

The Birth of Octuplets: A Research Puzzle / Twin Research Reviews: Natural Twinning Rate; Survival at, or Before, Thirty Weeks Gestation; Unique Mirror-Imaging Effects / News Highlights: Twin Robbery at KaDeWe?; Twins Born Together and Apart; Twinning Rates in Candido Godoi

Nancy L. Segal

California State University, United States of America

The Birth of Octuplets: A Research Puzzle

This essay was co-authored with Ammar Altowaiji¹ and Craig K. Ihara, Ph.D.²

¹ *Department of Psychology, CSU Fullerton;* ² *Department of Philosophy, CSU Fullerton*

Naturally occurring higher order multiple births are high risk and rare. The rate of triplets+ (triplets, quadruplets and more) did, however, increase by 400% between 1980 and 1998, due to the increased availability of artificial reproductive technologies and advanced maternal age at conception. In contrast, the last decade witnessed a steady decline in the birth rate of triplets+. Statistics provided by the Center for Disease Control show a rate of 161.8/100,000 triplets+ births as of 2005, compared with 176.9/100,000 in 2004 (Martin et al., 2007). The birth rates of quadruplets, quintuplets and other higher order multiples, examined separately, also decreased. These downward trends have been explained by the American Society of Reproductive Medicine's (ASRM) recommendations for limiting the number of embryos transferred in assisted reproductive procedures.

Medical professionals, developmental specialists and the general public are captivated by these extraordinary births, but not necessarily for positive reasons. Physicians emphasize the health risks to mothers and infants. Developmental specialists underscore

the physical and behavioral delays suffered by many premature infants. The public points to the parental challenges posed by raising multiple birth children.

A pressing concern is the establishment of appropriate guidelines for embryo implantation. Revised recommendations, released in 2004 by the ASRM and the Society for Assisted Reproductive Technology (SART), favor the transfer of no more than one to two embryos in a single procedure for women under 35 years of age, barring unusual circumstances. The transfer of two to three embryos, at most, is advised for women between 35 and 37 years of age. Four embryos, at most, are advised for women between 38 and 40 years of age, and five embryos, at most, are advised for women above the age of 40 years (ASRM Guidelines, cited in *Medical News Today*, 2006). Establishing appropriate guidelines and prenatal counseling programs for families undergoing fertility treatments are important goals.

Reappraisal of assisted reproductive practices has received recent medical and societal attention, given the January 26, 2009 birth of octuplets to

a 33-year-old Southern California woman. Nadya Suleman, a mother of six children all artificially conceived, had been implanted with her six remaining embryos. Not only were all six implantations successful, but two of the embryos divided to produce two monozygotic (MZ) twin pairs. The reproductive, developmental and rearing issues raised by this case have been extensively debated, and will not be revisited here. The present essay considers the unusual research possibilities posed by these octuplets and other higher order multiples. However, this exercise is not intended to detract from the serious physical and emotional issues associated with their birth.

Permutations and combinations are ways of organizing members of a set into separate subsets. Permutations are ordered sequences of elements, whereas combinations are unordered. For example, a pair of DZ triplets (A, B and C) would yield six permutations

Address for correspondence: Nancy L. Segal, Department of Psychology, California State University, Fullerton, CA 92834, USA. E-mail: nsegal@Exchange.FULLERTON.EDU

if the goal was to arrange them in subsets of two: AB, BA, AC, CA, BC and C B. In contrast, this same set of DZ triplets would yield only three unique pair combinations: AB, AC and BC. Twin researchers have often included triplets in their data files in the form of both permutations and combinations. Combinations yield unique pairs that are counted only once, whereas permutations would yield additional pairs, utilized in double entry data procedures.

The possibilities raised by organizing octuplets into smaller multiple birth sets are striking. The results are displayed in Table 1 below; formulas for computing these values and a website for calculating them are also provided. The number of permutations, especially for septuplets, is staggering. However, the most useful

pairing for psychological and medical research would most likely be twins. Investigators could take advantage of the 56 twin pair permutations and 28 twin pair combinations yielded by the octuplets.

Other interesting pairings not displayed in Table 1 are also possible. It is known that four of the Suleman octuplets are members of two MZ twin pairs. Restricting attention to twins, the octuplets provide 26 unique DZ twin pairs, as well as two MZ twin pairs. At present, the gender of the MZ pairs is unknown (although one MZ twin pair must be male because the octuplets include only two female infants). If zygosity is ignored, the yield is 16 same-sex pairs (15 male and 1 female) and 12 opposite sex pairs.

The 26 DZ twin pairs referenced above are unique with respect to individual pair members, but not with respect to pair relatedness. Consider that the octuplets include 4 individuals who are part of an MZ twin pair (A1, A2 and B1, B2), leaving four individuals who are fully DZ (C, D, E and F). A1 can be paired with C, D, E and F, yielding four genetically unique DZ twin sets. However, if A2 is paired with C, D, E and F this produces four genetically equivalent DZ pairings. Similarly, B1 can be paired with C, D, E and F, resulting in a different set of four genetically distinct DZ twin sets, while B2 paired with C, D, E and F yields genetically equivalent pairings. One other unique DZ twin pair can be derived by pairing A1 with B1; the

remaining pairs (A2-B2; A1-B2 and B1-A2) are genetic replications of A1-B1. Other unique DZ twin sets include C-D, C-E, C-F, D-E, D-F and E-F, for a total of fifteen.

Comparing similarities in behavioral and physical development, both within and between related MZ and DZ twins raised together, is potentially very informative. One of us (NS) described this approach in *Indivisible by Two: Lives of Extraordinary Twins* (Segal, 2007) with reference to a naturally conceived MZ-DZ male quadruplet set. The two sets of MZ co-twins displayed similar eating and sleeping patterns as infants, whereas the DZ co-twins (created by pairing members from the two MZ sets) displayed striking differences. The quads' mother intended to 'decouple' the twins by having each child room with a DZ co-twin, but this experiment failed; the children's contrasting behaviors made this arrangement difficult. Consequently, the members of the MZ twin pairs were kept together. The quads' parents saw these events as an important lesson in the how genetic factors shape early behaviors.

The future of the California octuplets is uncertain. Hospital personnel have decided against releasing the babies to their mother until their safety can be assured. It is unlikely that they will take part in behavioral-genetic studies any time soon. Hopefully, all eight babies will continue to thrive. Note: The last octuplet was released from the hospital in mid-April.

Table 1

Organizing Octuplets Into Smaller Birth Sets: Combinations and Permutations

Group Size	Permutations ¹	Combinations ²
Twins	56	28
Triplets	336	56
Quadruplets	1,680	70
Quintuplets	6,720	56
Sextuplets	20,160	28
Septuplets	40,320	8
Octuplets	40,320	1

Note: ¹Permutations: $n! / (n - r)!$ ²Combinations: $n! / r! (n - r)!$ Note: $0! = 1$
Calculations: <http://joemath.com/math124/Calculator/factorial.htm#Permutations>

Twin Research Reviews

Natural Twinning Rate

New data from Cardiff and Glamorgan in Wales, drawn from the Cardiff Birth Survey, indicate a rise in the natural twinning rate (Faisel et al., 2008). Pregnancy outcomes were inspected for eight 5-year periods, spanning 1965 and 2004. Total twinning rates (based on natural and assisted conceptions) declined from 13.1/1,000 (between 1965 and 1969) to 10.3/1,000 (between 1980 and 1985). A subsequent upswing

was then observed, with a rate of 15.7/1,000 in the years 1995 to 1999, and 2000 to 2004. After excluding iatrogenic pregnancies (twin births due to fertility treatments), it was estimated that the natural age-adjusted twinning rate rose from 10/1,000 (between 1980 and 1984) to 13.3/1,000 (between 2000 and 2004). Factors thought to underlie this trend include advanced maternal age at conception and various nutritional factors, such as multivitamin use. It was emphasized that advanced maternal

age alone was probably not responsible for the recent upward trend because the increase was observed across different age groups.

Note

The study by Martin et al. (2007) cited above found that the United States' twinning rate remained stable from 2004 to 2005. Twins were born in 32.2/1,000 live births in both years. This figure includes twins from both natural and assisted conceptions.

Twin Survival at, or Before, 30 Weeks Gestation

Twins are more likely than non-twins to be born prematurely and to suffer greater physical risks. The nature of twins' health outcomes, relative to those of singletons born at, or before, thirty weeks gestation is of interest. British investigators examined the neonatal death rates of 479 twins and 1,538 non-twins between 1998–2001 and 2002–2005 (Ray & Platt, 2009). Mortality rates did not differ between the two groups when restricting the samples to births at thirty weeks. In contrast, twins born between 23–25 weeks gestation showed a higher rate of early and neonatal deaths than non-twins. However, this effect was noted only in the 1998–2001 cohort.

Unique Mirror-Imaging Effects

Mirror-imaging effects occur in approximately 25% of MZ twin pairs (Segal, 2000). Commonly observed reversed traits in MZ co-twins are handedness (left, right) and hair whorl (clockwise, counterclockwise). A recent report documented a rare instance of mirror-image reversal in a female MZ twin pair. The twins were born at 34 weeks with a single chorion and single amnion (Thacker et al., 2009). Each twin was diagnosed with heterotaxy syndrome (HS), a condition involving an abnormal arrangement of the usual left-right body axis. HS affects between 1/6,000 and 1/10,000 individuals in live births. Both genetic and environmental factors have been implicated in the etiology of this disorder. The co-

twins in question displayed mirror-image reversal of the thoracic and abdominal viscera (organs within the body cavities).

The investigators noted that the beginnings of left-right asymmetry occur early in the developing embryo. The earliest indication of abnormal organ asymmetry is found in the heart tube that undergoes rightward looping. Among some dicephalus and thoracopagus conjoined twins, factors affecting the laterality of organ development in one twin can affect development in the other twin. It was suspected that comparable events occurred in the present case. Studying mirror-image reversal in ordinary MZ twins may provide clues to the genesis of HS.

News Highlights

Twins with Mixed Race Parents

Fraternal twins, Lauren and Hayleigh, were born in 2001 to Dean Durrant and Allison Spooner of Great Britain (Associated Press, 2009). The twins' striking physical differences attracted worldwide attention. Lauren has light skin, red hair and blue eyes, while Hayleigh has dark skin, dark hair and dark eyes. It turns out that both their parents were born to couples from mixed marriages. Researchers have, therefore, speculated that the twin children inherited different sets of relevant genes from their mother and father. In 2008, the couple made news again when they delivered a second set of fraternal female twins, Leah and Miya. Leah is light-skinned like her mother (and older sister Lauren), while Miya is dark-skinned like her father (and older sister Hayleigh). The frequency of such twins is rare, yet may be rising due to the increased number of mixed marriages.

Twin Robbery at KaDeWe?

Kaufhaus des Westens (KaDeWe) is a famous Berlin department store, the second largest in Europe after Harrods. In January 2009, KaDeWe became famous for a robbery in which watches and jewelry, worth up to 100,000

euros, were taken (Kulish, 2009). A rope ladder and a glove left at the crime scene provided investigators with DNA that they hoped would help identify the three suspects. However, one DNA sample was traced to two people — identical twins, Abbas and Hassan O. This situation clearly complicates the case because each twin can claim that his co-twin was responsible for the robbery. However, police investigators are now wondering if both twins were involved since the possibility of four suspects has been raised.

The article stated that German policies do not allow for the most advanced tests that would enable discrimination of the MZ co-twins. Recent work has demonstrated the presence of epigenetic differences between MZ co-twins, as well as greater epigenetic differences between MZ than DZ co-twins (Kaminsky et al., 2009). However, tests that would allow the correct twin culprit to be identified (if only one were involved) are not available.

Twins Born Together and Apart

Newborn twins from Rochester, Michigan recently arrived on different days, month and years. Tariq Griffin was born on January 1, 2009 at 12:17 am, 26 minutes after his twin brother,

Tarrance, who was born on December 31, 2008 (*Honolulu Star Bulletin*, 2009). This event recalled a pair of DZA female twins who participated in the Minnesota Study of Twins Reared Apart. The twins were born on different days and in different months, complicating their search for one another and delaying their reunion for some time. Note: I was born on the same day as my twin sister, just 7 minutes earlier. However, now that we live on opposite coasts our birth orders have 'reversed' because she celebrates her birthday 3 hours earlier.

Twinning Rates in Candido Godoi

The name Josef Mengele is synonymous with evil. Mengele was the infamous Auschwitz physician who performed brutal medical experiments on twins, dwarves and individuals with genetic anomalies (Segal, 1985; 1992). He inflicted unimaginable pain and suffering on many men, women and children. The experiments had no scientific merit, as determined by an interdisciplinary panel in 1985, in Jerusalem, at the conclusion of a public hearing on Mengele's war crimes. This event coincided with the 40th anniversary of the liberation of Auschwitz.

Mengele's name surfaced recently in connection with the extraordinarily high twinning rate in Candido Godoi, a small Brazilian farming town (Barrionuevo, 2009). A survey identified thirty-eight sets of naturally conceived twins, born to eighty families residing in a one and a half square mile area. A recent book by Jorge Camarasa (2008) (not reviewed by this author; it is published in Spanish) indicates that Mengele visited this region in the early 1960s. He fled Germany at the end of World War II to avoid capture for his horrific concentration camp activities (Evans, 2009). It has been suggested that Mengele conducted experiments that resulted in the town's high twinning rate. This idea is supported by a local doctor who believes that the citizens (many of German descent) are withholding information. Others disagree, claiming that the explanation for the elevated twinning rate remains unknown.

Any link between Mengele and the high twinning rate in Candido Godoi is untenable for a number of reasons. According to reporter Barrionuevo, no one can prove for certain that Mengele conducted the alleged twinning experiments. Furthermore, the high twinning rate was widely noticed in the early 1990s, well past Mengele's death in 1979. There is no known mechanism by which he, or anyone, could produce an effect on the twinning rate years beyond his death. The claim that Sao Pedro, an area of Candido Godoi, has the highest twinning rate in the world has not been confirmed. Finally, why would Mengele do anything to attract attention if he were on the run? Paulo Sauthier, a historian who runs a

museum there, regretted any association between Mengele and the people of the town.

Note

The article by Barrionuevo wrongly dismissed genetic factors as possibly responsible for the town's twinning rate. It stated that 'a genetic predisposition to twins would be more likely if most of the twin pairs were identical'. Just the opposite is true.

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