



TEXAS

Department of State Health Services
 Birth Defects Epidemiology and Surveillance

BIRTH DEFECT RISK FACTOR SERIES: TRIPLOIDY

DEFINITION

A normal human conceptus possessed 46 chromosomes: 23 derived from the mother and 23 from the father. Triploidy is a chromosomal abnormality where three complete sets of the haploid genome instead of the normal two sets are present within the conceptus. A triploid conceptus will possess 69 chromosomes. The most common triploid karyotypes and their distribution are presented in table 1. The low frequency of 69,XY suggests that either the process by which this karyotype occurs is uncommon or the karyotype has lower survivability than the other karyotypes. Triploidy may occur with aneuploidies, resulting in complex karyotypes (e.g., karyotype 70,XXY,+21). Triploidy may also be found with mosaicism, where some of the cells in the body have a triploid chromosome complement and other cells in the body have a different chromosome complement, either normal diploid (e.g., karyotype 69,XXY/46,XX) or abnormal (e.g., karyotype 69,XXY/70,XXY,+21). Generally, triploidy is incompatible with life, and is associated with miscarriage and hydatidiform moles (Balakier 2002).

Table 1. Distribution of triploidy cases represented by karyotype* in several studies

Study	69,XX X	69,XX Y	69,XY Y
Daniel 2001	42%	58%	0%
McFadden 2000	49%	49%	2%
Miny 1995	41%	59%	0%
Neuber 1993	41%	57%	2%
Ohno 1991	37%	63%	0%
Uchida 1985	43%	55%	2%
Jacobs 1982	31%	68%	1%
Niebuhr 1974	36%	60%	3%

*Includes mosaicisms and variations where another form of aneuploidy occurs along with the triploidy

ETIOLOGY

Triplody can occur in up to 2% of conceptuses; it is a common factor in first trimester spontaneous abortions (Brancati 2003). It can be recurrent, and maternally derived cases appear to live longer than paternally derived cases (Brancati 2003). Cases with diploid/triploid mosaicism also appear to have a longer survival time than triploidy cases (Forrester 2003). There are three different mechanisms that may produce triploidy:

- 1) nondisjunction in meiosis I or meiosis II of spermatogenesis (sperm formation), resulting in an extra set of paternal chromosomes (diandry)
- 2) nondisjunction in meiosis I or meiosis II of oogenesis (egg formation), resulting in an extra set of maternal chromosomes (digyny)
- 3) double fertilization of a normal egg, resulting in an extra set of paternal chromosomes (dispermy)

One investigation as reported that the "three relevant reproductive processes—meiosis and gametogenesis, fertilization, and early embryonic development are 'remarkably imprecise'" (Hassold 1986, in Golubovsky 2003). As recent developments in reproductive science have unfolded, these mechanisms have been explored, and new information has been gathered.

It has been reported that mechanism 1 accounted for 23.6% of triploidy cases, mechanism 2 for 10%, and mechanism 3 for 66.4% (Jacobs 1978). As shown in table 2, a number of studies, particularly older studies, found that the majority of triploidy cases were of paternal origin (Daniel 2001, Redline 1998, Uchida 1985, Jacobs 1982, Jacobs 1978, Kajii 1977) while more recent studies found the majority of triploidy cases to be of maternal origin (Baumer 2000, McFadden 2000, McFadden 1993). Paternal origin for triploidy is higher at certain gestational ages while maternal origin for triploidy is higher at other gestational ages (McFadden 2000, Zaragoza 2000). Thus the wide variation in parental origin between the various studies may be due to the studies using cases derived from different stages of fetal death.

Most cases of triploidy due to paternal origin result from dispermy (Baumer 2000, Zaragoza 2000, Kajii 1977). Several studies have reported that the majority (62-77%) of cases of triploidy of maternal origin result from nondisjunction in meiosis II (McFadden 2000, Zaragoza 2000, Jacobs 1982), although another investigation found the nondisjunction to be evenly distributed between meiosis I and meiosis II (Baumer 2000).

Maternal age has not been found to be associated with any of the three mechanisms by which triploidy occurs (Baumer 2000). One investigation observed that the XXX/XXY ratio changes from 1:2 to 2:1 and proportion of hydatidiform moles (triploidy of paternal origin) decreases with increasing maternal age, indicating that digyny is more important for older women and diandry more important for younger women (Neuber 1993).

One study identified no association between parental origin of the triploidy and phenotype (Kajii 1977). However, more recent studies reported paternal origin but not maternal origin to be associated with the hydatidiform mole phenotype of triploidy, although parental origin does not always result in hydatidiform mole (Zaragoza 2000, Redline 1998). Triploidy of maternal origin has also been associated with giant oocytes (Plachot 2003, Balakier 2002).

Table 2. Parental origin of the extra set of chromosomes in triploidy reported by various studies

Study	Maternal origin (%)	Paternal origin (%)
Daniel 2001	39%	61%
Baumer 2000	80%	20%
McFadden 2000	63%	37%
Redline 1998	34%	66%
Miny 1995	71%	29%
McFadden 1993	75%	25%
Uchida 1985	36%	64%
Jacobs 1982	33%	77%
Jacobs 1978	15%	85%
Kajii 1977	13%	88%

PHENOTYPE

There is wide variation in the clinical features associated with triploidy, ranging from a normal phenotype to multiple major birth defects. Cases of triploidy are grouped into two fetal and placental phenotypes that roughly correspond to the parental origin of the extra set of chromosomes (McFadden 1991):

Type I: well formed fetus with a normal or microcephalic head and a large placenta with cystic changes - associated with diandry

Type II: fetus with growth restriction and a large head and a small, noncystic placenta - associated with digyny

The professional literature has described the birth defects and other abnormalities associated with triploidy (Phillipp 2004, Sergi 2000, Doshi 1983, Wertenlecki 1976). These anomalies include fetal growth restriction, partial hydatidiform mole (the placenta and fetus are partially comprised of vesicular villous structures resembling grapes), macrocephaly, hydrocephaly, holoprosencephaly, micrognathia, microphthalmia, bulbous nose, small mouth, malformed and low set ears, coloboma of the eye, cataracts, cleft lip and/or palate, syndactyly of the third and fourth digits of the hands or feet, simian crease of the hand, rocker bottom feet, ventricular septal defects, atrial septal defects, pulmonary hypoplasia, diaphragmatic hernia, intestinal malrotation, cystic kidney, adrenal hypoplasia, ovarian hypoplasia, and abnormal male genitalia (hypospadias, micropenis, undescended testicles). Neural tube defects may be found in 25% and abdominal wall defects in 10-18% of triploidy cases. Cases with diploid/triploid mosaicism tend to have a milder phenotype than completely triploid cases, but usually suffer from mental retardation (Daniel 2003, Tantravahi 1986).

PRENATAL DIAGNOSIS

Triploidy may be prenatally diagnosed through cytogenetic analysis of cells obtained through such procedures as amniocentesis and chorionic villus sampling (Nagaishi 2004). Fetal nuchal translucency in the first trimester is frequently increased for fetuses with triploidy (Yaron 2004, Spencer 2000, Jauniaux 1997, Pandya 1995). Triploidy has been associated with elevated maternal serum alpha fetoprotein (AFP) and total and beta-human chorionic gonadotropin (hCG) levels and low maternal serum pregnancy-assisted plasma protein-A (PAPP-A) levels in the first trimester (Yaron 2004, Spencer 2000, Jauniaux 1997). However, first-trimester nuchal translucency and maternal serum screening is not routinely performed in the United States. Triploidy has been associated with two distinct patterns of maternal serum AFP, hCG, and estriol levels in the second trimester (Benn 2000, Schmidt 1994, Canick 1993, Fejgin 1992, Mason 1992, Oyer 1992, Kohn 1991, Freeman 1989, Pircon 1989a, O'Brien 1988):

- 1) elevated AFP, elevated hCG, and low or normal estriol
- 2) low or normal AFP, low hCG, and low estriol

Second-trimester amniotic fluid AFP has been reported to be normal in the presence of triploidy except when there is also an open neural tube present (Freeman 1989). (See table 3 for a review of maternal serum marker levels and nuchal translucency in relation to triploidy.) However, second-trimester maternal serum screening in the United States does not systematically screen for triploidy. Moreover, one investigation found that the proportion of triploidy cases in a population at increased risk of Down syndrome as a result of maternal serum screening was not greater than expected for the general population (Ryall 2001). And fetuses with triploidy typically do not have a consistent pattern of abnormalities on prenatal ultrasound (Pircon 1989b). Thus cases of triploidy will frequently be prenatally diagnosed incidentally as a result of cytogenetic analysis for other reasons such as advanced maternal age.

Table 3. Maternal serum marker and nuchal translucency levels in pregnancies with triploidy

Trimester	AFP	total hCG	uE3	beta-hCG	PAPP-A	NT
First	high	High	-	High	low	high
Second	high	High	low/normal			
Third	low/normal	Low	low			

AFP - alpha-fetoprotein

hCG - human chorionic gonadotropin

uE3 - estriol

PAPP-A - pregnancy-assisted plasma protein-A

NT - nuchal translucency

PREVALENCE AND PREGNANCY OUTCOME

Triploidy has been estimated to occur in 1-2% of all clinically recognized conceptions (Forrester 2003, Jacobs 1978). However, the majority of triploid conceptuses do not survive to term. It has been assessed that only one-third of triploidy conceptuses survive past 15 weeks gestation (Warburton 1994) and that for every triploidy conceptus that survives to term, approximately 1200 conceptuses result in fetal death (Doshi 1983). Triploidy has been reported in 1-13% of spontaneous abortions that were studied (Redline 1998, Ford 1996, Kalousek 1993, Neuber 1993, Ohno 1991, Shepard 1989). Triploidy is found in 8/10,000 chorionic villus samplings (Association of Clinical Cytogeneticists Working Party on Chorionic Villi in Prenatal Diagnosis 1994) and 4/10,000 amniocenteses (Horger 2001). The live birth

rate for triploidy is 1/10,000 live births (Stoll 2001, Jacobs 1982, Jacobs 1974). As a result of prenatal diagnosis, a portion of triploidy fetuses will be electively terminated. An investigation in Europe reported an elective termination rate of 82% for triploidy (De Vigan 2001). One study reported 100% of fetuses prenatally diagnosed with triploidy were electively terminated (Horger 2001).

MORTALITY/SURVIVAL

Triploidy is lethal, with no survivors reported beyond 10.5 months of age (Forrester 2003, Sherard 1986). Postnatal survivors usually have the type II phenotype with the extra chromosomes of maternal origin (Hasegawa 1999, Graham 1989). Infants with triploid/triploid mosaicism will have longer survival than infants with true triploidy (Tantravahi 1986).

SEX

The sex ratio of triploidy is linked to the distribution of sex chromosomes (table 1). Males account for 51-69% of triploidy cases (McFadden 2000, Miny 1995, Neuber 1993, Ohno 1991, Uchida 1985, Jacobs 1982).

PARENTAL AGE

Neither maternal nor paternal age has been associated with triploidy risk (Ford 1996, Rochon 1990, Uchida 1985, Niebuhr 1974). However, as outlined in the Etiology section, maternal age does appear to be related to the type of triploidy (Neuber 1993).

DIABETES

One investigation found no association between maternal gestational diabetes and triploidy (Moore 2002).

OTHER

Animal studies have identified increased risk of triploidy with colchicine (an alkaloid used to treat gout), hypoxia, and heat shock (Niebuhr 1974). One study reported that 50% of mothers of triploidy conceptuses had preconceptional abdominal radiation exposure (Uchida 1985). Triploidy has also been potentially linked to delayed fertilization resulting from prolonged menstrual cycles or the cessation of oral contraceptives (Niebuhr 1974). Triploidy has been reported in conceptuses resulting from in vitro fertilization (Angell 1986, Ulmer 1985) and in conceptuses of women who have recurrent miscarriages (Carp 2001).

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Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*