child. Dizygotic (DZ) or fraternal twins are produced from two different ova fertilized by two different sperms whereas monozygotic (MZ) or identical twins derive from a single ova dividing into two separate embryos. Conjoint twins are also identical but not separated. Compare to the prevalence of monozygotic twins which is almost constant, the prevalence of dizygotic twins varies over time across the different places in the world. In animal society, twins are also prevalent and diversified like as reported in 2016 in South Africa, the world first twin puppies of Irish Wolfhound named Cullen and Romulus were born as the identical twin. Armadillo is another example to give birth to monozygote. Callitrichines, or clawed New World monkeys, always give birth to twins because they produce multiple ova in their reproductive cycle.

History and Background of Twin Studies

The history of twin studies began with Galton's study (Galton 1876); thus, he is considered as the father of twin studies and also the founder of the eugenics movement. The term "eugenics" means "well-born" and was coined by him. Galton failed to explain the cause of observed behavioral similarities in twins. In 1905, the first twin study with psychological testing was published by E. L. Thorndike. He also stated the influence of nature and nurtured on mental abilities for twins. To answer the question of the important role of

J. Vonk, T. K. Shackelford (eds.), *Encyclopedia of Animal Cognition and Behavior*,
https://doi.org/10.1007/978-3-319-47829-6_24-1

common environment and experience on the mental development, he reasoned that:

a. Twins should be more alike with increasing age.
b. Similarity of ordinary siblings not more than 4–5 years apart should resemble the similarity of twin pairs.
c. If experience influences mental abilities, then twins should be more similar for abilities that require training compared to those less subject to training.

He disputed the fact of the effect of experience on mental illness.

In the mid-1920s, two kinds of twins, MZ and DZ were first recognized. In 1924, Herman W. Siemens from Germany first proposed that the role of genetic factors for diseases or traits can be compared by comparing identical to fraternal twins reared together, thus introducing the classic twin method. In 1934, Wilson questioned the environmental impact on twins. In the same year, Helmut von Bracken found that identical twins experienced a higher degree of attachment compared to fraternal twins. Rosanoff and colleagues (1938) conducted their studies on schizophrenia, criminality, and delinquency in twins to conclude the role of social factors in developing abusive attitudes.

Weinberg was a popularizer of the "differential method," which uses a simple calculation to estimate the number of expected identical pairs in a given population of twins. He also created the first "morbidity tables" used in medical statistics, as well as an age-correction method subsequently used by several twin researchers. Germany also contributed to twin research immensely. In 1928, Hans Luxenburger published the first schizophrenia twin study followed by another study performed by Johannes Lange in 1929. The most unethical practices were performed during World War II by some German physicians notoriously labeled as "Nazi Medical Experiments." During that time, the prisoners in the camp were experimented upon without their consent. The Auschwitz and Roman twins were infested with bacteria and other pathogens for genetic studies. Following this sad history of twin studies, several animal and clinical studies were performed throughout the decades.

Beside all these studies, the most well-known twin study was Minnesota Studies of Twin Reared Apart (MSTRA) conducted by Thomas Bouchard and his colleague between the year 1979 and 2000. In 1990, Buchard and his colleague reported the correlation of physical variable, IQ, and personality test scores in monozygotic twins reared apart (MZA) and reared together (MZT). In brief, the result was tabulated below.

Features	Correlation for MZA	Correlation for MZT
IQ	0.69 (48 pairs)	0.88 (40 pairs)
Personality test score	0.50	0.50

Based on the result in the context of psychology and sociobiology, the team of MSTRA concluded that this is because of strong genetic influence and the similarity in the score is not due to shared family environment. The study was published in Science in the year 1990 where they mentioned that monozygotic and dizygotic twins who were separated early in life and reared apart are a nature's experimental beauty and also provide the ample and powerful opportunity to study the influence of environment and genetics on human characteristics.

Importance of DZ Study

Despite some methodological and ethical issues, twin research continued beyond this unfortunate history due to several reasons, including due to failure of molecular approaches in describing psychiatric disorders, genetic theories for economic and political needs, and few important publications on twin research between 1961 and 1970 (as published by Jay Joseph in his book "The Gene Illusion" and "The Trouble with Twin Studies").

Twin study is one of the most potent and valuable tools in genetics research to assess and analyze the importance and influence of genetic factors on phenotypic and trait variation in humans. Understanding which genes are responsible for natural twinning and to know how they control ovarian functions is critical for applications in female fertility and infertility.

Epidemiology and Prevalence

During the seventeenth century, birth registration was recorded in church registries and was officially introduced in 1749 in Sweden and Finland (Erikson 1962). From statistics recorded therein, it was possible to calculate twinning rates (TR). The TR (number of twin maternities/1000 maternities) varies geographically across Europe/North Africa, Sub-Saharan Africa, and Asia. The highest TR is observed in sub-Saharan Africa (23/1000) and the lowest in Asia (5–6/1000, Bulmer 1970). Based on international variation in TR, Little classified it as low prevalence (2–7/1000, e.g., Hawaii, Japan, and Taiwan), intermediate prevalence (9–20/1000 North Africa, America, Asia, Oceania, and Europe), and high prevalence (≥20/1000 Nigeria, Seychelles, Transvaal, Zimbabwe) TR countries. Among the high prevalence countries, Yoruba is reported as the highest prevalence of TR (33–66.5/1000) where 1 in every 12 families has twins (Nylander 1971, 1978). In 1900, TR decreased, and from 1970 onwards, it increased steadily in most countries (Imaizumi 1997). Such demographic variations arise due to several reasons, which can be the environmental, physiological, feeding habit, genetic, etc.

Twinning Promoting Factors: From the TR found all over the world, it has been documented that there is an increased TR in the last two decades. The contributing factor that promotes the TR includes the use of various fertility treatments like in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), intrauterine insemination (IUI), and ovulation induction (OI).

Factors Affecting Twinning Rate

Principal factors that affect the twinning rate are maternal age, parity, and genetic inheritance. Several factors contributing to alteration of twinning rate are:

(A) Increased maternal age: for example, a fourfold increase in TR from age 15 to 35. Maternal age and parity are well correlated and increase the risk of dizygotic twins (Bulmer 1970).
(B) Body type: for example, tall women (≥165 cm) with high BMI (≥30) are much more at risk (1.5–2 times) of giving birth to twins than women of small stature (≤155, Basso et al. 2004; Bortolus et al. 1999; Nylander 1981).
(C) Smoking: Women who smoke are at higher risk of giving birth to twins compared to non-smokers (Parazzini et al. 1996).
(D) Seasonal variation: Conception during summer and autumn are reported to contribute higher rates of DZ in several countries (Eriksson and Fellman 2000). The seasonal variation in day length causes the alteration in hormonal level, which may be the cause of multiple ovulations. Seasonal foods and food supply were considered as contributing factors for DZ (Eriksson and Fellman 2000).
(E) Iatrogenic factors: Oral contraceptives and Folic acid also influence DZ (Li et al. 2003). Folic acid consumption during conception increases the risk of DZ (Vollset et al. 2005). Soon after stopping oral contraceptives, conception leads to increased risk of DZ (Rothman 1977). Although there are some contradictory findings regarding the association between oral contraceptives and DZ, the overall pattern can be described as recovery from exogenous steroids causing an increase of FSH level temporarily via hypothalamo-pituitary-ovarian axis (HPO), which leads to multiple ovulations (Jernstrom et al. 1995).
(F) Genetic factors: Because height is correlated with dizygote births as the first link of twinning with heredity, Weinberg (1901) reported that mothers, sisters, and daughters of the mother with twins had an increased risk of having twins and the percentage probabilities are 39, 95, and 30%, respectively. Despite the concept of the female line contribution in DZ

as supported by other scientists strongly (Bulmer 1970; Wyshak and White 1965), Greunlich (1934) reported the contribution of paternal heriditary factors in DZ also. Meullemens and colleagues (1996) reported an autosomal monogenic dominant model by analyzing pedigree of 1422 Dutch and Flemish families with DZ twins, which supports inheritance from both parents. Semen quality may influence DZ twinning (Asklund et al. 2007).

Hypotheses

From the previous research, four hypotheses are developed.

1. Increase in multiple ovulation frequencies leading to an increase in the frequency of spontaneous DZ.
2. The concentration of FSH is above a certain threshold by extending the time or by increasing the number of responding antral follicle to FSH during follicle selection.
3. Women with a family history of multiple births are already predisposed to multiple ovulations.
4. Gene mutations affecting multiple ovulation rates are most likely from FSH pathway of synthesis, maturation, and release of the dominant follicle.

Although during pregnancy, complications are prevalent in producing twins rather than singleton births. Two hypotheses have been put forward to explain the twinning rate of humans.

A. The insurance ova hypothesis: The hypothesis states that increased production of multiple ovarian follicles will increase the probability of survival and at least one of them being fertilized. Therefore, conceiving twins is the by-product of encouraging fertility (Anderson 1990).
B. Natural selection hypothesis: This hypothesis consults the effect of environments that promote twins or singletons as the reproductive output.

1. In an experiment conducted by Lumma and colleagues (1998) in the archipelago of Aland, Aboland, and the mainland of Finland, to their surprise, they found that enriched food source islands were inducing twinning frequency whereas, in the poorer mainland environment, singletons are preferred to maximize the reproductive success.
2. Similarly, during World War II, the scarcity of foods provokes singleton births, and again in subsequent years, food enrichment encourages twin births (Bulmer 1970).

Mechanism

Mechanism of controlling dizygotic twinning is a complex phenomenon and still obscure. Multiple ovulations due to improved nutrition and particular gene mutations are reported in animals. Increasing follicular recruitment was found in those mothers who give birth to twins (Martin et al. 1991b). There are mainly two ways by which the control mechanism works.

1. Hypothalamo-pituitary-ovarian axis is the complex regulatory network that controls the ovulation. Two important gonadotrophin hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), secreted from the pituitary alter the pattern of the menstrual cycle. In the characteristic pattern of the menstrual cycle, in the early phase, FSH concentration begins to increase and, in a feedback manner, the hormone secretes from growing follicles, (Inhibin) inhibits hypothalamus and pituitary to secrete FSH – causing FSH levels to fall. Development of one dominant follicle takes place when the concentration of FSH exceeds the threshold level, and for multiple follicle developments, FSH (independent of LH pulse) is more, or FSH exceeds the threshold for too long.
2. Ovarian follicular control – Although this pathway responds to the external FSH and LH signals and ensures the oocyte development, two closely related growth factors expressed specifically in the oocyte, bone morphogenetic protein 15 (BMP15), and growth differentiation factor 9 (GDF9) play another major role (Shimasaki et al. 2004). These two factors

bind to the receptor expressed on ovarian cells, which ensures oocyte growth and development.

Genetic Variants and DZ

Apart from these two control mechanisms, genetic variants of FSH receptor (e.g., Thr307Ala and Asn680Ser), causing the increase in sensitivity towards FSH, contributes to variation in DZ (Ayman et al. 2000). The genetic variant's contribution to DZ is still contradictory (Montgomery et al. 2001). Bone morphogenetic protein receptor1B (BMPR1B, Duffy et al. 2001) and methylenetetrahydrofolate reductase (MTHFR, Montgomery et al. 2003), Inhibin alpha (INHA, Montgomery et al. 2000) are also enlisted among those genes that play a role in DZ. Female carriers of Fragile-X syndrome (FRAXA) are also reported to have an increased risk of DZ (Kenneson and Warren 2001). Carriers of FMR1 permutation are also at risk of DZ (Welt et al. 2004). Substitution of C to T in PPRAG gene (encoding peroxisome proliferator-activated receptor ($PPAR_{\gamma}$) is also associated with DZ (Busjahn et al. 2000).

Sex of Twins

Because DZ is more common than MZ throughout the world, the question arises of the frequency of same-sex (SS) DZ and opposite sex (OS) DZ. French statistician Jacques Bertillon (1874) first speculated that the DZ = 2OS twins + MZ twins. Later Weinberg (1901) formalized Bertillon data and proposed two assumptions known as Weinberg's differential rule (WDR). The WDR states that (a) probability of conception of the male and female fetus are equal ($P = 0.5$). (b) The sexes of DZ twins are determined independently. So, DZ = equal number of (OS+SS). But the ratio is slightly more towards boys (105:100). The Trivers Willard hypothesis pointed at some doubt with the second hypothesis of WDR and stated that parental conditions have an impact on sex ratios. According to this hypothesis, parents in enriched food and other physiological conditions give birth to males, and, in poor environmental and physiological conditions, to females. Similar effects for OS and SS have been observed; if conditions are good, both are male, but if conditions are poor, both are female (Trivers and Willard 1973). OS is considered evolutionarily and developmentally disadvantageous compared to SS; then, the WDR hypothesis of independent sex determination for DZ is violated, and SS will be produced more than OS.

Chimerism

When an organism contains cells derived from more than one zygote, this is referred to as chimerism. Although chimerism is a rare event, monochorionic dizygote (MC/DZ) twin is a comparatively new area of research. Blood chimerism has been found commonly in MC/DZ. Monochorionic twin pregnancies have complications related to vascular anastomoses, which cause twin-twin transfusion syndrome. There are many such cases; for example, at birth, male recipient twins have two bloodlines, 30% 46XY and 70% 46XX, whereas female donors have 18% 46XY and 82% 46XX (Chen et al. 2013). No anomaly in reproductive growth has been reported except few cases like a girl having Down syndrome with blood chimerism (Bogdanova et al., 2010). She was a normal female with normal genitalia and fallopian tubes, but aplasia in the uterus, which may be due to the Mullerian inhibiting substance (MIS).

Conclusion

In the course of multiple ovulations, when two sperm fertilizes two ova, dizygotic twins are formed. The worldwide variation of twin frequency reflects that South African Yoruba people have a high probability of having twins. Several assisted reproductive technologies like IVF, ICSI, IUI, and OI contribute to increasing the frequency of DZ production. The enriched environment and different factors like folic acid consumption, smoking, high BMI, and increased maternal age favor the process of DZ. Because enriched food sources promote DZ, the natural selection hypothesis comes forward along with insurance ova hypothesis to increase the chance of fertilization. The search for mechanisms behind multiple ovulations establishes the hypothalamo-pituitary-ovarian axis. Several genes like GDF9 and BMP15 control the ovarian follicles. Other gene variants that contribute to the DZ processing are BMPR1B, MTHFR, INHA, FRAXA, and PPARG. Twin research continues in spite of ethical issues because of its potential impact on behavioral genetics, psychology, and different diseases.

Cross-References

- ▶ Behavioral variation
- ▶ Gonadotropic hormone
- ▶ Gonads
- ▶ Hypothalamus
- ▶ Zygote

References

Anderson, D. J. (1990). On the evolution of human brood size. *Evolution, 44*, 438–440.

Asklund, C., Jensen, T. K., Jørgensen, N., Tabor, A., Sperling, L., & Skakkebæk, N. E. (2007). Twin pregnancy possibly associated with high semen quality. *Human Reproduction, 22*, 751–755.

Ayman, A. H., Moshynska, O., Saxena, A., & Feyles, V. (2000). Association between mutations of the follicle-stimulating-hormone receptor and repeated twinning. *The Lancet, 356*(9233), 914.

Basso, O., Nohr, E. A., Christensen, K., & Olsen, J. (2004). Risk of twinning as a function of maternal height and body mass index. *Journal of American Medical Association, 291*, 1564–1566.

Bogdanova, N., Siebers, U., Kelsch, R., et al. (2010). Blood chimerism in a girl with Down syndrome and possible freemartin effect leading to aplasia of the Müllerian derivatives. *Human reproduction, 25*(5), 1339–1343.

Bortolus, R., Parazzini, F., Chatenoud, L., Benzi, G., Bianchi, M. M., & Marini, A. (1999). The epidemiology of multiple births. Human reproduction update, 5(2), 179–187.

Bulmer, M. G. (1970). *The biology of twinning in man*. Oxford: Oxford Clarendon Press.

Busjahn, A., Knoblauch, H., Faulhaber, H. D., et al. (2000). A region on chromosome 3 is linked to dizygotic twinning. *Nature Genetics, 26*(4), 398.

Chen, K., Chmait, R. H., Vanderbilt, D., Wu, S., & Randolph, L. (2013). Chimerism in monochorionic dizygotic twins: Case study and review. *American Journal of Medical Genetics Part A, 161*(7), 1817–1824.

Duffy, D. L., Montgomery, G. W., Hall, J., et al. (2001). Human twinning is not linked to the region of chromosome 4 syntenic with the sheep twinning gene FecB. American journal of medical genetics, 100(3), 182–186.

Eriksson, A. (1962). Variations in the human twinning rate. *Human Heredity, 12*, 242–250.

Eriksson, A. W., & Fellman, J. (2000). Seasonal variation of livebirths, stillbirths, extramarital births and twin maternities in Switzerland. *Twin Research and Human Genetics, 3*, 189–201.

Galton, F. (1876). The history of twins as a criterion of the relative powers of nature and nurture. *Journal of the Anthropological Institute of Great Britain and Ireland, 5*, 391–406.

Greunlich, W. W. (1934). Heredity in human twinning. *American Journal of Physical Anthropology, 19*, 391–443.

Imaizumi, Y. (1997). Trends of twinning rates in ten countries, 1972–1996. *Acta Geneticae Medicae et Gemellologiae: Twin Research, 46*(4), 209–218.

Jernstrom, H., Knutsson, M., & Olsson, H. (1995). Temporary increase of FSH levels in healthy, nulliparous, young women after cessation of low-dose oral contraceptive use. *Contraception, 52*(1), 51–56.

Kenneson, A., & Warren, S. T. (2001). The female and the fragile X reviewed. *Seminars in Reproductive Medicine, 19*(2), 159–166.

Li, Z., Gindler, J., Wang, H., Berry, R. J., et al. (2003). Folic acid supplements during early pregnancy and likelihood of multiple births: A population-based cohort study. *The Lancet, 361*(9355), 380–384.

Lummaa, V., Haukioja, E., Lemmetyinen, R., & Pikkola, M. (1998). Natural selection on human twinning. *Nature, 394*(6693), 533.

Meulemans, W. J., Lewis, C. M., Boomsma, D. I., et al. (1996). Genetic modelling of dizygotic twinning in pedigrees of spontaneous dizygotic twins. *American Journal of Medical Genetics, 61*(3), 258–263.

Montgomery, G. W., Duffy, D. L., Hall, J., et al. (2000). Dizygotic twinning is not linked to variation at the α-inhibin locus on human chromosome 2. *The Journal of Clinical Endocrinology & Metabolism, 85*(9), 3391–3395.

Montgomery, G. W., Duffy, D. L., Hall, J., Kudo, M., Martin, N. G., & Hsueh, A. J. (2001). Mutations in the follicle-stimulating hormone receptor and familial dizygotic twinning. *The Lancet, 357*(9258), 773–774.

Montgomery, G. W., Zhao, Z. Z., Morley, K. I., Marsh, A. J., Boomsma, D. I., Martin, N. G., & Duffy, D. L. (2003). Dizygotic twinning is not associated with methylenetetrahydrofolate reductase haplotypes. *Human Reproduction, 18*(11), 2460–2464.

Nylander, P. P. S. (1971). Ethnic differences in twinning rates in Nigeria. *Journal of Biosocial Science, 3*(2), 151–158.

Nylander, P. P. (1978). Causes of high twinning frequencies in Nigeria. *Progress in Clinical and Biological Research, 24*, 35–43.

Nylander, P. P. (1981). The factors that influence twinning rates. Acta geneticae medicae et gemellologiae: twin research, 30(3), 189–202

Parazzini, F., Chatenoud, L., Benzi, G., Cintio, E. D., Pino, D. D., Tozzi, L., & Fedele, L. (1996). Pregnancy: Coffee and alcohol intake, smoking and risk of multiple pregnancy. *Human Reproduction, 11*(10), 2306–2309.

Rosanoff, A. J. (1938). *Manual of psychiatry and mental hygiene* (7th ed. rewritten and enlarged). New York: Wiley.

Rothman, K. J. (1977). Fetal loss, twinning and birth weight after oral-contraceptive use. *New England Journal of Medicine, 297*(9), 468–471.

Shimasaki, S., Moore, R. K., Otsuka, F., & Erickson, G. F. (2004). The bone morphogenetic protein system in mammalian reproduction. *Endocrine Reviews, 25*(1), 72–101.

Trivers, R. L., & Willard, D. E. (1973). Natural selection of parental ability to vary the sex ratio of offspring. *Science, 179*(4068), 90–92.

Vollset, S. E., Gjessing, H. K., Tandberg, A., et al. (2005). Folate supplementation and twin pregnancies. *Epidemiology, 16*(2), 201–205.

Weinberg, W. (1901). Beiträge zur physiologie und pathologie der mehrlingsgeburten beim menschen. Archiv für die gesamte Physiologie des Menschen und der Tiere, 88(6-8), 346–430.

Welt, C. K., Smith, P. C., & Taylor, A. E. (2004). Evidence of early ovarian aging in fragile X premutation carriers. *The Journal of Clinical Endocrinology & Metabolism, 89*(9), 4569–4574.

Wyshak, G., & White, C. (1965). Genealogical study of human twinning. *American Journal of Public Health and the Nations Health, 55*(10), 1586–1593.