A COMPREHENSIVE EXAMINATION OF HUMAN TRIPLOIDY AND DIPLOID/TRIPLOID MIXOPLOIDY

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Jason Christopher Carson

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This thesis was presented

by

Jason Christopher Carson

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and approved by

Thesis Advisor:
Urvashi Surti Ph.D
Associate Professor
Pathology
School of Medicine
University of Pittsburgh

Committee Member:
Eleanor Feingold Ph.D.
Associate Professor
Human Genetics
Graduate School of Public Health
University of Pittsburgh

Committee Member:
Susanne M. Gollin Ph.D.
Professor
Human Genetics
Graduate School of Public Health
University of Pittsburgh

Urvashi Surti, Ph.D.

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Jason C. Carson, MS

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Triploidy is the presence of 69 chromosomes instead of the normal diploid number of 46 and can occur in a complete form or in a mixoploid state in which there are populations of diploid and triploid cells in the same individual. The extra haploid set can be of paternal or maternal origin. Triploidy is one of the most common chromosome aberrations seen in 1-2% of all recognized pregnancies and can lead to partial mole which can in turn lead to serious complications for the mother and fetus. Given the high incidence of chromosome abnormalities including triploidy and its impact on individuals with chromosomally abnormal pregnancies, a greater understanding of their etiology has a potential to contribute greatly to public health by enhancing the management and possible future prevention. Though complete triploidy is not compatible with postnatal survival, mixoploid individuals are capable of surviving into adulthood. Both syndromes have a broad phenotypic spectrum though it is generally less severe in mixoploids. Though much has been learned in the nearly half century since the first case report of diploid/triploid mixoploidy was published, many questions still remain. A major issue is a large between study difference in the ratio of diandric to digynic triploidy and the prevalence of partial hydatidiform mole. Additionally, there is a clear parent-of-origin effect on fetal and placental morphology as well as developmental age that is believed to be related to genomic imprinting. The goals of this paper include summarizing the current body of knowledge on triploidy and diploid/triploid mixoploidy, examining the remaining questions, and a side-by-side comparison of the two syndromes. An exhaustive literature search was undertaken which produced many case reports of triploidy and diploid/triploid mixoploidy as well as studies on the mechanisms leading to triploidy, phenotypic

characteristics, and the characteristics of triploid cells. It appears that the complex pattern surrounding parental origin of the extra haploid set of chromosomes may have contributed to between study ascertainment bias. More complex studies with careful attention to detail must be undertaken to fully understand the etiology and pathophysiology of triploidy

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PREFACE

I would first like to thank my thesis advisory committee, Dr. Urvashi Surti, Dr. Eleanor Feingold, and Dr. Susanne Gollin, for their expert advice and guidance. Additionally, Lori Hoffner was also a great source of advice as my unofficial fourth committee member. I would also like to thank my mom for always being there for me and encouraging me. I would also like to thank my professors at Allegheny College for providing me with an excellent undergraduate education that has proven invaluable in my pursuit of this degree. Finally, I would like to thank my pediatric otologist, Dr. Charles Bluestone, and my pediatric ophthalmologist, Dr. Albert Biglan, for encouraging me to continue to learn all I could about my physiological shortcomings. You have all played a very important role in my life and education and for that, I am eternally grateful. I would also like to dedicate this paper to my dad who I thought of every time I lost my patience with Microsoft Office.

1.0 INTRODUCTION

Triploidy is defined as the presence of an extra haploid set of chromosomes for a total of 69 rather than the normal diploid number of 46 chromosomes. It is believed that 1% of all fertilized eggs are triploid and that triploidy is present in 1-3% of all recognized pregnancies (ROSENBUSCH 2008; ZARAGOZA *et al.* 2000). Triploidy is also present in 99% of molar pregnancies than include an embryo or fetus (MALAN *et al.* 2006). Triploidy is one of the three most common causes of pregnancy loss along with trisomy 16 and monosomy X, though its extremely high occurrence rate is often overlooked (EGOZCUE *et al.* 2002; ROSENBUSCH *et al.* 2002).

It is believed that 98-99% of all triploid conceptuses end in spontaneous abortions (PHILIPP *et al.* 2004). Triploidy is estimated to account for anywhere from 4.5% to more than 10% of all spontaneous abortions and miscarriages as well as accounting for 5% of those that are karyotyped (DEVRIENDT 2005; NIEBUHR *et al.* 1972; ROYSTON and BANNIGAN 1987; ZARAGOZA *et al.* 2000). It is the most common chromosomal aberration seen among first trimester abortuses, accounting for 15-30% of such cases (BRANCATI *et al.* 2003; PETTENATI *et al.* 1986; TUERLINGS *et al.* 1993). Among all spontaneous abortions, triploidy is thought to account for 10-21% of those found to have cytogenetic abnormalities (BETTS *et al.* 1989).

Triploidy is estimated to occur in 1 out of every 50-56,000 term births (GALAN *et al.* 1991; MARASCHIO *et al.* 1984). Long intrauterine survival is extremely rare for triploid conceptuses with only 0.08% of such pregnancies believed to reach term (FORRESTER and MERZ 2003). Various studies have indicated that triploidy may account for 0.6% of all stillbirths and 0.002% of all livebirths, though among triploids only 1-2% are either stillborn or liveborn (ZARAGOZA *et al.* 2000). It has been estimated that

approximately 1 in 10-20,000 triploid conceptuses result in livebirth (NIEBUHR 1974; ROSENBUSCH *et al.* 2002).

The vast majority of triploid conceptuses likely fail before implantation, with only 10-13% of cultured triploid zygotes reaching the blastocyst stage (GOLUBOVSKY 2003; MALAN *et al.* 2006). Indeed, triploidy is believed to be one of the most common fertilization errors responsible for early embryonic failure at the cleavage or implantation stage. The early development of triploids often tends to fall behind that of normal diploid embryos, with developmental arrest being quite common and occurring around 5.1 weeks gestation on average (NIEBUHR 1974). Genotype as well as the presence or absence of a discernable embryo also appears to play a role in the developmental potential of triploid conceptuses. In the absence of an embryo, 69,XXX and 69,XXY conceptuses usually arrest at 3-4 weeks as opposed to nine weeks when an embryo is present. On the other hand, 69,XYY conceptuses almost never proceed beyond four weeks of development. Development beyond 10 weeks of gestation is considered unusual in non-mosaic fetuses with most pure triploid conceptuses thought to die between three and six weeks of gestation (BLACKBURN *et al.* 1982; GIURGEA *et al.* 2006). A recent study found eight triploid conceptuses among 12,322 patients undergoing routine first trimester screening from 10-14 weeks gestations suggesting that the prevalence of triploidy may be as high as one in 1540 during this period (YARON *et al.* 2004)

It is very rare for triploid conceptuses to reach the fetal period. The prevalence of triploidy is thought to be 1 in 3,500 at 12 weeks of gestation but declines to 1 in 300,000 by 16 weeks (DALMIA *et al.* 2005). It is thought to account for 0.03% of 10-14 week fetuses and 0.002% of 16-20 week fetuses (BARKEN *et al.* 2008). The vast majority of triploid conceptuses spontaneously abort at 10-20 weeks with most of these being diandric in origin (ZARAGOZA *et al.* 2000). Those rare triploid fetuses that survive beyond 20 weeks of gestation usually result in stillbirths (GIURGEA *et al.* 2006).

The majority of human triploids are thought to be diandric in origin since dispermy is relatively common with digynic triploidy arising from errors in oogenesis being much rarer (MIGEON *et al.* 2008). It is estimated that 73-85% of triploids are diandric, with the remaining 15-27% being digynic in origin

(DOSHI *et al.* 1983; TUERLINGS *et al.* 1993). Assuming that all male and female gametes have an equal chance at contributing to the formation of a triploid conceptus, one would expect to observe an XXX(33%) : XXY(50%) : XYY(17%) genotype distribution (PIETERS *et al.* 1992). However, the actual observed frequencies for all triploids at all gestational ages are more along the lines of XXX(37%) : XXY(60%) : XYY(3%) (FORRESTER and MERZ 2003). Based on an assumption that the 69,XYY genotype has no more of an adverse effect on viability than 69,XXX or 69,XXY and that most triploids are of diandric origin, the observed genotype distributions do not appear to fit well with expected values (MCFADDEN and LANGLOIS 2000). That is, one would expect values to be somewhat closer to the 1:2:1 ratio predicted for all diandric triploids. However, assuming that 80% of triploids are of digynic origin yields a ratio of XXX(4) : XXY(5) : XYY(1), a value much closer to the actual observed values. Of course, this does not take into account that 69,XYY triploids do in fact appear to be at a severe disadvantage in terms of viability.

A number of studies have noted the genotype distributions in populations of triploid conceptuses. As shown in table 1, the XXX : XXY : XYY distribution in nearly 1400 cases of triploidy covering several studies appears to approximate the 4:5:1 distribution suggested by McFadden and Langlois (2000) which assumes 80% of triploids are of digynic origin. It should however be noted that the total number of triploids from these studies does not represent any particular gestational age, but more closely reflects the population of triploid gestations as a whole. It is also worthwhile to note that of the 48 XYY triploids, 36 were in a group of triploids ascertained through preimplantation genetic diagnosis in a study by McWeeney et al. (2009). The ratio among this group of triploids was XXX(189) : XXY(188) : XYY(36). This group is also unique in having an equal proportion of XXX and XXY triploids. This phenomenon could potentially be explained by a high proportion of XXX digynic triploids in this group that would have aborted very early thus avoiding detection in other studies which only ascertained triploids through spontaneous abortion or prenatal cytogenetic testing in later stages of gestation. The remaining XYY triploid from this study was a first trimester spontaneous abortion.

Table 1. Genotype distribution of triploidy in selected studies

Study	Major study population	XXX	XXY	XYY
Szulman et al., 1981	SA, 7-27 weeks	15	39	1
Jacobs et al., 1982	SA, 5-29 weeks	33	70	1
Proctor et al., 1984	SA, 7-21 weeks	4	7	0
Uchida & Freeman, 1985	Early SA, SB, LB	44	57	2
McFadden & Kalousek, 1991	Fetal 3n, ≥ 10 weeks	9	5	0
Warburton et al., 1991	SA, 7-17 weeks	84	99	2
Miny et al., 1995	GA 9-33 weeks	7	10	0
Staessen & Van Steirteghem, 1997*	IVF/ICSI fertilized zygotes	43	48	5
Baumer et al., 2000	SA, LB, 8-37 weeks	20	11	0
McFadden & Langlois, 2000	<10-34 weeks	36	42	1
Zaragoza et al., 2000	SA 5-19 weeks	36	53	3
Forrester & Merz, 2003	All karyotyped births	15	22	1
McFadden & Robinson, 2006	SA 8-18 weeks	12	15	0
McWeeney et al., 2009	PGD through 3rd trimester	264	235	37
	Totals	**622**	**713**	**53**
	Percentage of 1388 Total Cases	44.81%	51.37%	3.82%

* = Also includes triploid mosaics, ICSI = Intracytoplasmic sperm injection, IVF = *in* vitro fertilization, LB = Live Birth, PGD = Preimplantation Genetic Diagnosis, SA = Spontaneous Abortion

Since X and Y bearing sperm have an equal likelihood of fertilizing an oocyte, the expected genotype frequencies for digynic triploidy are a straightforward XXX(1) : XXY(1). The expected genotype ratios for diandric triploidy are XXX(1) : XXY(2) : XYY(1) (MIGEON *et al.* 2008). However, the predicted large number of 69,XYY triploids is not observed. Rather, the actual observed genotype frequencies for diandric triploidy are approximately 69,XXX(27%) : 69,XXY(70%) : 69,XYY(3%) (GENEST *et al.* 2002). Table 2 summarizes the genotype distributions of triploids according to parental origin from a number of studies conducted over the past 30 years. An additional note regarding the study of Jacobs et al. (1982) is that these authors reported a single case of 69,XYY triploidy however were not able to definitively determine the parental origin in this case. For this reason, the authors did not include this case of 69,XYY triploidy among their results. However, since it can be fairly safely assumed that all 69,XYY triploids are of diandric origin, this case was included as a diandric triploid for the purpose of

this paper. As can be seen in table 2, the ratio of XXX to XXY digynic triploids is fairly close to the expected 1:1 ratio. Among diandric triploids, the ratio of XXX to XXY is also fairly close to the expected 1:2 ratio for these two genotypes, however the number of XYY diandric triploids is far less than the number of XXX diandric triploids.

Table 2. Genotype distributions of triploidy according to parental origin in selected studies

Study	**Major Study Population**	**Total Cases***	**Diandric**				**Digynic**		
			XXX	**XXY**	**XYY**	**Total**	**XXX**	**XXY**	**Total**
Jacobs et al., 1982	SA 5-29 weeks	79	15	42	1	58	9	12	21
Procter et al., 1984	SA, 7-21 weeks	6	2	4	0	6	0	0	0
Uchida et al., 1985	Early SA, SB, LB	68	15	27	2	44	14	10	24
Miny et al., 1995	GA 9-33 weeks	17	1	4	0	5	6	6	12
Baumer et al., 2000	SA, LB, 8-37 weeks	25	1	4	0	5	13	7	20
McFadden & Langlois, 2000	GA <10-34 weeks	38	5	8	1	14	14	10	24
Zaragoza et al., 2000	SA 5-19 weeks	87	21	36	3	60	12	15	27
McFadden & Robinson, 2006	SA 8-18 weeks	27	3	5	0	8	9	10	19
	Totals	**347**	**63**	**130**	**7**	**200**	**77**	**70**	**147**
	Percentage of Total				**XXX = 31.50% XXY = 65.00% XYY = 3.50%**			**XXX = 52.38% XXY = 47.62%**	
*** = Reflects only cases where parental origin was successfully determined, GA = gestational age, LB = live births, SA = spontaneous abortion**									

It has been suggested that a large number of 69,XYY conceptuses may be created but that they don't survive past implantation. Some support for this hypothesis comes from a study by Staessen and Van Steirteghem (1997) in which they examined the genotypes of tripronuclear zygotes following in vitro fertilization. These authors obtained a ratio of XXX(9) : XXY(10) : XYY(5). Though they suggested these values were not significantly different from the expected 1:2:1 ratio, there appears to be a significant difference. Another survey found 8.7% of triploids ascertained by preimplantation genetic diagnosis had a 69,XYY karyotype, but this value fell to 0.7% of triploid pregnancies ascertained during the first trimester (MCWEENEY *et al.* 2009). This survey did not identify any 69,XYY triploids beyond

the first trimester. These authors suggested that an imbalance between maternally and paternally derived chromosomes or between X chromosomes and autosomes may be responsible for this reduced viability. Also, in vitro studies have supported the theory that 69,XYY cells have a reduced viability when compared to 69,XXY or 69,XXX cells (NIEBUHR 1974).

The predicted proportions of diandric versus digynic triploidy have changed over the past few decades. Up through the 1980's it was largely accepted that the majority of triploids were diandric in origin and that the majority of these also exhibited a partial hydatidiform molar phenotype (ZARAGOZA *et al.* 2000). However, later reports indicated that only 15% of triploids were partial moles, a drastic change from earlier figures based on cytogenetic analysis. Ascertainment bias may have played a role in possibly overestimating the proportion of triploids complicated by partial mole. It has been noted that earlier studies of placental pathology in triploidy often analyzed cases culled from larger studies of only molar gestation thereby increasing the detection of PHM in conjunction with triploidy (MCFADDEN and PANTZAR 1996). It is now accepted that even though partial mole is almost always associated with diandric triploidy, triploidy is not necessarily associated with partial mole. These findings of a much lower than previously thought frequency of PHM in conjunction with triploidy also seem to lend support to more recent molecular evidence that digyny rather than diandry is the more prevalent mechanism leading to the creation of triploid conceptuses (MCFADDEN and PANTZAR 1996).

Early cytogenetic studies seemed to indicate a clear preponderance of diandry as the origin of most triploid conceptuses. In a study using Q- and C-banding techniques to identify cytogenetic polymorphisms in triploid conceptuses and their parents, Jacobs et al. (1978) determined that 66.4% of all triploids resulted from dispermy with an additional 23.6% from diplospermy and only 10% of digynic origin. The first indication that this may not be the case came from a 1993 DNA polymorphism study which determined that 6/8 triploids where the parental origin was determined were of digynic origin (MCFADDEN *et al.* 1993). This result was later supported by several additional molecular polymorphism studies. A 1994 study using random highly polymorphic loci determined that 6/6 triploid fetuses progressing into the third trimester were of digynic origin (DIETZSCH *et al.* 1995). Another study using

variable number of tandem repeat (VNTR) analysis determined digynic origin in 7/12 cases with the remainder being diandric (MINY *et al.* 1995).

This paper has several goals and objectives. It will begin with a more detailed examination of historical studies that attempted to elucidate the parental origins of triploidy as well as the prevalence of the partial hydatidiform mole (PHM). This section will also include an examination of the sources of bias and error and how this may explain the vastly different results obtained in more recent molecular studies compared to those obtained in older cytogenetic studies. Next is a discussion of the pronuclear stage of the fertilized zygote and the first cleavage division and what role these events may play in the creation of triploid embryos. This will be followed by a more detailed discussion of the mechanisms, both theoretical and observed, that may lead to complete triploidy or diploid/triploid mixoploidy. Next is a discussion of the overall characteristics of triploid cells and how they behave *in vivo* and *in vitro*. This section includes a discussion on X-inactivation patterns as well as tissue specificity in diploid/triploid mixoploid individuals. The general phenotypic trends of complete triploidy will then be examined followed by a comparison with the phenotype of diploid triploid mixoploidy. Finally, this paper aims to look at the complex relationships surrounding the parental origin of the extra haploid set of chromosomes in triploidy. The final section of this paper is devoted to a literature review of all published cases of diploid/triploid mixoploidy as well as a sampling of cases of complete triploidy. This review will first examine the genotype and parent-of-origin distributions. An examination of the different methods used to ascertain the parental origin will follow this section. Finally, a comparison of the phenotypic traits by parental origin as well as between complete triploidy and 2n/3n mixoploidy will be undertaken.

2.0 THE PREVALENCE OF DIGYNY, DIANDRY, AND PARTIAL HYDATIDIFORM MOLE

2.1 EARLY CYTOGENETIC STUDIES: DIANDRY AND PHM PREDOMINATE

The first major cytogenetic study to investigate the parental origins of triploidy was published in 1978 and later expanded upon in 1982 (JACOBS *et al.* 1978; JACOBS *et al.* 1982b). These authors were able to successfully determine the parental origin of 78 triploid spontaneous abortions (SA) by analyzing Q- and C-band heteromorphisms on fetal and parental bloods. Their results indicated that 57 triploids were of diandric origin while 21 were digynic accounting for 73% and 27% respectively. Furthermore, through the use of statistical methods, the authors were able to determine the probable meiotic error that lead to the creation of a triploid conceptus. Among the diandric triploids, 41 were believed to have resulted from dispermy while the remainder was believed to have been the result of diplospermy I or dispermy. Among the digynic triploids, eight were felt likely to have arisen from a maternal meiosis I error while the remaining 13 were felt likely the result of a maternal meiosis II error (JACOBS *et al.* 1982b).

A later study using cytogenetics to determine the parental origin of a large number of triploid early SA found fairly similar results with 52 cases being diandric and 29 being digynic (UCHIDA and FREEMAN 1985). These authors also determined that 33 of the diandric cases resulted from dispermy with the remaining 19 resulting from diplospermy while 20 of the 29 digynic cases were the result of a maternal meiosis II error. These two studies were the only large scale cytogenetic surveys of triploidy and were fairly similar except that while Uchida and Freeman (1985) surveyed only early abortions, Jacobs et al. (1982) surveyed all spontaneous abortions in their study. Additionally, Uchida and Freeman

also included twelve stillbirths and livebirths in their study populations, though gestational ages were not provided for any specimens.

Additionally, at least two smaller scale cytogenetic studies have been published. Proctor et al. (1984) found twelve cases of triploidy among 164 spontaneous abortions examined over a 2 ½ year period. Among these 12 cases, the parental origin was able to be determined in six. All were found to have arisen through dispermy (PROCTER *et al.* 1984). One of the last cytogenetic studies was also arguably one of the most pivotal as it was the first such study to describe the phenotypic differences between diandric and digynic triploids (MCFADDEN and KALOUSEK 1991). Their description of diandric triploids being characterized by a well-grown, proportionate fetus with a large cystic placenta and of digynic triploids being characterized by severe asymmetric intrauterine growth retardation, relative macrocephaly and a small non-cystic placenta has since become the gold standard for ascertaining parental origin based on phenotype alone. Based on these findings, the authors divided triploidy into two syndromes. The diandric triploidy phenotype was termed type I triploidy while the digynic triploidy phenotype was termed type II triploidy. The authors also performed cytogenetic analysis on one type I fetus and two type II fetuses to determine parental origin and determined that the type I fetus was diandric and that one of the type II fetuses was digynic with the remaining type II fetus being uninformative.

Szulman et al. (1981) carried out a histological survey of 92 cytogenetically confirmed cases of triploidy in an attempt to determine the frequency of partial hydatidiform mole. They determined that 79 specimens were partial moles and that these moles virtually always aborted in the second trimester with a mean gestational age of 16.9 weeks. Among the 13 nonmolar triploids, virtually all aborted during the first trimester with six aborting before 10 weeks (SZULMAN *et al.* 1981). However, this study did not attempt to identify the parental origins of these triploid moles. A second study that cytogenetically examined all cases of histologically confirmed molar pregnancy found that 75/80 cases were triploid, but again did not examine the parental origin of these molar pregnancies (JACOBS *et al.* 1982a). However, these two studies cemented the assumption that greater than 80% of triploids were partial moles.

Further support for this theory came from a second study by the same group which showed that all diandric triploids with sufficient tissue to establish a histological diagnosis were partial moles (JACOBS *et al.* 1982b). In their examination of 12 cytogenetically confirmed cases of triploidy, Procter et al. (1984) determined that 8/10 triploid placentas with sufficient material for histological examination were partial moles. However, this included only two of the six cases confirmed to have been diandric in origin. Uchida and Freeman (1985) reported that only 19/52 diandric triploids were partial moles, however these authors did not specify what proportion of these 52 cases had sufficient placental material to establish the diagnosis. It can be said that the prevalence of partial mole in these earlier studies was based more on ascertainment than technology. That is, these cases were identified mainly through the use of gross and/or microscopic examination in the absence of more modern methods in use today.

2.2 LATER MOLECULAR STUDIES: DIGYNY IS MORE COMMON, PHM IS LESS COMMON

As molecular genetics techniques began to emerge in the early 1990's, the results of early cytogenetic studies began to come into question. Even the study by McFadden and Kalousek (1991), though still a cytogenetic study, found that the type II digynic triploid phenotype was far more common among their sample. A 1995 molecular polymorphism study found 12 digynic triploids but only five diandric cases (MINY *et al.* 1995). A later microsatellite polymorphism study also found only five diandric triploids, all arising from dispermy, while finding 20 digynic triploids (BAUMER *et al.* 2000). These authors also reported an equal frequency of maternal meiosis I and meiosis II errors as the origin for digyny, but noted that a high rate of pericentromeric crossovers during oogenesis may have lead to some misinterpretation of results.

The first molecular study to show digynic triploidy to be more common was published in 1993 though these results were expanded upon in a later publication (MCFADDEN *et al.* 1993; MCFADDEN and LANGLOIS 2000). This study used molecular polymorphisms to determine that 11/14 cases with fetal

development and ranging from 11 to 34 weeks gestational age were of digynic origin. Among the non-fetal group which included conceptuses of less than 10 weeks gestational age as well as those of greater than 10 weeks but lacking a discernable embryo or fetus, the authors found 11 diandric and 13 digynic triploids. Among the digynic triploids, they found that 18 arose from maternal meiosis II error while only six arose from maternal meiosis I error. A later study by the same group reported eight diandric triploids and 19 digynic triploids, with 10 in the latter group arising from maternal meiosis II error, among their study population of triploid embryos with gestational ages ranging from 8-18 weeks (MCFADDEN and ROBINSON 2006).

Most published molecular studies on the origins of triploidy have been based on fairly small samples. The largest molecular study on the origins of triploidy was also the only such study that agreed with the earlier cytogenetic studies with respect to the prevalence of diandric versus digynic triploidy. This study reported that 60 triploids were of diandric origin and 27 were of digynic origin (ZARAGOZA *et al.* 2000). Of the diandric cases, 27 were thought to have arisen from dispermy, four from diplospermy I and two from diplospermy II. Meiosis II error was the most common mechanism leading to digynic triploidy accounting for 14 of the 20 cases where it could be determined.

For the most part, these molecular studies found that partial mole was not as common a feature of triploidy as previously reported. Miny et al. (2000) reported that five of their 17 triploids were partial moles and that four of the five diandric triploids were PHM. Interestingly, they also reported one digynic triploid as exhibiting a partial molar phenotype. At least two other studies have reported the occurrence of digynic triploid partial moles (JACOBS *et al.* 1982b; UCHIDA and FREEMAN 1985). However, most recent studies have come to the conclusion that digynic triploid PHM do not actually exist (REDLINE *et al.* 1998; ZARAGOZA *et al.* 2000). A 1996 report indicated that of 53 cases of triploidy with some fetal development, only 15% were partial moles (MCFADDEN and PANTZAR 1996). Finally, Zaragoza et al. (2000) reported that only 33 of 58 diandric triploids with sufficient material were partial moles and further noted that the frequency of PHM increased with gestational age.

Tables 3 and 4 clearly show the discrepancies in results. The majority of diandric triploids were identified through cytogenetic studies while the majority of digynic triploids were identified through molecular studies. If not for the predominance of diandric triploidy in the molecular study published by Zaragoza et al. (2000), there would be far more digynic triploids ascertained through molecular studies than diandric triploids. The differences are also apparent when looking at the proportions of partial mole in earlier versus later studies. The earliest three studies suggest that partial mole is associated with approximately 70-97% of triploids while later studies suggest that no more than 39% of triploids are partial moles. There appears to be somewhat less consistency with determining the proportion of diandric triploids that are partial moles with values ranging from 33% to 100%. Digynic triploid partial moles were actually reported in three studies, however more recent evidence has cast serious doubt on these classifications as digynic partial moles are now believed not to exist.

Table 3. Prevalence of diandric versus digynic triploidy

	Mode	**Diandric**	**Digynic**
Jacobs et al., 1982	Cytogenetics	58	21
Procter et al., 1984	Cytogenetics	6	0
Uchida et al., 1985	Cytogenetics	52	29
Miny et al., 1995	Molecular	5	12
Baumer et al., 2000	Molecular	5	20
McFadden & Langlois, 2000	Molecular	14	24
Zaragoza et al., 2000	Molecular	60	27
McFadden & Robinson, 2006	Molecular	8	19
Overall Totals		**208**	**152**
Cytogenetics Study Totals		**116**	**50**
Molecular Study Totals		**92**	**102**

Table 4. Prevalence of the partial hydatidiform mole among triploid conceptuses

	All Triploids			Diandric Triploids			Digynic Triploids		
Study	**Total**	**PHM**	**% PHM**	**Total**	**PHM**	**% PHM**	**Total**	**PHM**	**% PHM**
Szulman et al., 1981	82	79	96.34%	N/A	N/A	N/A	N/A	N/A	N/A
Jacobs et al., 1982	106	74	69.81%	54	54	100.00%	15	3	20.00%
Procter et al., 1984	10	8	80.00%	6	2	33.33%	N/A	N/A	N/A
Uchida et al., 1985	81	19	23.46%	52	19	36.54%	29	1	3.45%
Miny et al., 1995	17	5	29.41%	5	4	80.00%	12	1	8.33%
McFadden & Pantzar, 1996	53	8	15.09%	N/A	N/A	N/A	N/A	N/A	N/A
Zaragoza et al., 2000	88	33	38.82%	58	33	56.90%	27	0	0
Totals	**434**	**226**	**52.07%**	**164**	**106**	**64.63%**	**88**	**5**	**5.68%**

2.3 EXPLAINING THE DISCORDANT RESULTS

A number of possible explanations have been put forth to explain the differences in results obtained from early cytogenetic studies and those obtained from more recent molecular studies. It has been suggested that at least some of the difference can be attributed to the greater accuracy and reliability of molecular techniques over conventional cytogenetic techniques (MCFADDEN *et al.* 1993). Several early cytogenetic studies even made note of the limitations of determining parental origin based on cytogenetic methods alone (JACOBS *et al.* 1978; JACOBS *et al.* 1982a). This bias is mainly a result of interpretation bias in the sense that different investigators may judge the presence or absence of informative heteromorphisms differently (ZARAGOZA *et al.* 2000). When comparing band width or intensity, different investigators may use different criteria for determining if these markers on homologous chromosomes are alike or different. As a result, some investigators may interpret a set of markers as being informative while a different investigator may interpret the same set of markers as being uninformative. Because cytogenetic techniques rely on examining C- or Q-banded chromosomes, the banding technique also plays a major role. The intensity and clarity of the bands will vary from slide to slide and consequently, so will the appearance of informative heteromorphisms. Finally, these techniques are limited by the low number of heteromorphisms present in the population. These heteromorphisms are often limited to the size and

intensity of bands containing non-coding stretches of heterochromatin as well as the secondary constrictions and satellites of the acrocentric chromosomes.

It may also be possible that the inaccuracy of cytogenetic techniques for determining the parental origin of triploidy is being overestimated. When using cytogenetic heteromorphisms to determine the parental origin of a single chromosome trisomy, these techniques may be less accurate since the investigators have only a single chromosome to examine for markers. However, when attempting to determine the parental origin of triploidy, the investigators have an entire extra set of chromosomes on which to compare markers. The observation that the single large molecular study reported by Zaragoza et al. (2000) found proportions of diandric and digynic triploidy that were similar to those reported in the two largest cytogenetics studies may lend support to this theory.

Molecular genetics techniques can virtually eliminate all of the inherent difficulties of cytogenetic techniques. Since these techniques are automated and the results computer generated, the possibility of interpretation bias is effectively eliminated. Unlike cytogenetics techniques, molecular techniques examine the DNA sequence itself so that the identification of informative polymorphisms is much more straightforward. An additional advantage of molecular techniques is the ability to establish the dosage of different alleles so that even if only two distinct alleles are present in a triploid cell line, it may still be possible to determine the parental origin in some cases by observing which allele has a double dose. Finally, since molecular techniques examine sequence polymorphisms, there are many more loci that can be examined and thus a greater chance of finding informative loci as well as having more informative loci per case.

Another concern that may contribute to error in molecular studies as well as cytogenetic studies is meiotic crossing over since such events can change the makeup of the chromosome by creating new patterns of heteromorphisms. Most cytogenetic studies attempted to use polymorphisms located very close to the centromeres and assume that crossing over hasn't occurred between the centromere and heteromorphism (JACOBS *et al.* 1978). McFadden and Langlois (2000) used markers located less than five centimorgans from the centromeres feeling that this would virtually eliminate this source of error.

This sort of error primarily comes into play when attempting to ascertain the meiotic stage at which the error leading to triploidy occurred and has even been cited as a likely explanation for the results obtained in at least one study (BAUMER *et al.* 2000).

Probably the most often cited source of bias is the method by which specimens are ascertained. Small sample size has been cited on a number of occasions, though McFadden et al. (1993) claimed this wasn't a significant source of error due to the high degree of prevalence of the type II digynic triploidy phenotype in their study. In light of the complex relationship between the parental origin of the extra haploid set of chromosomes and gestational age, it has been strongly suggested that the gestational age of specimens in different studies may strongly bias the results. It has been noted that most early cytogenetic studies examined spontaneous abortions from a wide range of gestational ages and that these studies did not attempt to correlate gestational age with parent-of-origin (MCFADDEN *et al.* 1993; MCFADDEN and LANGLOIS 2000; MINY *et al.* 1995). Conversely, the study reported by Miny et al. (1995) included only fetuses surviving to the point at which they were ascertained through routine cytogenetic diagnosis or after abnormal ultrasound findings. Gestational age of specimens is of particular importance since diandric triploids are more likely to spontaneously abort while digynic triploids are more likely to survive into the fetal period (MCFADDEN *et al.* 1993). At least one study has reported an apparent spike in the number of triploid fetuses being ascertained at 18-22 weeks gestations (BAUMER *et al.* 2000). The authors attributed this spike to elective abortions following routine prenatal screening and diagnosis. It is possible that with the increased availability and prevalence of routine prenatal screening, the gestational age effects on triploidy may become more difficult to see, at least later in gestation. This is because the majority of such cases surviving until the time of prenatal screening will be therapeutically aborted such that there will appear to be a spike in all triploid gestations during that period when such screenings take place.

The between study differences in the rate of partial mole, diandric triploidy and digynic triploidy can probably be largely attributed to biased selection of the study population. It has been suggested that placentas showing partial molar degeneration or other abnormal morphology are more likely to be

examined than those with normal morphology thus leading to an overestimate of the prevalence of PHM and diandric triploidy (MCFADDEN *et al.* 1993). Redline et al. (1998) also suggested that some studies may suffer from referral bias in which the participants were referred due to some specific risk for partial mole or otherwise abnormal gestation. It has also been noted that cytogenetic studies predominantly examined spontaneous abortions of 8-20 weeks gestational age regardless of phenotype and with some specimens containing only extrafetal material (ZARAGOZA *et al.* 2000). Conversely, molecular studies are often restricted to cases with a well formed fetus or embryo or those with gestational ages less than 10 weeks. These latter points becomes important when considering the prevalence of diandric triploidy and PHM since both groups separately and as a whole are less likely to contain fetuses than digynic triploids. It is also known that diandric triploids with a partial molar placenta in which the fetus has died are more likely to be retained *in utero* for a longer period of time due to sustained elevated levels of hCG produced by the hypertrophic trophoblast.

It has also been suggested that selection criteria in some studies may preferentially enrich for digynic triploidy or diandric triploidy (ZARAGOZA *et al.* 2000). Those studies examining very early spontaneous abortions or pregnancies surviving well into the second trimester may show a predominance of digyny while those studies examining late first trimester or early second trimester gestations with abnormal placentas may show a predominance of diandry. The observation of a complex relationship between gestational age and parent-of-origin lends support to this hypothesis (ZARAGOZA *et al.* 2000). It is also possible that improved technology and better ascertainment may partially explain the differences (MCFADDEN and LANGLOIS 2000). Pregnancy can be detected earlier now than it could 20 or 30 years ago and there is a greater understanding of the need to examine all spontaneous abortions and otherwise abnormal pregnancies.

There are a number of factors that could potentially explain the differences in the prevalence of partial mole between earlier and more recent studies. One important factor is the strictness of criteria for establishing the diagnosis for partial mole. Molar pregnancies weren't well described before the 1980's and so different investigators may have used different criteria for establishing the diagnosis. Similarly,

the mode of ascertaining the diagnosis of PHM may have played a significant role. Some studies may have relied on gross appearance alone to establish the diagnosis, though this could have biased results in both directions. Grossly hydropic placentas that were assigned a diagnosis of PHM without being examined under the microscope may have turned out to be nonmolar had such microscopic examination been undertaken. This scenario could potentially explain the observation of digynic triploid partial moles in some studies. Conversely, macroscopically normal placentas diagnosed as nonmolar may have in fact shown some molar changes had they been examined under the microscope, especially at earlier gestational ages. The effect of gestational age may be of even greater importance when comparing earlier and later surveys. Earlier studies such as that reported by Szulman et al. (1981) identified their partial moles from populations of spontaneous abortions when the characteristic features were well developed. However, with increased used of prenatal screening allowing for earlier termination of pregnancy, it is now possible to examine placental morphologies at earlier gestational ages where the characteristic features of PHM may not have yet developed.

Also of note is that most studies before 1980 did not distinguish between partial mole and complete mole (JACOBS *et al.* 1982a). Furthermore, these earlier studies tended to only examine triploid conceptuses with signs of molar change or culled triploid specimens only from larger samples of placentas with molar change (MCFADDEN *et al.* 1993; MCFADDEN and PANTZAR 1996). These sampling methods may have largely contributed to earlier results suggesting that most triploids were diandric and partial moles. Finally, missed diagnosis may have played a role. Early partial moles could potentially be missed if the characteristic features haven't become apparent or late partial moles may be missed because tissue degeneration and fibrosis may mask some of the characteristic features (REDLINE *et al.* 1998).

A number of additional sources of error may exist. One possibility is false paternity in which the legal father is not the biological father (JACOBS *et al.* 1978). This could lead to misinterpretation of results. It has also been suggested that some studies may be biased towards advanced maternal age since cytogenetic screening is more frequent and routine in this group (MCFADDEN and PANTZAR 1996). Though there doesn't appear to be a maternal age effect for the occurrence of triploidy alone, at least one

study reported a distinct maternal age effect for triploidy with concurrent aneuploidy (UCHIDA and FREEMAN 1985).

Finally, a potentially important source of error that doesn't seem to receive much attention is the way in which the age of specimens is determined. Some studies use developmental age while others use gestational age and still others use menstrual age. When comparing specimen ages between studies, it is of great importance to be sure that the same method of determining age is used otherwise the results may be skewed. An additional problem when determining gestational age is recall bias which can be introduced by inaccurate recollection of the timing of the last menstrual period (REDLINE *et al.* 1998). Using developmental age provides its own set of difficulties since it is well established that triploid gestations are often growth retarded and that growth of different parts is often discordant. This is also a problem when considering the retention time of aborted specimens since those missed abortion specimens retained *in utero* for a longer period of time will show a higher degree of growth discordance than those with recent fetal demise or therapeutic termination of an abnormal living fetus. A final point to consider is the use of crown-rump length (CRL) as a means of establishing gestational age. Warburton et al. (1991) noted that the tables correlating CRL with gestational age were revised sometime after 1976 and so there may be some discordance between studies conducted before and after this revision took place.

Overall, it appears that the studies of Jacobs et al. (1982) and Uchida and Freeman (1985) are the most reliable of the cytogenetics studies in determining the true ratio of diandric to digynic triploidy. This is because these studies ascertained their specimens from a series of consecutive spontaneous abortions and were able to determine the parental origin in a large number of samples. These studies are limited primarily by the accuracy of cytogenetic results in determining parental origin and by the methods and criteria used to establish the diagnosis of partial hydatidiform mole. The study by Zaragoza et al. (2000) is probably the single best molecular study of parental origin since it includes the largest sample size. However, this study also has its limitations. This study included two different populations of specimens from two different institutions located in Cleveland and Pittsburgh (ZARAGOZA *et al.* 2000). Though the cases ascertained in Cleveland were part of a consecutive series of karyotyped spontaneous

abortions, the Pittsburgh cases were not. Rather, the Pittsburgh cases were ascertained for a variety of reasons including advanced maternal age and abnormal placental morphology, factors which may enrich for partial mole and thus diandric triploidy. Indeed, when looking at the Cleveland and Pittsburgh results separately, clear differences can be seen. Though diandric triploidy predominated in both populations, the ratio was 39:23 in Cleveland but 21:4 in Pittsburgh. The authors of this study also noted a slightly higher incidence of PHM among the Pittsburgh group, though they stated that this difference was not statistically significant.

It should also be noted that the results from the Cleveland population in the Zaragoza et al. study had been published previously (REDLINE *et al.* 1998). It is possible that this subset of the population from the study by Zaragoza et al. (2000) may provide the best estimates yet of the population frequencies of digynic triploidy, diandric triploidy, and partial hydatidiform mole. This is possible since this population was obtained from a consecutive series of spontaneous abortions unlike the Pittsburgh population. The only possible drawback is that this study examined only SA of less than 20 weeks developmental age thus excluding later fetal deaths which may have yielded a higher proportion of digynic triploids.

The remaining studies, both cytogenetic and molecular, are largely hampered by small sample sizes and the mode and timing of ascertainment of specimens. Though the study by Proctor et al. (1984) culled cases of triploidy from a series of consecutive abortions, this sample included only 12 triploids of which parental origin was determined in only six. Though the study by McFadden and Kalousek (1993) was pivotal in establishing the phenotypic differences between diandric and digynic triploids, the fact that they were selecting cases with fetal development automatically enriches for digyny since digynic triploids are more likely to have a recognizable fetus than diandric triploids. Similarly, studies by Miny et al. (1995) and Baumer et al. (2000) examined specimens that were obtained primarily through abnormal routine prenatal cytogenetics results and/or abnormal sonography results. Since this population is largely centered on the mid-second trimester of gestation, these studies will again enrich for digynic triploidy.

McFadden and Langlois (2000) attempted to avoid some of these problems by examining both embryonic and fetal triploids, however this study also presents several methodological problems. Firstly,

because this study population included cases that were therapeutically aborted after abnormal prenatal screening, this would automatically enrich from specimens surviving to the age at which such screening typically take place. Of perhaps greater concern is manner in which the authors defined their groups. Fetuses were defined as being greater than 10 weeks gestational age while embryos were defined as having a gestational age of less than 10 weeks. However, the embryo group also included an "other" subgroup which was defined as specimens of greater than 10 weeks gestational age but lacking a discernable embryo or fetus (MCFADDEN and LANGLOIS 2000). It should also be noted that all four specimens that fell into this "other" category were found to be of diandric origin. Even if this group had been included in the fetal group, digyny would have still predominated though the results would have been less striking. It would seem more logical to have included all specimen of greater than 10 weeks gestational age in the fetal group regardless of the presence or absence of fetal development.

Though many studies have been undertaken in an effort to determine if most triploids are diandric or digynic and how often triploidy is associated with partial mole, they all suffer from some degree of bias. In order to truly understand the complex nature of triploidy and partial mole, a study would have to take into account the entire body of knowledge that is currently available regarding triploidy. Such a study would best be carried out using a large series of consecutive abortions as a source for triploid specimens. Such a study should entirely exclude therapeutic abortions of live fetuses since inclusion of such a group would bias towards fetuses of a gestational age where prenatal diagnosis may precede such abortions. Additionally, therapeutic abortions would also bias towards abnormal fetal or placental morphology. Such a series should ideally include more than 50 triploid specimens in which the parental origin can be determined. In light of the complex relationship between parental origin of the extra haploid set of chromosomes and gestational age, the gestational age of all specimens should be carefully noted. It would also be prudent to divide these cases into several groups based on gestational age such as early embryonic, late embryonic, early fetal, et cetera. Additionally, placental morphology should be examined both grossly and microscopically in all cases with particular note again being paid to gestational age and parental origin. Finally, though molecular studies are currently the norm, it may be

prudent to examine both cytogenetic and DNA polymorphisms in such a study. Doing so could help to establish just how accurate or inaccurate early cytogenetics results were as well as potentially shedding some light on the differences between cytogenetic and molecular results. In short, such a study would require extreme attention to detail in order to eliminate as many sources of bias and error as possible.

3.0 MECHANISMS GIVING RISE TO TRIPLOIDY

3.1 PRONUCLEAR STAGES AND EARLY MITOTIC ERROR

The mitotic machinery of the zygote plays a major role in the proper incorporation and segregation of the parental pronuclei during the first few cell divisions. Of particular importance are the zygotic centrioles and centrosomes which are paternally derived (GOLUBOVSKY 2003). These structures play a critical role in the proper segregation of chromosomes during the first zygotic division. Whereas digynic triploid zygotes contain a single pair of active centrioles and can engage in relatively normal mitosis, dispermic triploid zygotes inherit two pairs of active centrioles and are thus more prone to gross mitotic error (GOLUBOVSKY 2003; MALAN *et al.* 2006). Tripolar spindles arise following dispermy and are capable of producing diploid or triploid blastomeres (GIURGEA *et al.* 2006). The bipolar spindles of digynic triploid zygotes results in a lower incidence of mosaicism, at least in the very early cleavage stage.

The majority of information on tripronuclear zygotes and tripolar spindles comes from the study of embryos following *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (MALAN *et al.* 2006). Tripronuclear zygotes arise when two gametes from one parent fuse with one gamete from the other parent. This phenomenon has been reported in 5-7% of all IVF or ICSI fertilized zygotes, with the majority of them being found to have a triploid chromosome constitution (ROSENBUSCH *et al.* 1997). A study by Staessen and Van Steirteghem (1997) indicated that tripronuclear zygotes can cleave at a rate comparable to that of normal dipronuclear zygotes. The majority of 3PN zygotes observed following IVF have been shown to progress to the cleavage stage and often result in complete triploidy (ROBINSON *et al.* 2007). Most remaining cases are either fully diploid or diploid/haploid mosaics resulting from exclusion of a pronucleus or irregular cleavage.

Dispermic tripronuclear zygotes will generally proceed down one of three possible developmental paths (GOLUBOVSKY 2003). Approximately 25% of cases will result in a bipolar spindle leading to mitosis and the formation of two triploid blastomeres with stabilization of the triploid state. (MALAN *et al.* 2006). Alternatively, the exclusion of a single haploid set from the metaphase plate at the first cleavage division can result in the formation of 2n, 2n/3n, or n/2n clones of cells (GOLUBOVSKY 2003). This scenario is thought to occur in 14-32% of cases. Androgenetic complete mole can arise if the excluded haploid set is paternal in origin and subsequently undergoes endoreduplication to become diploid.

Finally, the formation of a tripolar spindle at the first cleavage division can result in highly aberrant segregation in 50-60% of cases (GOLUBOVSKY 2003). This occurs because the three haploid sets of chromosomes will remain relatively separate within the oocyte (GOLUBOVSKY 2003). This zygote will first divide into three cells and then into six as opposed to dividing into two and then four cells in normal 2PN zygotes. This chaotic segregation can result in mosaicism and gross aneuploidy in daughter blastomeres. It has also been proposed that triploidy may arise from tripolar division of a tetrapronuclear zygote (NIEBUHR 1974). This scenario would agree with aberrant segregation of tripronuclear cells, however, there is little experimental evidence supporting this theory. This latter scenario could potentially help to explain the origins of several unusual cases. Gropp et al. (1964) described a case of a patient with non-syndromic cleft palate and an approximately triploid cell line that was apparently restricted to the epithelium overlying the palatal defect. Also, Sellyei et al. (1971) reported detecting a few 69,XYY cells in the peripheral lymphocytes of a normal adult undergoing genetic screening due to an apparent chromosomal defect in his son. It is possible that both of these cases originated from the isolated occurrence of tetraploid cells in the affected tissues which then underwent abnormal tripolar cleavage to produce the triploid line. This may be especially pertinent in the latter case considering the apparent extremely low viability of 69,XYY cells.

Triploidy arising through mitotic error has been proposed, but currently remains unproven in humans (ZARAGOZA *et al.* 2000). One hypothesis involves an error occurring at the pronuclear stage such

as premature duplication of a pronucleus. A similar hypothesis involves aberrant reduplication of a sperm or ovum nucleus. Both of these mechanisms would result in triploid zygotes where two of the three haploid sets will show complete homozygosity. It has been suggested that mitotic error may play a role in diploidization of tripronuclear digynic zygotes after intracytoplasmic sperm injection (GOLUBOVSKY 2003). Finally, mitotic errors in germ cell precursors could lead to the formation and subsequent reduction of a tetraploid oogonium or spermatogonium resulting in diploid gametes (NIEBUHR 1974).

Another mechanism that is thought to be highly unlikely involves the defective segregation of a haploid set of chromosomes from the metaphase plate during the first zygotic division (DANIEL *et al.* 2003; NIEBUHR 1974). Due to the random alignment of chromosomes along the metaphase plate, one would expect a random distribution of maternally and paternally derived chromosomes to comprise the additional or lost haploid set. Consequently, different parental origins would be expected for disomy or trisomy of each individual chromosome; a phenomenon which has not yet been observed. The rule thus far has been a consistent parental origin for each chromosome in the triploid line and biparental disomy for the diploid line (DANIEL *et al.* 2003)

3.2 DISPERMY

Diandric triploidy produced from normozoospermic males are usually by way of dispermy, whereas those from oligozoospermic males are usually by way of diplospermy (GOLUBOVSKY 2003). Dispermy is the most common cause of diandric triploidy and is believed to account for approximately 66% of all triploids (ROSENBUSCH *et al.* 2002; ZARAGOZA *et al.* 2000). A study by Zaragoza et al. (2000) found that 37/43 diandric triploids in which the meiotic origin could be determined were the result of dispermy. A second study that specifically examined the origins of diandric triploidy found dispermy to be the origin in 14/14 cases (MCFADDEN *et al.* 2002b). It may also account for up to 86% of triploid embryos obtained following conventional IVF (STAESSEN and VAN STEIRTEGHEM 1997).

Dispermy is believed to play a more important role in the origin of triploidy than incorporation of the second polar body (TUERLINGS *et al.* 1993). Dispermic fertilization results in the formation of a tri-pronuclear zygote with two paternal pronuclei which has three possible developmental outcomes (GOLUBOVSKY 2003; ROSENBUSCH 2008). The zygote could divide into diploid and triploid blastomeres ultimately giving rise to a 2n/3n mixoploid embryo. Alternatively, the zygote could spontaneously eliminate an odd haploid set to produce a normal diploid zygote or an assortment of different aneuploid clones. Finally, the formation of a tripolar spindle could lead to chaotic segregation of chromosomes leading to gross aneuploidy and cell death with the occasional survival of some trisomic cells.

Diandric diploid/triploid mixoploidy may require a unique set of circumstances for its formation (DANIEL *et al.* 2003). This mechanism is thought to involve simultaneous fertilization of a normal ovum by two separate haploid sperm with only one male pronucleus immediately fusing with the female pronucleus. The second male pronucleus would then remain in the cytoplasm until after the first zygotic division at which time it would fuse with one of the resultant blastomeres. Wegner et al. (2009) described this process as "post-zygotic triploidization". The ability for pronuclei to remain separated from the nuclear genome for some period of time has previously been demonstrated (DANIEL *et al.* 2003). The concept of delayed incorporation of a paternal pronucleus into a blastomere following simultaneous fertilization is believed more probable than true delayed dispermy which would involve sperm penetration of a blastomere (WEGNER *et al.* 2009). However, simultaneous fertilization by 2 sperm would likely result in complete diandric triploidy in most cases.

The concept of dispermy presents some logistical problems mainly in the form of mechanisms built into oocytes designed to prevent such an occurrence. The initial penetration of a sperm head into the ovum causes an instantaneous depolarization of the ovum plasma membrane blocking penetration by additional sperm (DANIEL *et al.* 2003). This is theoretically not a problem for non-mixoploid triploids arising from the simultaneous penetration of two sperm into the ovum and such a mechanism has been observed in the laboratory. It has been proposed that a number of factors related to the functional capacity of both gametes may be involved in polyspermy (ROSENBUSCH *et al.* 1997). Defective oocytes

may have an impaired zona reaction and block to dispermy by way of absent, delayed, or incomplete release of cortical granules from the oocyte. Defective block to polyspermy could also be affected by cracks in the zona pellucida caused by different assisted reproduction technologies or other means (PIETERS *et al.* 1992; ROSENBUSCH *et al.* 1997).

3.3 DIPLOSPERMY

Diplospermy is the rare occurrence of a sperm that contains a diploid rather than haploid number of chromosomes. An early study by Jacobs et al. (1978) suggested that up to 23.6% of all triploids were the result of diplospermy. However, later reports revised this figure to 8.3% of all diandric triploids (EGOZCUE *et al.* 2002; HSU *et al.* 2008). It is currently estimated that ~0.06% or six in 10,000 of all clinically recognized triploid pregnancies result from paternal meiotic error (ZARAGOZA *et al.* 2000). Diplospermy is seen at a rate of 0.2-0.3% in normozoospermic males, but may be as high as 2% among oligozoospermic males (ROSENBUSCH 2008). A study by Macas et al. (2001) showed that 2.45% (4/163) of the abnormal male pronuclei obtained following ICSI were diploid among a population of males with cryptozoospermia, oligoasthenoteratozoospermia, or azoospermia. This figure also constituted 1/3 of the 12 total abnormal male pronuclei obtained in this study. It should however be noted that this study only used fluorescent markers for chromosomes 18, X, and Y, to identify abnormal pronuclei. Thus it is possible that some observed X-,18,18 sperm may have actually been rare double aneuploids. Also, aneuploid sperm with chromosome anomalies involving chromosomes other than X, Y, or 18 would have been missed in this study. Diplospermy is also the most common chromosome abnormality seen in males with meiotic disorders preventing normal spermatogenesis as well as those with other chromosome abnormalities such as balanced translocations (EGOZCUE *et al.* 2002). Rates of diplospermy may approach 9.6% in these groups.

Diplospermy can arise from failure of either the first or second meiotic division though meiosis I errors are more common (ZARAGOZA *et al.* 2000). A third possibility is the reduction of a tetraploid

spermatogonium (ROSENBUSCH 2008). Failure of the first meiotic division yields a diploid 46,XY sperm in which all loci which are heterozygous in the father will have both alleles transmitted to the sperm (NIEBUHR 1974; ROBINSON *et al.* 2007). Failure of the second meiotic division will result in 46,XX or 46,YY sperm that are homozygous at all pericentromeric loci. Any heterozygosity seen distal to the centromeres in this latter case will be a result of meiotic crossing over. It is believed that a significant proportion, if not the majority, of diploid sperm are capable of fertilization (ZARAGOZA *et al.* 2000). Male pronuclei resulting from diplospermy will be able to engage in relatively normal synergy and segregation as opposed to the chaotic mitoses seen in dispermy because only one paternal centrosome is delivered into the ooplasm (HSU *et al.* 2008). Diplospermic fertilization results in the formation of a diploid male pronucleus and a seemingly normal dipronuclear zygote following extrusion of the second polar body (ROSENBUSCH 2008). This fact makes it difficult to identify triploidy based on the number and size of pronuclei since diploid male pronuclei may not appear larger than normal haploid pronuclei.

Diplospermy has several important repercussions when dealing with assisted reproductive technology, especially intracytoplasmic sperm injection. Infertile males, a group known to have an increased rate of diplospermy, may undergo ICSI and have an increased risk of forming zygotes with a diploid male pronucleus (ROSENBUSCH 2008). This is especially true among patients with severe oligoasthenoteratozoospermia (ULUG *et al.* 2004). Triploid conceptuses resulting from diplospermy are not usually apparent at the pronuclear stage as there will be a single diploid male pronucleus and the zygote will appear to be normal and dipronuclear.

3.4 INCORPORATION OF POLAR BODIES

Errors in the formation of the oocyte polar bodies are thought to be a major contributor to digynic triploidy. Incorporation of the second polar body into one of the blastomeres following the first mitotic division is thought to contribute to diploid/triploid mixoploidy of digynic origin (QUIGLEY *et al.* 2005). This mechanism can be proven by examining a large set of pericentromeric markers in the triploid cell

line (VAN DE LAAR *et al.* 2003). Two haploid sets derived in this manner would be expected to show complete homozygosity at these markers since the second polar body chromatids are the sister chromatids of those found in the maternal pronucleus. Any heterozygosity seen at more distal markers will be the result of meiotic crossing over. This mechanism is thought more credible than true delayed dispermy since the second polar body is already within the oocyte and may fail to be extruded (DANIEL *et al.* 2003). It has been theorized that intracytoplasmic sperm injection may cause retention of the second polar body (ROSENBUSCH 2008). Sperm injection may lead to deterioration of the meiotic spindle resulting in the 23 polar body chromatids remaining within the ooplasm and becoming incorporated into the maternal pronucleus. Alternatively, the damaged spindle microtubules could result in the formation of an extra nucleus within the ooplasm which could later lead to segregation errors in early cleavage divisions or mosaicism (STAESSEN and VAN STEIRTEGHEM 1997).

Involvement of the first polar body seems unlikely because of its diploid state, but can't be ruled out as a possible exceptional circumstance (VAN DE LAAR *et al.* 2003). For instance, the first polar body may divide into two haploid cells with one of these fusing with the diploid zygote. Bieber et al. (1981) reported a case of twins with a normal 46,XY male coexisting with a holoacardiac 69,XXX fetus and suggested first polar body fertilization as a mechanism leading to the formation of the triploid twin. The authors suggested that this may occur due to the proximity of the first polar body to the ovum within the perivitelline space of the zona pellucida. Analysis of leukocyte histocompatibility haplotypes of the normal and holoacardiac twin revealed inheritance of different paternal haplotypes suggestive of separate fertilization events. Studies using electron microscopy have yielded observations that show sperm penetrating polar bodies suggesting this mechanism is possible (BIEBER *et al.* 1981).

Several mechanisms involving abnormal division of the primary oocyte may lead to diploid/triploid chimerism (NIEBUHR 1974; VAN DEN BERGHE and VERRESEN 1970). Abnormal division of the primary oocyte could result in the formation of two equally sized secondary oocytes or, in essence, a very large first polar body. Both of these could then be fertilized by separate sperm with one failing to extrude a second polar body. In theory, chimeras resulting from this mechanism would have three distinct

maternal and two distinct paternal haploid sets. Alternatively, van den Berghe and Verressen (1970) proposed a mechanism that would result in a chimera with four maternal and one paternal haploid set. This mechanism would involve fertilization of a large first polar body or oocyte by a single haploid sperm with both failing to extrude a second polar body. The result would be a chimera with a population of digynic triploid cells and a population of diploid parthenogenetic cells that would be homozygous at all markers. A similar scenario would involve formation of the second polar body in both cells with one of them subsequently being incorporated in a blastomere.

Another proposed mechanism for the formation of 2n/3n mixoploid zygotes involves the complete failure of polar body formation in the maturing oocyte (ZHANG *et al.* 2000). This would lead to the formation of a tetraploid ovum which, when fertilized, would result in a pentaploid zygote. This zygote would then divide into diploid and triploid components. However, this mechanism seems unlikely since one component would be parthenogenetic. Complete failure of polar body formation has been reported in at least one instance (RUDAK *et al.* 1990). Oocytes obtained from this patient appeared to have two maternal pronuclei, but turned out to be tetraploid with both pronuclei being diploid. At least one of these aberrant oocytes was fertilized during IVF and resulted in a pentaploid zygote.

An unusual mechanism that could potentially lead to digynic triploidy involves the fertilization of two fused ova or two separate ova by a single haploid sperm (DANIEL *et al.* 2003; ZARAGOZA *et al.* 2000). This mechanism has been suggested as the origin in at least one case of human triploidy (JACOBS *et al.* 1978). This mechanism suggests the rare occurrence of two separate maternal genomes contributing to a single conceptus (ZARAGOZA *et al.* 2000). The meiotic outcomes for this mechanism of "dieggy" would be the same as what would be expected from digynic triploids resulting from reduction of an initially tetraploid oogonium (ZARAGOZA *et al.* 2000). A digynic triploid showing reduction to homozygosity at some pericentromeric markers but non-reduction at others may be suggestive of this mechanism (MCFADDEN and ROBINSON 2006).

3.5 MEIOTIC ERROR AND GIANT OOCYTES

Abnormal oogenesis can also contribute to the formation of a diploid ovum and lead to digynic triploidy if fertilized. It is believed that up to 0.2% of ova may have a meiotic failure of some sort (ROSENBUSCH *et al.* 2002). The majority of diploid ova are believed to result from errors in the second meiotic division with a minority resulting from meiosis I errors (ZARAGOZA *et al.* 2000). Maternal meiosis II errors are believed to be the second most frequent cause of all triploids behind dispermy. McFadden and Langlois (2000) found that 18/24 digynic triploid embryos and fetuses were the result of meiosis II errors with the remainder being meiosis I errors. However, a second study found equal proportion of meiosis I and meiosis II errors among digynic triploids (BAUMER *et al.* 2000). However, these authors noted a high number of pericentromeric crossovers among their cases making some assignments difficult and possibly leading to incorrect assignments. Failure of the first meiotic division with subsequent failed formation of the first polar body would be indicated by a diploid ovum that is heterozygous at all centromeric markers for which the mother is heterozygous (MCFADDEN and ROBINSON 2006). Similarly, failure of the second meiotic division with subsequent failed formation of the second polar body would result in a diploid ovum that is homozygous at all centromeric markers. Either type of error is thought to occur in 0.2% of all female meioses (ROSENBUSCH *et al.* 2002).

The contribution of giant oocytes has also been considered, though the formation of digynic triploidy through fertilization of a diploid giant oocyte in considered improbable (ROSENBUSCH *et al.* 2002). These giant gametes are two times the size of normal female gametes, are tetraploid, and result either from nuclear but not cytoplasmic division of an oogonium or fusion of two oogonia (ROSENBUSCH 2008; ROSENBUSCH *et al.* 2002). A study by Rosenbusch et al. (2002) found that giant oocytes may occur at a frequency of 0.26%. These giant primary oocytes can mature to the second meiotic division by either maintaining their binucleate state or undergoing fusion of the two separate nuclei. Binucleate oocytes are thought to account for approximately 96% of all abnormal ova in humans (ROSENBUSCH *et al.* 2002). Maintenance of the binucleate state will result in the formation of a 3PN zygote with two

maternal pronuclei when fertilized. However, if the two nuclei underwent fusion, this would result in an apparently normal 2PN zygote when fertilized, however the maternal pronucleus would be diploid.

Immature giant binucleate oocytes existing at the germinal vesicle stage have two possible routes of maturation (ROSENBUSCH 2008). The union of both haploid set can give rise to a 2n metaphase II oocyte after having extruded a single first polar body. Monospermic fertilization will then result in the formation of a haploid male pronucleus and a diploid female pronucleus after extrusion of a diploid second polar body. Alternatively, if the binucleate state is maintained then the mature oocyte would have two haploid chromosome complements and two haploid first polar bodies. Monospermic fertilization will then result in one male pronucleus and two haploid female pronuclei after extrusion of two haploid second polar bodies.

3.6 POSTZYGOTIC DIPLOIDIZATION OF TRIPLOIDS

The observation of dispermic triploid zygotes has led to the concept of postzygotic diploidization of triploid zygotes (PDT) (MALAN *et al.* 2006). This concept has allowed for investigation of PDT through the loss of entire haploid sets and has provided new insights into the mechanisms leading to mixoploidy, chimerism, hydatidiform mole, and twinning. This mechanism is thought to only play an important role in dispermic triploidy where there are two sets of paternally derived active centrioles whereas it is quite rare in digynic triploids where there is a single set of active centrioles.

It has been suggested that postzygotic diploidization may play a role in the origins of uniparental disomy (GOLUBOVSKY 2003). This is based on the notion of each genome semi-independently segregating from the other two along the metaphase plate during tripolar cleavage. This deviation from the segregation of entire haploid sets as a whole could thus result in a diploid cell line where two homologues of at least one chromosome are inherited from the same parent. Following tripolar cleavage, it is predicted that 1/3 of mitoses may result in a uniparental state for one pair of homologues while 1/9 of mitoses may result in a uniparental state for two pairs of homologues. Currently there is no evidence

supporting the independent segregation of chromosomes according to parental origin once pronuclear fusion has occurred (GIURGEA *et al.* 2006). Any abnormalities are thus presumed to occur between the time of fertilization and fusion of the pronuclei.

It has also been suggested that an additional non-disjunction event during diploidization may lead to aneuploidy within the resultant diploid cell line, though the occurrence of 2n/3n mixoploidy in conjunction with aneuploidy of the diploid line is extremely rare (QUIGLEY *et al.* 2005). Postzygotic diploidization may also provide an explanation for cases involving the coexistence of a hydatidiform mole with a twin fetus whether it be a triploid partial mole and diploid fetus or a diploid complete mole and triploid fetus, though this latter case has never been seen (GOLUBOVSKY 2003). It may also provide an alternative to the empty egg scenario when explaining the co-existence of a diploid fetus with a diploid androgenetic complete mole. In this scenario, tripolar division leads to formation of an n/2n clone of cells where either paternal haploid set can be included in the 2n clone and give rise to a diploid fetus of either sex. The 1n clone containing the other paternal haploid set then undergoes endoreduplication and forms into a homozygous complete mole with a 46,XX karyotype.

Rosenbusch and Schneider (2009) described an interesting case that may indicate another possible mechanism leading to the diploidization of triploid zygotes. The authors describe an oocyte being prepped for ICSI that appeared to have two polar bodies, but subsequently underwent a premature cytokinesis. This event involved the incorporation of one pronucleus into a cytoplasmic fragment and extrusion of a third polar body-like structure. This seemed to result in the zygote being 2PN with both pronuclei in the larger half, however, further examination revealed a third pronucleus in the smaller fragment. Karyotyping of this 3PN zygote revealed triploidy with one haploid set appearing to include an acentric fragment (ROSENBUSCH and SCHNEIDER 2009).

3.7 OTHER FACTORS CONTRIBUTING TO THE OCCURRENCE OF TRIPLOIDY

Several other mechanisms may contribute to the formation of digynic triploidy though to a lesser extent. It is thought that fertilization of immature oocytes may lead to triploidy as a result of them not being ready to complete meiosis (ZARAGOZA *et al.* 2000). It is also thought that this immaturity may also result in an inability to complete imprinting and that this in turn may underlie the phenomenon of digynic triploids either aborting early or surviving late into gestation. Comparison of allele-specific expression of imprinted loci between both groups of digynic triploids has been proposed as a means of testing this hypothesis (ZARAGOZA *et al.* 2000). The block to polyspermy reaction may also be hindered by immaturity of the zona pellucida, cytoplasmic granules, and vitelline membrane (PAL *et al.* 1996).

Similarly, aging oocytes may also play a key role in the formation of triploid conceptuses (NIEBUHR 1974). Older ova have been shown to have an increased likelihood of having a defective block to polyspermy mechanism or failing to extrude the second polar body. A failure of the block to polyspermy may also be secondary to an acquired defect in the zona pellucida in aged oocytes (PAL *et al.* 1996). Some evidence has suggested that the interval between the first day of the last menstrual period and the probable ovulation date is longer in triploid cases as opposed to controls (NIEBUHR 1974).

Another possibility is endoreduplication within the maternal pronucleus (ROSENBUSCH 2008). This would result in the formation of diplochromosomes with four instead of the usual two chromatids with these then separating into two sets of normal maternal chromosomes. This mechanism could be detected by aberrant maternal pronuclear formation or by karyotyping of abnormal zygotes. On karyotyping, diplochromosomes would initially appear as undivided metaphase chromosomes which would then separate to form a diploid but completely homozygous pronucleus. Similarly, it is theoretically possible to get diandric triploidy through abnormal endoreduplication of the paternal pronucleus, though this mechanisms has not yet been observed (ROSENBUSCH 2008) .

A number of extrinsic factors have been hypothesized to increase the risk of triploid conceptuses, not the least of which is assisted reproduction technology. The incidence of triploidy following *in vitro*

fertilization may range from 2-9% and has been hypothesized to be linked with some chemical agents used to suppress formation of the second polar body (NIEBUHR 1974; PIETERS *et al.* 1992). A tripronuclear state has been observed in approximately 5% of zygotes following IVF and can lead to triploidy (ROBINSON *et al.* 2007). Most of these cases result in the formation of 2n or 2n/n mixoploid embryos while only a small proportion displayed pure triploidy when advancing to the cleavage stage. Frequently, 2n/3n or 2n/n chimeras have been observed in the 2-8 cell stage following assisted reproduction. It has also been suggested that the freezing and thawing of embryos could lead to blastomere fusion which could then result in mosaic polyploidy (BALAKIER *et al.* 2000). Though most embryos exhibiting this phenomenon are not transferred, those that are usually fail to implant or end in an early abortion. It has been suggested that the use of propanediol as a cryoprotectant may play a role in blastomere fusion. Another possible indication of a link between IVF and triploidy is an observed excess of 69,XYY zygotes following conventional IVF which may be indicative of an increased rate of dispermy (ULUG *et al.* 2004).

Early studies suggested that becoming pregnant within six months of discontinuing the use of oral contraceptives may increase the risk of triploidy (FULTON *et al.* 1977; NIEBUHR 1974). These studies showed that among spontaneous abortions obtained from women becoming pregnant within six months of discontinuing oral contraceptive use, 24-28% were triploid and that 23% of the triploids were mosaic. However, later studies have not been able to affirm such a link, possibly due to a change in the formulation of contraceptive drugs (JACOBS *et al.* 1978). It had been suggested that this phenomenon was related to a temporary rise in the concentration of luteinizing hormone following discontinuation of synthetic progesterone (NIEBUHR 1974).

Unlike trisomies, there does not appear to be a link between advanced maternal age and the occurrence of triploidy (FORRESTER and MERZ 2003). However, a study by McFadden and Langlois (2000) found that the average maternal age for non-fetal digynic triploids (34.5 y/o) was significantly higher than that for non-fetal diandric triploids (30.8 y/o). These authors noted that this may have been a result of different modes of ascertainment for these two groups since seven digynic cases were

ascertained due to cytogenetic screening for advanced maternal age while the majority of diandric cases were ascertained following abnormal placental findings on ultrasound. Maternal diabetes also does not appear to be a risk factor (FORRESTER and MERZ 2003).

3.8 MOSAIC OR CHIMERA?

One interesting question that arises when discussing cases involving the presence of both diploid and triploid cells is whether this should be considered mosaicism or chimerism. Generally, mosaicism is derived from a single fertilized zygote whereas chimerism is derived from separate zygotes. Diploid/triploid chimerism may result from the fusion of separate diploid and triploid conceptuses (VAN DE LAAR *et al.* 2003). A similar mechanism would involve a slightly later fusion of a diploid and triploid conceptus with resorption of adjoining chorion. This latter mechanism was proposed to explain the occurrence of apparent monozygotic twins with one being diploid and the other triploid and having discordant sexes (BIEBER *et al.* 1981). Finally, it has been suggested that the vanishing twin phenomenon may explain some of these cases (ENGLISH *et al.* 2000; TUERLINGS *et al.* 1993). Callen et al. (1991) reported a case of a normal 46,XX infant with a 46,XX/69,XXY placenta where a large portion of the placenta was determined to have originated from a vanished twin indicated by the presence of an empty small second gestational sac.

Wegner et al. (2009) suggested that neither mosaicism nor chimerism were appropriate terms based on two arguments. The first argument is that chimerism requires the contribution of two independent zygotes. The second argument is that mosaicism requires that the secondary cell line be derived from a preexisting primary cell line. It has also previously been suggested that mosaicism should be restricted to differing populations of cells derived from errors involving the segregation of a single gene or chromosome (ROBINSON *et al.* 2007). It has been suggested that the term “mixoploidy” should be used to describe all such cases involving the coexistence of multiple cell lines with different ploidy levels

(WEGNER *et al.* 2009). This works on the assumption that all such cases are originally diploid with the triploid line arising from a secondary incorporation of an additional haploid set.

Though some cases can be definitively classified as chimerism, a definitive classification of mosaicism would be much more difficult based on the above definitions. This is because though it is possible to determine the parental origin of the extra haploid set, it is generally not possible to determine the timing of its incorporation. If the zygote is initially triploid but then loses a haploid set in the first zygotic division, then this would appear to be mosaicism since the diploid cell line was derived from an initially triploid zygote. However, if the zygote is initially diploid but an additional haploid set is incorporated into one of the blastomeres following the first zygotic division, this scenario seemingly doesn't fit either definition. Both cell lines are derived from the same initial zygote so this is not a chimera, but the derived cell line originated from the addition of an entire haploid set rather than an error involving the original diploid set, so this is not a mosaic. It would seem that most cases exist in a sort of gray area between mosaicism and chimerism and that mixoploidy is indeed the single best description of such cases.

3.9 RECURRENT TRIPLOIDY

There have been several reports of women with recurrent triploid pregnancy, the majority of which have been of maternal origin (BRANCATI *et al.* 2003; HUANG *et al.* 2004). Overall, the recurrence rate for triploidy is not believed to be significantly higher than the general population rate (BAR-AMI *et al.* 2003). Though no definitive mechanism has yet been identified, a genetic error during oogenesis appears to be a likely cause. Abnormal regulation of polar body and pronucleus formation has been implicated as the cause of multiple molar pregnancies in one couple (REUBINOFF *et al.* 1997). Brancati et al. (2003) reported a case of a woman with three consecutive triploid pregnancies in which molecular analysis of the latter two revealed digynic origin. Subsequently, Huang et al. (2004) reported a woman who also had three consecutive triploid pregnancies with microsatellite analysis on the most recent demonstrating

maternal origin. Bar-Ami et al. (2003) reported on a couple who had two consecutive early spontaneous abortions that were not karyotyped, followed by two mid-trimester abortions for triploidy. Though the parental origin of the extra haploid set was not investigated in this case, the two triploid conceptuses had apparently normal placentas, suggesting digynic origin. The observation of several oocyte abnormalities following induced superovulation also points to a digynic origin in this case (BAR-AMI *et al.* 2003).

Pergament et al. (2000) reported a case of multiple apparent digynic triploid embryos in a woman seeking assisted reproduction treatment following two previous triploid gestations. This conclusion was based on the observation of two triploid embryos following ICSI, a technique which should largely exclude dispermic triploidy though not necessarily diplospermy. Because sperm injection occurred after the formation of the first polar body, the authors speculated that a defect in maternal meiosis II was present. The authors also proposed several alternative mechanisms (PERGAMENT *et al.* 2000). These include endoreduplication of the maternal pronucleus, the formation of an additional maternal pronucleus due to irregularities in the second meiotic division, or formation of an empty first polar body following complete meiosis I nondisjunction. Additionally, Pal et al. (1996) described a case of a woman undergoing multiple cycles of IVF which produced an unusually high frequency of triploid embryos. The authors proposed a primary oocyte defect leading to an increased rate of polyspermy. Though technically a case of recurrent diandric triploidy, the underlying mechanism is a defect in the oocyte that increases the risk for polyspermy. The authors also suggested a meiotic defect with polar body retention leading to digynic triploidy (PAL *et al.* 1996).

A few cases of familial recurrent diandric mole have been linked to global imprinting failure due to a recessive mutation of a gene located at 19q13.3-13.4 (BRANCATI *et al.* 2003; HUANG *et al.* 2004). More recent evidence points to a mutation in the *NLRP7* gene possibly being linked to recurrent triploid partial moles as well as other types of mole (DEVEAULT *et al.* 2009). It remains unknown how this mutation may lead to recurrent partial mole, but it is theorized that it may lead to defective oogenesis or create a hostile environment for embryogenesis within the fallopian tubes or uterus. Some evidence indicates it may cause early cleavage abnormalities in vitro and in vivo (DEVEAULT *et al.* 2009).

4.0 CHARATERISTICS OF TRIPLOID CELLS

4.1 MITOSIS AND PROLIFERATION

Triploid cells differ in many ways from normal diploid cells. Some studies have indicated that triploid cells take longer to replicate their DNA and thus longer to complete mitosis along with having a decreased rate of proliferation (FULTON *et al.* 1977; NIEBUHR 1974). Some evidence for this phenomenon has been observed in humans. If this is indeed the case, then one would expect the proportion of triploid cells in mixoploid individuals to decline over time, a phenomenon which has been observed in several cases. One patient was described as having a 1:1 ratio of diploid to triploid cells in skin fibroblasts at the age of five, but this ratio had decreased to 4:1 by the time the patient was eleven years old (FULTON *et al.* 1977). Graham et al. (1981) described a patient with 2n/3n mixoploidy in whom the proportion of triploid cells in skin biopsies taken from the calf decreased between the ages of one day and nine months. However, another study found that diploid and triploid cells had similar generation times in vitro (GRAHAM JR. *et al.* 1981). A study of the mitotic behavior of triploid fibroblast cells by Book et al. (1962) identified grossly abnormal behavior. These anomalies involved highly disturbed spindle formation and function leading to anaphase lag and ultimately gross aneuploidy and apoptosis in daughter cells. However, other labs have not reported similar findings.

Very limited work has been done to examine the meiotic behavior to triploid cells. Separate studies done on the oocytes of two triploid fetuses both reported similar findings (GOSDEN *et al.* 1976; LUCIANI *et al.* 1978). The principal observation was the presence of multiple chromosome configurations observed during leptotene and pachytene. These configurations were thought to represent univalents, bivalents, and trivalents. It was also observed that chromosomes could repeatedly change pairing partners

even along the same chromosome arm. It was also noted that synapsis cannot occur between three chromosomes and that only two chromosomes could be paired at any one time (GOSDEN *et al.* 1976).

4.2 X CHROMOSOME INACTIVATION

Triploid cells have also provided a unique opportunity to study the phenomenon of X chromosome inactivation (XCI). An early study of X inactivation in triploid cells found that 69,XXX triploids occur in one of two types (JACOBS *et al.* 1979). They can either exist with virtually all cells having one inactive X or they may have different populations of cells with one or two inactive X's. The authors did not identify any cases in which the majority of cells had two inactive X's. They also noted that there did not appear to be any correlation with the parental origin of the extra haploid set of chromosomes and the pattern of X inactivation. One of the more interesting findings of this study was that the number of late replicating X's in cells grown from fetal tissues was significantly lower than in cells grown from extrafetal tissues. The authors proposed two reasons for this phenomenon (JACOBS *et al.* 1979). First they suggested the possibility of tissue specific XCI in triploidy with fetal tissues tending to have a greater number of active X's. Alternatively, they suggested that fetal development may be more likely when two active X's are present as opposed to one.

This study also observed a significant effect with respect to gestational age. Extrafetal tissues taken from gestations with longer in utero survival tended to have an increased number of late replicating X's relative to gestations that were aborted earlier (JACOBS *et al.* 1979). Though apparent in all genotype classes, this phenomenon appeared most pronounced in the 69,XXY group. It is suggested that the presence of two active X's in fetal tissues may be advantageous at least during the early part of gestation while the presence of one active X may favor development of extraembryonic tissues. The authors proposed three possible explanations for this phenomenon, all of which suggest a certain degree of non-uniformity in the process of X inactivation in triploid cells. In essence, X inactivation in XXY or XXX triploid cells operates in such a way as to potentially create clones of cells with anywhere from zero

inactive X's in XXY cells to two inactive X's in XXX cells. This process also appears to be completely random. These observations seem to suggest the existence of autosomal factors that may be involved in the process of X inactivation.

The study of XCI in triploid cells has produced evidence of a putative autosomal transfactor that may be involved in the process (MIGEON *et al.* 2008). The observation that XXX and XXY triploids have two active X's in the majority of their cells has led to the hypothesis that three copies of this putative transfactor allows for two X's to remain active in at least a portion of cells.. However, 69,XXX cells with two Barr bodies have been demonstrated (NIEBUHR *et al.* 1972). Other studies of X inactivation in XXX and XXY triploid cells have shown that the rates of XCI can be quite variable though 69,XXX females tend to have one inactive X in the majority of their cells while 69,XXY males tend to have zero inactive X's (MARASCHIO *et al.* 1984). One interesting case of 48,XXYY/72,XXXYY mixoploidy was found to have no cells with two inactive X's in the triploid cell line while all diploid cell had one of their two X chromosomes inactivated (SCHMID and VISCHER 1967).

A study by Migeon et al. (2008) showed that 17/30 cases had mixed populations of cells with either one or two active X's. This observation could possibly reflect a certain level of instability in the X inactivation process. This study also confirmed earlier reports indicating that the presence of two active X's in skin fibroblasts is highly stable. The authors conclude that most triploid specimens have two active X's regardless of the parental origin of the extra X and that mixed populations of cells with one or two active X's originate at the time of X inactivation. They also noted that their observations are consistent with what would be expected if there is indeed an autosomal transfactor that plays a role in X inactivation. First, if two copies of this transfactor are sufficient for one inactive X, three copies may not be sufficient for two inactive X's. Second, variable tissue concentrations of this transfactor may lead to populations of cells with different numbers of inactive X's. Finally, there may be tissue-specific selection for or against cells with differing numbers of inactive X's (MIGEON *et al.* 2008).

4.3 DIPLOID/TRIPLOID MIXOPLOIDY AND TISSUE SPECIFICITY

In the context of 2n/3n mixoploidy, triploid cells often appear to demonstrate some degree of tissue specificity. The most striking feature is that lymphocytes are, in the vast majority of cases, entirely diploid with the triploid line only first being detected in skin fibroblasts (SHAFI *et al.* 2007). Triploid cells are detected solely in fibroblasts in roughly 70% of cases though the ratio of diploid to triploid cells is extremely variable (GOLUBOVSKY 2003; QUIGLEY *et al.* 2005). On the rare occasion that triploid cells are detected in lymphocytes, they are usually present in less than 5% of cells (WULFSBERG *et al.* 1991). There have been several notable exceptions to this rule. Ginnsberg et al. (1981) reported a 46,XY(1)/69,XXY(102) lymphocyte karyotype in an infant who died three hours after birth. A later report described a 4 ½ year old child with a 46,XX(57%)/69,XXX(43%) lymphocyte karyotype (CARAKUSHANSKY *et al.* 1994). There are a number of hypotheses to explain this phenomenon including selective elimination of triploid cells during the early differentiation of the hematopoietic system and a growth disadvantage of triploid lymphocytes *in vivo* and *in vitro* (FLORI *et al.* 2003). An additional theory suggests that this observation may be an artifact resulting from either an *in vitro* growth disadvantage of triploid cells or an inability of triploid lymphocytes to respond to phytohemagglutinin stimulation. Two cases may provide support for this hypothesis. The first is a report on a 2n/3n child whose bone marrow showed 57% triploid cells, but lymphocyte analysis only revealed 4% triploid cells (PETTENATI *et al.* 1986). An additional report describes a 46,XX/92,XXXX mixoploid child where 4n cells were found in 5/100 bone marrow cells but were entirely absent from peripheral lymphocytes (AUGHTON *et al.* 1988). These latter authors noted that bone marrow chromosome studies can be done without the need for additional culturing thus virtually eliminating the occurrence of *in vitro* artifacts.

It has been proposed that diploid cells have a selective advantage over triploid cells in certain tissues during early development and will ultimately replace them with this phenomenon being particularly prominent in the development of the hematopoietic system (GOLUBOVSKY 2003; SCHMID and VISCHER 1967). This phenomenon also appears to be prevalent in amniocytes where triploid cells appear

to be less able to proceed through mitosis and are apparently lost during metaphase evaluation (FLORI *et al.* 2003). The varying level of triploid cells in differing tissues is thought most likely due to a tissue specific degree of growth disadvantage in comparison with diploid cells (DANIEL *et al.* 2003). It has been proposed that the survival of 2n/3n fetuses may be dependent on the degree to which triploid cells are excluded from the fetus proper. Thus, 2n/3n fetuses exhibiting confined placental mosaicism for the triploid line have the best chance of survival with viability decreasing as the proportion of triploid cells within the fetus increases. The existence of a selective process during early embryogenesis in which triploid cells are actively assigned an extraembryonic fate has been proposed (DANIEL *et al.* 2003). This active sequestration of triploid cells to extraembryonic tissues has been proposed as a reason why mixoploidy is less often detected than pure triploidy as opposed to mixoploidy simply being a rarer phenomenon. Niebuhr (1974) proposed that this segregation may begin as early as the two-cell stage in which one blastomere is diploid and the other triploid. In this scenario, the diploid blastomere ultimately gives rise to the embryo proper while the triploid blastomere gives rise to extraembryonic tissues.

5.0 PHENOTYPIC CHARACTERISTICS OF COMPLETE TRIPLOIDY

5.1 PRENATAL DEVELOPMENT AND POSTNATAL SURVIVAL

Phenotypically, triploid conceptuses can exhibit an extremely wide range of characteristics ranging from grossly malformed to rarely almost normal in cases of 2n/3n mixoploidy (DOSHI *et al.* 1983). It has been suggested that the traits associated with triploidy can be viewed as a collection of those seen in individual autosomal trisomies, particularly those for chromosomes 13, 18, and 21 (GINSBERG *et al.* 1981). The spectrum of anomalies seen in triploidy, and even tetraploidy, has been noted to not necessarily be more severe than those seen in individual trisomies. This observation has led to the suggestion that the ratios between different chromosomes or parts of chromosomes is more important than the absolute number of chromosomes (GINSBERG *et al.* 1981). However, no direct relationship between gene dosage and metabolic activity has been found. Triploidy has been noted to most closely resemble trisomy 18, though it may also mimic trisomy 13 (BUTLER *et al.* 1969; GINSBERG *et al.* 1981). A large number of triploid spontaneous abortions contain severely malformed embryos if one is present at all, a phenomenon that mimics that seen in 45,X Turner syndrome (BUTLER *et al.* 1969).

A number of abnormalities within the intrauterine environment have been noted in triploid gestations. These include polyhydramnios as well as a large placenta exhibiting signs of molar degeneration (GALAN *et al.* 1991; THARAPEL *et al.* 1983). Polyhydramnios has been noted in 64% of cases in which amniotic fluid volume was monitored (BLACKBURN *et al.* 1982). Placental anomalies are believed to occur in roughly 22% of triploid gestations (MCWEENEY *et al.* 2009). An earlier survey of triploid spontaneous abortions indicated that 38% of placentas showed grossly cystic villi while 51% showed normal or clubbed villi and 11% showed hypoplastic villi (WARBURTON *et al.* 1991). These authors also noted that cystic villi were more likely to be identified in specimens retained in utero for a

longer period of time. Additionally, XXY placentas appeared more likely to show cystic changes than XXX placentas, an observation consistent with the fact that XXY will be diandric more often than XXX. Additional potential complications include maternal toxemia, preeclampsia, and premature labor and delivery (BLACKBURN *et al.* 1982; FULTON *et al.* 1977). Such complications were observed in 41/44 cases in a survey conducted by Blackburn et al. (1982).

One of the most common features is intrauterine growth retardation (IUGR) which has been noted in up to 66% of cases and is thought to result from a generalized deficiency in the proliferative ability of triploid cells or aberrant placental maturation and function (BETTS *et al.* 1989; SCHWAIBOLD *et al.* 1990). Placental dysfunction is thought to be a major cause of hypoplasia, IUGR, and ultimately intrauterine demise of triploid fetuses. Those triploid gestations that survive until birth are typically premature and growth retarded with a low to very low birth weight (DOSHI *et al.* 1983; NIEBUHR 1974; NIEBUHR *et al.* 1972). Crown-heel length generally corresponds to weight (NIEBUHR 1974). It is thought that low birth weight may be a result of decreased mitotic potential of triploid cells as evidenced by an observed generalized immaturity of the internal organs relative to the gestational age of triploid fetuses (GINSBERG *et al.* 1981). Some cases show severe hypoplasia of the internal organs (SCHWAIBOLD *et al.* 1990).

Liveborn triploid infants do not usually survive longer than a few hours to days with average postnatal survival being around 20 hours (DOSHI *et al.* 1983; SCHWAIBOLD *et al.* 1990). Longer postnatal survival is often correlated with a more normal appearing placenta rather than an absence of severe anomalies, though only about 30% of examined triploid placentas show normal histology (GALAN *et al.* 1991; SCHWAIBOLD *et al.* 1990). The longest reported postnatal survival was 10 ½ months in a 69,XXY male infant in which human leukocyte antigen (HLA) typing suggested a digynic origin of the extra haploid set (SHERARD *et al.* 1986). This child showed limited weight gain and development. Though no diploid cells were found in bone marrow, blood, or skin fibroblasts; the authors could not rule out the presence of a cryptic diploid line. Such a cryptic cell line may have been present in the placenta which was not studied in this case. Pneumonia, respiratory disease, and other respiratory problems are frequently noted as the cause of death in triploid liveborns (SHERARD *et al.* 1986; TAKABACHI *et al.*

2008). Alternatively, it has been suggested that death may result from biochemical dosage imbalances (DOSHI *et al.* 1983).

5.2 GENERAL MALFORMATION PATTERNS

A wide variety of malformations have been noted in triploid fetuses and liveborns. Common cranial defects include dysplastic skull bones, particularly of the calvarium, and an unusually large posterior fontanelle (RAMSEY *et al.* 1998; THARAPEL *et al.* 1983). Macrocephaly was noted in 16% of cases in a survey by Blackburn et al. (1982). Other common facial features include a broad nasal bridge, epicanthic folds, hypertelorism, and low set malformed ears (NIEBUHR *et al.* 1972; VAN DE LAAR *et al.* 2003). Hypertelorism and ear anomalies have been reported in 15-20% and 27% of cases respectively (BLACKBURN *et al.* 1982; GINSBERG *et al.* 1981). Triploidy often presents with some degree of ocular anomalies including coloboma, microcornea, ovoid cornea, and microophthalmia (DOSHI *et al.* 1983; GINSBERG *et al.* 1981; VAN DE LAAR *et al.* 2003). Blackburn et al. (1982) reported ocular anomalies in 39% of cases. The specific types of ocular anomalies suggest a defect very early in embryogenesis (GINSBERG *et al.* 1981). Oral anomalies are also common and can include cleft lip and/or palate, seen in 15% of cases; macroglossia; and micrognathia (CHANG *et al.* 2001; DOSHI *et al.* 1983; GALAN *et al.* 1991; VAN DE LAAR *et al.* 2003).

Limb and skeletal anomalies are also very common in triploidy. A high frequency of skeletal muscle abnormalities has been noted, particularly increased bulk of the thigh muscles (SCHWAIBOLD *et al.* 1990). Gosden et al. (1976) examined thigh muscle tissue from a 69,XXX triploid fetus showing increased muscle bulk and noted an unusually increased number of myotubes. This phenomenon is thought to result from an increased differentiation of cells which may be responsible for the well developed appearance of the thigh muscles. The authors suggested that this increased differentiation was secondary to abnormal intercellular communication and that this phenomenon may also explain the myocardial hypertrophy seen in some cases of triploidy (GOSDEN *et al.* 1976). Syndactyly of fingers 3-4

is one of the hallmark features of triploidy occurring in up to 72% of cases (BETTS *et al.* 1989). Another report cited that 3-4 syndactyly of the fingers and 2-3 syndactyly of the toes occur in approximately 47% of cases (BLACKBURN *et al.* 1982). Clinodactyly and/or camptodactyly of the fifth finger, single transverse palmar crease, flexion deformities of the upper limbs, and various talipes deformities of the feet are also common (BLACKBURN *et al.* 1982; NIEBUHR 1974).

A large number of internal anomalies involving every organ system have been noted in cases of triploidy. Some cases have been noted to show a generalized and severe hypoplasia of all internal organs, a feature thought to be related to a diminished proliferative capacity of triploid cells (ROYSTON and BANNIGAN 1987). Central nervous system anomalies are present in up to 57% of cases and include various malformations of the brain, hydrocephalus, and spina bifida (NIEBUHR 1974; PETTENATI *et al.* 1986). Holoprosencephaly also appears to be a somewhat common feature of complete triploidy. A literature review carried out by Bekdache et al. (2009) turned up 15 cases of holoprosencephaly associated with triploidy of which eight of nine cases where the type was defined were of the alobar type. Including the case reported by Bekdache et al. as well as another recently reported case, there have been 17 reports of holoprosencephaly associated with triploidy of which 10 were of the alobar type (BEKDACHE *et al.* 2009; SOLOMON *et al.* 2009). Abnormalities of the limbic system, hypothalamus, and pituitary as well as complete or partial agenesis of the corpus callosum have also been reported (PETTENATI *et al.* 1986). It has also been suggested that abnormalities of the forebrain may be closely associated with ophthalmologic abnormalities (BLACKBURN *et al.* 1982).

Congenital heart defects have been noted in 47-50% of cases with most involving septal or valvular defects (BETTS *et al.* 1989; DOSHI *et al.* 1983; NIEBUHR 1974). A study by Blackburn et al. (1982) indicated the rate of heart defects may be as high as 86%. Pulmonary hypoplasia and abnormal lobation of the lungs are also common with the latter being reported in up to 33% of cases (CHANG *et al.* 2001; DOSHI *et al.* 1983). Deformities of the gastrointestinal tract are seen in around 42% of cases with hypoplasia or agenesis of the gallbladder being the most common finding (NIEBUHR 1974; PETTENATI *et*

al. 1986). Renal anomalies including hypoplasia, hydronephrosis, polycystic kidneys, and horseshoe kidney have been noted in 44% of cases (BETTS *et al.* 1989; DOSHI *et al.* 1983; NIEBUHR 1974).

One of the more common internal findings in triploidy is adrenal hypoplasia which is seen in 40-44% of cases (BETTS *et al.* 1989; PETTENATI *et al.* 1986). This feature is thought to be related to the production of maternal estrogens by way of the feto-placental unit and may be related to low maternal estriol late in pregnancy (MARASCHIO *et al.* 1984; NIEBUHR 1974).

Additionally, triploid infants often show hematopoietic anomalies. This most frequently manifests as extramedullary hematopoiesis, most commonly in the liver but occasionally involving the spleen, kidneys, and other tissues (DOSHI *et al.* 1983; ROYSTON and BANNIGAN 1987). This extramedullary hematopoiesis may be related to delayed maturation of the bone marrow (HOHLFIELD *et al.* 1997). It has been suggested that this phenomenon may be linked to fetal hypoxia resulting from inadequate function of a partially molar placenta. This phenomenon may also be linked to a biochemical abnormality directly associated with the triploid state and may point to an increased tendency towards hemolytic destruction of erythrocytes (DOSHI *et al.* 1983). Other commonly seen hematopoietic anomalies include macrocytosis, abnormally large platelets, and an increased number of nucleated red blood cells (DEAN *et al.* 1997; SMETS *et al.* 1995; WRIGHT and WALES 2004). Macrocytosis may be linked to the increased DNA content of erythroblasts and/or increased production of fetal hemoglobin (SMETS *et al.* 1995). In addition to increased hematopoiesis in the liver and spleen, Blackburn et al (1982) reported an increased concentration of iron pigment in the hepatic Kupffer cells. The authors suggested that these features may be related to increased hemolysis in triploid infants as the result of an increased concentration of red blood cell antigen. Hohlfield et al. (1997) carried out hematological examinations of 11 triploid fetuses and found that all fetuses were anemic and had micromegakaryocytes as well as a number of other findings.

Omphalocele, umbilical hernia, or other abdominal wall defects are thought to account for more than half of all anomalies affecting the trunk in triploidy (BLACKBURN *et al.* 1982; DOSHI *et al.* 1983). Omphalocele is thought to occur due to failure of the midgut loop to return to the abdominal cavity from

the extraembryonic coelum around 6-10 weeks of gestation due to defective embryonic folds (LIN *et al.* 1998). This could be interpreted as another indicator of disturbed morphogenesis in the presence of an extra haploid set of chromosomes. Several other anomalies also appear to be somewhat common in triploidy including hypoplasia of the thymus, abnormal dermatoglyphics, and postnatal growth deficiency in those rare cases of longer postnatal survival (DOSHI *et al.* 1983; NIEBUHR 1974)

5.3 GENITAL ABNORMALITIES

Abnormalities of both the external and internal genitalia are quite common in triploidy and the severity of these defects may be influenced by both genotype and presence of Barr bodies. The most severe genital abnormalities have been observed in liveborns with no Barr bodies (NIEBUHR 1974). It has been proposed that the severity of genital malformations is inversely correlated with the presence of Barr bodies (GRAHAM JR. *et al.* 1981). Cases where at least a proportion of cells contain Barr bodies may have less severe genital abnormalities, however this may not hold true in cases of 46,XY/69,XXY mixoploidy in which the triploid line has two active X chromosomes. Recently, it has been suggested that the *Dax1* gene on chromosome Xp21.3-p21.2 may play a role in the genital anomalies seen in triploidy (MCFADDEN *et al.* 2000). The gene product is thought to antagonize *SRY* and is responsible for the dosage-dependent sex-reversal seen in 46,XY,dup(Xp) individuals. Because individuals with 47,XXY Klinefelter syndrome develop as males, it is assumed that the extra copy of *Dax1* is silenced by X inactivation in these cases. However, the highly irregular X inactivation seen in triploid cells can result in populations of cells with 2 active X's and thus overexpression of *Dax1*. In this respect, the authors suggest that those 69,XXY cases without gonadal dysgenesis or other severe genital abnormalities may have predominantly cells with a single active X chromosome.

Genital abnormalities are seen in roughly 15% of 69,XXX triploids (MCFADDEN *et al.* 2000). When present, hypoplastic ovaries are often the only genital abnormalities seen in such cases (NIEBUHR 1974). . There have been two reports of 69,XXX fetuses with hypoplastic external genitalia, unicornuate

uterus, and ovarian dysgenesis with few or no oocytes present (CUNNIFF *et al.* 1991). Ovarian dysgenesis and the associated absence of primordial follicles are thought to be the result of early death of oocytes during embryonic development due to meiotic pairing abnormalities introduced by the extra set of chromosomes (CUNNIFF *et al.* 1991). Often there is a severely reduced number of primordial follicles (DOSHI *et al.* 1983; SCHWAIBOLD *et al.* 1990). Hyperplasia of the ovarian hilum cells has also been noted and said to be analogous to testicular Leydig cell hyperplasia (SCHWAIBOLD *et al.* 1990). This phenomenon is thought to be related to excess stimulation by β-hCG. There has also been one case of a 68,XX liveborn with a prominent clitoris not covered by the labia minora and absence of the fourchette (MERLOB *et al.* 1991). A survey by McFadden et al. (2000) also reported several cases with abnormal prominence or persistence of the primitive sex cords.

An estimated 97% of 69,XXY triploids have some degree of genital ambiguity (BETTS *et al.* 1989). Among the more commonly reported anomalies are slight to severe genital malformation, small penis, hypospadias, bifid scrotum, undescended testes, Leydig cell hyperplasia, and tubular hyperplasia with the presence of normal appearing germ cells (DOSHI *et al.* 1983; NIEBUHR 1974; THARAPEL *et al.* 1983). Blackburn et al. (1982) reported that the most common abnormalities were cryptorchidism (85%), micropenis (75%), and scrotal anomalies (61%). Occasionally the testes may be surrounded by a peripheral rim of immature ovarian tissue (KOS *et al.* 2005). There has been one report of a 69,XXY infant with an abnormal uterus and fallopian tubes (LEISTI *et al.* 1974). A second case has been reported as having severely dysgenetic undescended testes and rudimentary female internal genitalia (MCFADDEN *et al.* 2000). The intersex characteristics seen in 69,XXY triploidy are similar to those seen in 46,XX/46,XY or 45,X/46,XY mosaics (BUTLER *et al.* 1969). Considering that 47,XXY Klinefelter males are phenotypically male with no intersex characteristics, it has been suggested that the genital abnormalities are a result of abnormal interactions between the three haploid sets rather than an imbalance between autosomes and sex chromosomes (BUTLER *et al.* 1969; NIEBUHR 1974). It has been proposed that insufficient levels of luteinizing hormone may be responsible for the observed genital anomalies (JARVELA *et al.* 1993). Considering that digynic triploids have abnormally small placentas with markedly

decreased hCG and estriol, it has been suggested that these low hCG levels may compromise testosterone production by the Leydig cells and lead to incomplete virilization (MCFADDEN *et al.* 2000). It has been suggested that this may account for the findings of genital abnormalities in the presence of normal gonads in digynic triploids. There has only been a single report of liveborn 69,XYY triploidy reported in the literature (DELIGDISCH *et al.* 1978). This infant was born alive at 22 weeks but died immediately. Undescended testes with poorly developed Leydig cells, extreme micropenis, and agenesis of the scrotum were present along with numerous other severe anomalies incompatible with life including alobar holoprosencephaly.

5.4 ASSOCIATION WITH PARTIAL HYDATIDIFORM MOLE

Partial hydatidiform mole is the most common feature associated with triploid gestation with the majority of diandric triploid placentas believed to undergo partial molar degeneration (ZARAGOZA *et al.* 2000). It is estimated that 80-85% of diandric triploid pregnancies and abortuses have a partial molar placenta (DOSHI *et al.* 1983; MONTGOMERY *et al.* 1993). Partial mole has a strong association with diandric triploidy but is not associated with digynic triploidy, however it is not clear if all diandric triploids are destined to become partial moles (ZARAGOZA *et al.* 2000). Indeed, a study by Zaragoza et al. (2000) found that only ½ of diandric triploids also received a diagnosis of partial mole. The authors suggested that the diagnosis of PHM in diandric triploids may be related to the gestational age of the fetus since the characteristic features of partial mole may not appear until relatively late in gestation.

It has been hypothesized that the presence of a partial molar placenta may be related to Leydig cell hyperplasia seen in male fetuses (DOSHI *et al.* 1983). It is thought that this phenomenon may be related to increased production of hCG by the hypertrophic trophoblast. The observation of similar testicular findings in infants with choriocarcinoma lends support to this hypothesis. The synthesis of testosterone in the fetal testis is stimulated by hCG which can bind receptors within testicular Leydig cells and tubular epithelium (DOSHI *et al.* 1983).

Primary identifying characteristics for partial hydatidiform mole include circumferential trophoblast hyperplasia, hydropic villi, irregular villous contours, and dysmorphic villi (ZARAGOZA *et al.* 2000). Morphologically, villi can range from normal to cystic and include trophoblastic inclusion and occasional villous cistern formation (HOFFNER *et al.* 2008). Unlike complete moles, the placental vessels of partial moles often contain nucleated fetal erythrocytes indicative of more advanced fetal development (SURTI *et al.* 2005). Histologically, triploid partial moles can be difficult to distinguish from diploid hydropic abortuses (LEGALLO *et al.* 2008). Another source of misdiagnosis is the occasional presence of some features of partial mole in non-triploid conceptuses. It has been noted that the occurrence of trophoblast inclusions is rather common in trisomy 16 placentas and that these placentas may occasionally be mistakenly diagnosed as partial moles (JACOBS *et al.* 1982a).

Though less frequent and less severe than in complete mole, partial hydatidiform mole has the potential to lead to a variety of complications. The most serious of these is persistent gestational trophoblastic disease which may follow 0.5-5.0% of partial molar pregnancies (LEGALLO *et al.* 2008). Choriocarcinoma has also been reported following PHM, though the occurrence is rare (MEDEIROS *et al.* 2008). Another infrequent complication is the occurrence of theca lutein cysts which are observed in the maternal ovaries in up to 10% of triploid pregnancies. (FRATES and FEINBERG 2000). These cysts are a form of ovarian hyperstimulation resulting from excessive β-hCG secretion by the hyperplastic trophoblast. There has been one report of full blown ovarian hyperstimulation syndrome following a spontaneously conceived triploid gestation (LUDWIG *et al.* 1998). Early onset preeclampsia developing before 20 weeks of gestation is also a common finding with a few reported cases of triploidy complicated by severe HELLP syndrome (CRAIG *et al.* 2000; FALKERT *et al.* 2009; RAMSEY *et al.* 1998; STEFOS *et al.* 2002). This phenomenon is thought to result from poor trophoblastic proliferation of the deep maternal spiral arteries (PIETRANTONI *et al.* 1995). In the context of a diploid fetus coexisting with a triploid partial molar placenta, fetal mortality is often the result of anemia due to hemorrhaging from the abnormal placental vasculature (HSIEH *et al.* 1999).

Though rare, there are reports of normal diploid fetuses coexisting with triploid partial molar placentas (NIEMANN *et al.* 2008). It is estimated that roughly 1 in 22,000-100,000 partial moles occur in association with a twin fetus (GOLUBOVSKY 2003). Some studies have suggested that molar placentas are more common when the associated fetal karyotype is 69,XXY as opposed to 69,XXX (RAMSEY *et al.* 1998). A number of factors contribute to fetal survival including fetal karyotype, size and rate of degeneration of the molar placenta, and the occurrence of fetal anemia or other obstetric complications (HSIEH *et al.* 1999).

5.5 MOLAR GESTATION FROM TRIPLOID ZYGOTES

Cytological evidence suggests that diploidization of an initially triploid zygote can result in a diploid fetus with a triploid partial mole or a triploid fetus with a diploid complete mole (GOLUBOVSKY 2003). It is hypothesized that these sorts of associations may occur frequently but are not diagnosed due to very early fetal demise. It may also be possible to have a diploid biparental fetus coexisting with a diploid androgenetic complete mole with both deriving from a single dispermic triploid zygote. In this scenario, one of the male pronuclei will join with the female pronucleus while the second male pronucleus would undergo endoreduplication which would temporarily create a tetraploid state in the zygote (NIEMANN *et al.* 2008). The first zygotic division would then result in the biparental genome going to one blastomere and the diploid androgenetic genome going to the other. A similar result can be obtained following trispermic fertilization.

Yet another model involves the formation of a tripolar spindle following replication of all three pronuclei (HSU *et al.* 2008). The zygote would then divide into three blastomeres with one being heterozygous and diandric while the other two are biparental with different paternal and like maternal genomes. It may also be possible to get a virtually identical result following diplospermic fertilization (HSU *et al.* 2008). In this scenario, the diploid male pronucleus replicates prematurely with one of the daughter nuclei being separated in a cytoplasmic fragment and developing into an androgenetic complete

mole. The remaining diploid male pronucleus is then separated into two haploid sets by a bipolar spindle with each set fusing with one of the replicated maternal pronuclei. These can then go on to form separate biparental blastomeres with different paternal but identical maternal complements.

6.0 PHENOTYPIC CHARACTERISTICS OF DIPLOID/TRIPLOID MIXOPLOIDY

6.1 COMPARISON WITH COMPLETE TRIPLOIDY

Diploid/triploid mixoploidy has been a recognized syndrome for at least twenty-five years but is believed to be rare or underdiagnosed in adults with mental retardation and congenital abnormalities due to the infrequency of fibroblast karyotyping (GOLUBOVSKY 2003; VAN DE LAAR *et al.* 2003). . Both syndromes likely have similar phenotypes though the mixoploidy phenotype is often less severe and associated with longer survival (QUIGLEY *et al.* 2005; VAN DE LAAR *et al.* 2003). It has been suggested that the complete triploid phenotype may be blurred by the presence of a high proportion of diploid cells (NIEBUHR 1974). Overall, mixoploids tend to have a less severe phenotype than complete polyploids (EDWARDS *et al.* 1994). It is possible that some diploid/triploid mixoploids may show only placentamegaly and hemihypertrophy (NIEBUHR 1974). Viability is likely related to the tissue distribution of triploid cells, though there does not appear to be a strong correlation between percentage of diploid cells in examined tissues and survival (DEVRIENDT 2005; KARTESZI *et al.* 2006). It has been noted that the highly variable phenotypic spectrum of diploid/triploid mixoploidy mirrors the variability seen in other types of chromosomal mosaicism (RITTINGER *et al.* 2008). This seems especially true when considering the degree of mental retardation which can range from mild to severe. The internal findings in 2n/3n mixoploidy are less consistent and less severe than in complete triploidy (DOSHI *et al.* 1983; PETTENATI *et al.* 1986). Specifically, severe brain, cardiac, and renal anomalies are much less common in mixoploidy and their absence may contribute to longer survival.

6.2 GENERAL PHENOTYPIC TRAITS

The craniofacial anomalies seen in triploid mixoploidy are essentially the same as those seen in complete triploidy though they are often less severe. Among the more commonly seen anomalies are malformed and/or low set ears and microstomia which are seen in greater than 50% and 42% of cases respectively (VAN DE LAAR *et al.* 2003). Other commonly seen anomalies include a broad forehead, downslanting palpebral fissures, hypertelorism, micrognathia, a short upturned nose with a depressed bridge, and a triangular face (MULLER *et al.* 1993; QUIGLEY *et al.* 2005; WULFSBERG *et al.* 1991). Eye defects such as coloboma and microophthalmia are less common than in complete triploidy, but are still sometimes seen (VAN DE LAAR *et al.* 2003). Oral defects such as cleft lip and/or palate are also less common than in complete triploidy (FULTON *et al.* 1977).

Limb defects are seen in close to 100% of cases of diploid/triploid mixoploidy with 3-4 syndactyly of the fingers and/or 2-3 syndactyly of the toes being most common (PETTENATI *et al.* 1986; VAN DE LAAR *et al.* 2003). Syndactyly can also occur between other digits. Syndactyly and clinodactyly are seen in greater than 50% of cases. Clinodactyly of the fifth finger is also common as is camptodactyly. The camptodactyly has been described as "unusual and cup-like" and is considered a hallmark of the syndrome (RITTINGER *et al.* 2008). The presence of a single transverse palmar crease is also a common finding (WULFSBERG *et al.* 1991). The presence of a sandal gap between the first and second toes as well as short halluces are also a common finding having each been reported in approximately 45% of cases (VAN DE LAAR *et al.* 2003).

Muscular atrophy confined to the extremities has been documented in approximately 35% of the cases of diploid/triploid mixoploidy (SHAFI *et al.* 2007; VAN DE LAAR *et al.* 2003). Shafi et al. (2007) described a case of late onset myopathy in a 25 year old woman with 2n/3n mixoploidy and obtained the first histological evidence of myopathy. This case was considered to be a mild form of autosomal dominant central core disease and its co-occurrence with diploid/triploid mixoploidy in this patient was possibly a random event.

Internal anomalies in 2n/3n mixoploidy are both less common and less severe than in complete triploidy. A study by Doshi et al. (1983) reported no consistent internal findings. Cerebral anomalies, when present, most commonly involve partial or complete agenesis of the corpus callosum (VAN DE LAAR *et al.* 2003). It has been hypothesized that central nervous system anomalies may lead to anomalies in the limbic system, hypothalamus, or pituitary which in turn could lead to abnormalities of the adrenal glands or gonads (JARVELA *et al.* 1993). Heart defects are also less common than in complete triploidy (VAN DE LAAR *et al.* 2003). Other occasionally reported findings include congenital hypothyroidism secondary to thyroid agenesis and horseshoe kidney (VAN DE LAAR *et al.* 2003).

The longer survival of 2n/3n mixoploids has allowed for the observation of a number of anomalies involving growth and development. Early feeding difficulties have been reported in 38% of cases (VAN DE LAAR *et al.* 2003). Asymmetric growth with or without minor skeletal anomalies are also a common finding seen in up to 57% of cases (DONNAI *et al.* 1986; PETTENATI *et al.* 1986). It has been hypothesized that later growth asymmetry arises from early asymmetric distribution of triploid versus diploid cells in the blastodermic vesicle (FERRIER *et al.* 1964). It is thought that this imbalance may adversely affect the growth of embryonic tissues on one side of the body axis and that the child may never be able to recover from this early imbalance. This asymmetry may be restricted to only involving the face or only involving one or both limbs on one side of the body (GOLUBOVSKY 2003; MULLER *et al.* 1993). Postnatal growth retardation with or without delayed bone age has been noted in 70-74% of cases with 70% of these being noted prenatally (PETTENATI *et al.* 1986; VAN DE LAAR *et al.* 2003).

Mental and psychomotor retardation are a nearly universal feature of 2n/3n mixoploidy (MULLER *et al.* 1993; SHAFI *et al.* 2007). It is seen in greater than 50% of patients though with highly variable severity that appears to be independent of the proportion of triploid cells present (VAN DE LAAR *et al.* 2003). Mental retardation is often the initial presenting symptom leading to a diagnosis. Abnormal EEG activity with or without an associated seizure disorder is also seen in 44% of cases (MULLER *et al.* 1993; VAN DE LAAR *et al.* 2003).

Pigmentary dysplasia is an additional finding seen in 38% of patients (GOLUBOVSKY 2003; VAN DE LAAR *et al.* 2003). This feature often develops later in life and most closely resembles hypomelanosis of Ito. The hyper or hypopigmented streaks often follow Blaschko's lines and are a feature indicative of mosaicism (DEVRIENDT 2005). It has been hypothesized that this phenomenon may result from genetic differences between melanocytes migrating from the neural crest and the surrounding tissues of their destination (WULFSBERG *et al.* 1991). In other words, the melanocytes may be triploid and the dermal cells diploid or vice versa. Blaschko's lines are themselves thought to indicate the route of melanocyte migration during early embryogenesis.

A number of other miscellaneous anomalies are also seen with varying degrees of frequency in diploid/triploid mixoploidy. Neonatal respiratory distress has been reported in up to 44% of cases (VAN DE LAAR *et al.* 2003). Hypotonia is also common and occurs in greater than 50% of cases. Hematological anomalies such as dyserythropoietic anemia have also been reported (WRIGHT and WALES 2004). Hearing loss has also been reported (MULLER *et al.* 1993). Truncal obesity is also common and may develop later in childhood following a somewhat dystrophic appearance during infancy (SHAFI *et al.* 2007).

6.3 SEX AND GENOTYPE SPECIFIC TRAITS

Due to the different possible combination of sex chromosomes seen in diploid/triploid mixoploidy, there are a wide variety of genital anomalies associated with the syndrome. Males tend to have small to ambiguous genitalia depending on the sex chromosome complement of the two cell lines (QUIGLEY *et al.* 2005). Insufficient luteinizing hormone has been proposed as a possible cause of these anomalies and may be tied to hypothalamic problems (GRAHAM JR. *et al.* 1981; JARVELA *et al.* 1993). Cryptorchidism is also common and greater than 50% of males have a small phallus (VAN DE LAAR *et al.* 2003).

Females tend to have few if any abnormalities. There have been some reports of precocious puberty and ovarian agenesis, though the latter is much less common than in complete triploidy (VAN DE

LAAR *et al.* 2003). 46,XX/69,XXX mixoploids always have apparently normal female external genitalia (OKTEM *et al.* 2007).

Individuals with 46,XX/69,XXY mixoploidy can range from normal males to hermaphroditism with ovotestis disorder (OKTEM *et al.* 2007). This conforms to the rule that the presence of a Y chromosome induces testicular differentiation of the primitive gonad, however there has been a reported case of normal female phenotype in an individual with a 46,XX/69,XXY karyotype and ovarian expression of *SRY* (OKTEM *et al.* 2007). Molecular analysis found no mutations in *SRY* or its promoter sequences, however the patient was not tested for possible mutations in downstream targets of *SRY*. The authors proposed a mechanism by which double dose of the dosage-sensitive sex-reversal (*DAX1*) gene located on chromosome Xp21 may have caused sex-reversal by overriding *SRY*. This phenomenon has previously been shown in 69,XXY triploidy presenting with ambiguous genitalia or sex reversal (OKTEM *et al.* 2007). There is also an increased risk of gonadoblastoma in 46,XX/69,XXY mixoploidy (OKTEM *et al.* 2007).

The phenotypic spectrum of 46,XY/69,XXY mixoploids may be just as wide as that in 46,XX/69,XXY. One report describes a 46,XY/69,XXY fetus with completely ambiguous external genitalia, testes surrounded by a rim of immature ovarian tissue, and an absent prostate with an unusually large utricle in its place (BENDON *et al.* 1988). There has been a single case of very low grade 46,XY/69,XYY mixoploidy reported in the literature (SELLYEI *et al.* 1971). This was found in the blood of a phenotypically normal adult male undergoing genetic testing due to a putative genetic disorder in his son. The authors postulated that this may have had a somatic origin by way of tripolar division of a rare 92,XXYY tetraploid cell.

6.4 DIFFERENTIAL DIAGNOSIS

The large degree of phenotypic variability seen in diploid/triploid mixoploidy allows for a nearly equally wide range of potential differential diagnoses. The syndrome is most often said to mimic different

genomic imprinting disorders and present with different features being more prominent at different times of development (RITTINGER *et al.* 2008). Features reminiscent of Russel-Silver syndrome, of which 10% of cases are associated with UPD(7), may be evident at an early age (LAMBERT *et al.* 2001; ROBINSON *et al.* 1997). These features may include asymmetry, a triangular face, and a broad forehead. The onset of truncal obesity may be reminiscent of Prader-Willi syndrome (RITTINGER *et al.* 2008). Features resembling congenital hyperinsulinism and Beckwith-Wiedeman syndrome, both linked to defects in an imprinted gene cluster on chromosome 11p15, have also been seen (GIURGEA *et al.* 2006; RITTINGER *et al.* 2008). Finally, the precocious puberty seen in some cases is reminiscent of that seen in maternal UPD(14) (DEVRIENDT 2005). Imbalances in dosage sensitive or imprinted genes have been proposed as a possible explanation for this phenomenon (RITTINGER *et al.* 2008). The similarity between 2n/3n mixoploidy and various imprinting disorders such as BWS and SRS may be explained by imprinted genes being expressed on one haploid set and silenced on the other two or vice versa.

This syndrome may also mimic several other disorders that are not associated with imprinting defects. There appears to be considerable phenotypic overlap with Camera-Marugo-Cohen syndrome (LAMBERT *et al.* 2001). Pigmentary anomalies resemble those seen in hypomelanosis of Ito, a disorder that is often indicative of mosaicism (RITTINGER *et al.* 2008). Finally, there is considerable overlap with the even rarer syndrome of diploid/tetraploid mixoploidy (RITTINGER *et al.* 2008).

6.5 TRIPLOIDY AND TRISOMY

Approximately 7% of triploids occur in conjunction with numerical trisomies (GOLUBOVSKY 2003). This figure appears to be higher than average when considering that 50% of karyotypically abnormal pregnancies contain fetal trisomies and that 15-20% of pregnancies end in miscarriages which suggests 5% of recognized pregnancies contain trisomies. This co-occurrence is thought to be related to the generalized chromosome instability of triploid cells, at least during the pronuclear and early cleavage stages of development. A recent survey of embryos from women undergoing preimplantation genetic

screening, but without any known risk factors, has provided some support for this hypothesis (VANNESTE *et al.* 2009). The authors noted an unusually high rate of chromosome instability in cleavage stage embryos including whole chromosome imbalances. Considering that such instability was found in otherwise normal diploid embryos, it seems reasonable to infer that such instability would only be increased in triploid embryos due to the presence of an entire extra haploid set of chromosomes. These anomalies can occur as either additional aneuploidies in a single triploid line or as mixoploidy/aneuploidy in which there may be two or three different cell lines. As an example of the former, there have been multiple reported cases of fetuses exhibiting a 68,XX karyotype (MERLOB *et al.* 1991).

Trisomy and other chromosome abnormalities are thought to be less detrimental to the development of triploid fetuses than to that of otherwise diploid fetuses. It has been suggested that, in the presence of a triploid and an aneuploid cell line, the two constitutional anomalies may partially cancel each other out such that the resultant phenotype is less severe than when either anomaly occurs alone. This hypothesis was initially suggested based on the observation of two cases of 69,XXY/45,X mixoploidy in which the phenotypes were less severe than either complete triploidy or non-mosaic monosomy X (BETTS *et al.* 1989; QUIGLEY *et al.* 2005). An additional case of 2n/3n mixoploidy in conjunction with sex chromosome aneuploidy was reported in the case of an 11 month old child with severe mental retardation, multiple malformations, and a 48,XXYY/71,XXXYY karyotype (SCHMID and VISCHER 1967).

There have been several published reports of liveborn mixoploid/aneuploid infants with autosomal trisomies in which no normal diploid cell line was present. One particularly exceptional report describes a girl with a 47,XX,+15/69,XXX karyotype who lived for more than 3 ½ years (DEAN *et al.* 1997). Normal 46,XX cells were only found in amniotic fluid, amnion, and chorion. However, these accounted for only five of a combined total of 63 cells from these tissues and the authors could not be certain if this cell line actually existed or if it was some sort of contamination or artifact. No 46,XX cells were found in umbilical cord, cord blood, peripheral blood, bone marrow, muscle biopsy, or skin fibroblasts. All of these tissues were 47,XX,+15/69,XXX with the triploid cell line predominating in

each. She had multiple dysmorphic features and showed severe psychomotor delay prior to succumbing to complications from an upper respiratory infection at the age of 3 years and 8 months. The authors noted only one case of apparently non-mosaic trisomy 15 in a liveborn infant who survived 4 days (DEAN *et al.* 1997).

A second exceptional case reported by Dahl et al. (1988) describes a liveborn infant with a 46,XY,+2p/69,XXY karyotype. This child showed multiple external and internal anomalies and survived 5 weeks, but with no signs of development or medical improvement. The authors note that there have been no reports of liveborn complete trisomy 2p, though there have been several reports of segmental trisomies for 2p or 2q. All of this latter group were linked to parents who were balanced translocation carriers, however the parental karyotypes were normal in this case (DAHL *et al.* 1988). Some of the features in this case were noted to be consistent with those seen in segmental trisomy 2p.

7.0 PARENT-OF-ORIGIN EFFECTS

7.1 GENOMIC IMPRINTING

One of the most interesting aspects of triploidy is the effect that the parental origin of the extra haploid set of chromosomes has on phenotype. It is believed that the observed correlation between parental origin of the extra haploid set and resultant phenotype is directly related to genomic imprinting (CHANG *et al.* 2001). It has long been recognized that paternally expressed genes are critical for proper development of extraembryonic tissues while maternally expressed genes are essential for proper development of the embryo proper (MCFADDEN and KALOUSEK 1991). It has been suggested that this imprinting effect may account for an apparent advantage of digynic triploidy as a non-cystic placenta may be correlated with longer intrauterine survival (CHANG *et al.* 2001).

Evidence supporting large scale imprinting effects on placental morphology has been found. It has been shown that digynic triploidy with asymmetric IUGR is always associated with severe adrenal hypoplasia (MCFADDEN and ROBINSON 2006). As fetal growth of the adrenal glands is influenced by hCG, this finding points to insufficient production of this hormone by the small digynic placenta. On the other hand, diandric triploidy generally shows fairly normal growth and is generally not associated with adrenal hypoplasia (MCFADDEN and ROBINSON 2006). This could thus reflect the increased placental volume and/or syncytiotrophoblastic hyperplasia seen in diandric placentas. These findings all reflect studies suggesting that imprinted genes may be more important to placental development and that any effects on the fetus are secondary to those on the placenta (MCFADDEN and ROBINSON 2006).

7.2 EFFECTS ON EMBRYO MORPHOLOGY

The examination of embryos, triploid or otherwise, can be somewhat problematic for various technical and practical reasons (PHILIPP *et al.* 2004). Indeed most early abortion specimens are either incomplete or damaged during evacuation to the extent that they are of little use for morphological assessment. The malformation pattern seen in triploid embryos appears to be nonspecific (MCFADDEN and ROBINSON 2006). These embryos commonly show generalized growth disorganization or other nonspecific abnormalities that may be conducive to at least somewhat normal embryogenesis. Philipp et al. (2004) utilized transcervical embryoscopy to perform morphological examinations of missed abortions of less than eight weeks gestational age prior to dilation and curettage. Their survey included 18 triploid abortuses, 13 of which were 69,XXY and five 69,XXX. Structural defects were detected in 17 of these embryos and included facial anomalies (n = 15), limb anomalies (n = 13), microcephaly (n = 11), and neural tube defects (n = 10). The authors also noted that 12/18 cases showed signs of partial molar degeneration. It was suggested that the high rate of malformations was representative of severely disturbed morphogenesis that are rarely overcome in triploid conceptuses. The authors were unable to offer a hypothesis regarding the apparent overexpression of severe craniofacial and limb defects in embryos relative to fetuses. It is known that the parental origin of the extra haploid set of chromosomes is important in determining the placental and embryonic phenotype in up to 2/3 of cases (PHILIPP *et al.* 2004).

The general consensus is that there does not appear to be a discernable parent-of-origin effect on the phenotype of triploid embryos (MCFADDEN and ROBINSON 2006). The absence of apparent growth differences between digynic and diandric embryos suggests that these differences develop later during the fetal period. Evidence also suggests that growth differences may be more related to placental phenotype than to direct imprinting effects on the embryo or fetus (MCFADDEN and ROBINSON 2006). Overall, the morphology of triploid embryos appears to be fairly uniform consisting of craniofacial anomalies, microcephaly, and delayed limb development (MCFADDEN and KALOUSEK 1991).

7.3 EFFECTS ON FETAL MORPHOLOGY

The majority of the abnormalities seen in either complete triploidy or 2n/3n mixoploidy do not show any parent-of-origin effects (MCFADDEN and ROBINSON 2006). It has been suggested that observed parent-of-origin effects arise from an altered intrauterine environment which is dependent on placental morphology which in turn is dependent on the parental origin of the extra haploid set. Diandric triploidy, also known as type I triploidy, is characterized by relatively normal fetal growth with either relative microcephaly or proportionate fetal head size (MCFADDEN and KALOUSEK 1991). It is thought that this may be due to a higher degree of trophoblast development which provides more nourishment to the fetus. If IUGR is present, it is usually mild and symmetric (MCFADDEN and ROBINSON 2006). The adrenal glands of diandric triploids are usually normal. This is thought to be a result of increased placental volume and/or hyperplasia of the syncytiotrophoblast which in turn leads to increased levels of hCG. Diandric triploidy has also been associated with increased nuchal translucency on ultrasound (DALMIA *et al.* 2005; STEFOS *et al.* 2002).

Digynic, or type II, triploidy is most commonly associated with a strikingly abnormal fetus with severe asymmetric IUGR and relative macrocephaly (MCFADDEN and KALOUSEK 1991). The IUGR is thought most likely due to placental insufficiency and most commonly affects the limbs and trunk (BARKEN *et al.* 2008; MCFADDEN and KALOUSEK 1991). The relative macrocephaly can sometimes be to an extreme extent (MINY *et al.* 1995). Nuchal translucency is often normal on ultrasound (MCFADDEN and ROBINSON 2006). Severe adrenal hypoplasia is also a common finding along with small kidneys (MCFADDEN and ROBINSON 2006; MINY *et al.* 1995).

7.4 EFFECTS ON PLACENTAL MORPHOLOGY

The origin of the diandric and digynic triploid phenotypes remain somewhat unclear and puzzling, though it is now thought that it may have to do with a direct imprinting effect on placental morphology and function (MCFADDEN and KALOUSEK 1991). The parental origin of the extra haploid set of chromosomes in triploidy appears to play a major role in placental development and morphology. Diandric triploid gestations are believed more likely to present as partial hydatidiform moles and are less likely to contain fetal components than digynic triploids (ZARAGOZA *et al.* 2000). However, one study on a large series of triploid conceptuses ranging from 7-16 weeks gestational age found that only 8/53 had partial molar placentas (MCFADDEN and PANTZAR 1996). The authors noted that all eight partial moles were among 44 cases of less than nine weeks gestational age and that all four cases of partial mole that also had an embryo showed abnormal embryo morphology. All of the non-molar triploids in this study showed mainly non-specific placental changes. These placentas were mostly non-hydropic with occasional collapse of the villous stroma and autolysis of the trophoblastic epithelium.

There also appears to be a relationship between the gestational age of diandric triploids and the presence of a partial molar placenta. A study by Zaragoza et al. (2000) showed that only 33% of the placentas from triploid spontaneous abortions of less than 8.5 weeks gestational age showed partial molar changes while this value increased to over 50% for older abortuses. It is theorized that better trophoblast development and only partial cystic degeneration of the placenta may allow for more adequate fetal nourishment and thus better growth and development (MCFADDEN and KALOUSEK 1991). In other words, the level of fetal development in diandric triploids may be dependent on the degree of molar degeneration of the placenta. This is opposed to the generally small and hypoplastic condition of digynic placentas which may be incapable of providing sufficient nourishment to the developing fetus..

The placental morphology for digynic triploid conceptuses appears to be completely opposite to that seen for diandric triploids (ZARAGOZA *et al.* 2000). These placentas are often small and non-cystic with occasional fibrosis of the stromal cores (MCFADDEN and KALOUSEK 1991). It has been suggested

that the severe IUGR seen in digynic triploidy may result from placental insufficiency. However, it is not possible to distinguish a direct imprinting effect on the fetus from a placental function effect secondary to poor trophoblast development and stromal fibrosis (MCFADDEN and KALOUSEK 1991). The small placental size implies a lesser likelihood of intrauterine survival and possibly accounts for the preponderance of digynic triploidy seen in the early embryonic period (MCFADDEN and ROBINSON 2006).

It has been hypothesized that maternal serum hormonal levels may be an indicator of the placental status in triploid gestation (MINY *et al.* 1995). Large placentas with partial molar change as seen in diandric triploidy are often associated with increased maternal serum alpha fetoprotein (MSAFP) and hCG. Conversely, the small non-cystic placentas indicative of digynic triploidy are often correlated with normal levels of MSAFP as well as low hCG or unconjugated estriol (uE). There appears to be a distinct parent-of-origin effect on maternal serum markers during pregnancy.

Diandric triploidy usually correlates with elevated maternal serum hCG, free β-hCG, and alpha fetoprotein (AFP) (DALMIA *et al.* 2005; MINY *et al.* 1995; STEFOS *et al.* 2002). Additionally, Dalmia et al (2005) noted a slightly decreased level of pregnancy associated plasma protein A (PAPP-A) while Miny et al. (1995) found elevated uE in diandric triploid gestations. Elevated levels of hCG can become even more extreme in cases of twin triploid gestation associated with partial mole (FRATES and FEINBERG 2000). It has also been suggested that the degree to which levels of hCG are elevated may simply be related to placental mass (MCFADDEN *et al.* 2002a). Elevated levels of AFP are thought to be related to vascular abnormalities in the placenta that allow fetal AFP to leak into the maternal circulation (AVIRAM *et al.* 2008). The hormonal profile in diandric triploidy may be interpreted as showing an increased risk for trisomy 21 (YARON *et al.* 2004). Conversely, digynic triploids often present with decreased serum hCG, free β-hCG, and AFP (DALMIA *et al.* 2005; STEFOS *et al.* 2002). Levels of hCG as well as those for PAPP-A and uE can be markedly decreased (BARKEN *et al.* 2008; MCFADDEN *et al.* 2002a). The serum profiles for digynic triploidy are often interpreted as showing an increased risk for trisomy 18 (MCFADDEN *et al.* 2002a).

7.5 EFFECTS ON GESTATIONAL AGE

Generally, it is believed that the proportion of diandric versus digynic triploidy is dependent on the gestational age of the conceptus at the time of ascertainment (ROSENBUSCH 2008). Studies have shown that most diandric triploids have a developmental age greater than 8.5 weeks or greater than 10 weeks when an embryo or fetus is present (MCFADDEN and ROBINSON 2006). Such older abortuses also have an increased likelihood of being partial moles (ZARAGOZA *et al.* 2000). Diandry accounts for 50-60% of all early triploid abortuses and is the predominant parental origin for those abortuses between five and 18 weeks gestational age (MCFADDEN and ROBINSON 2006; ZARAGOZA *et al.* 2000). Diandric triploidy is generally present on the border between the embryonic and fetal periods of development (MCFADDEN and ROBINSON 2006).

On the other hand, those digynic triploid that end in spontaneous abortion tend to do so at an earlier age than diandric triploids (ZARAGOZA *et al.* 2000). Digynic triploidy predominates in triploid gestations of less than 8.5 weeks or those where a fetus is present (MCFADDEN and ROBINSON 2006).. It is generally accepted that digynic triploidy predominates in cases with embryonic development and during the fetal period while diandric triploidy is more commonly encountered around the boundary of the embryonic and fetal periods and are less likely to have identifiable embryos or fetuses (MCFADDEN and ROBINSON 2006). It is suggested that digynic triploidy may predominate at the gestational age where expectant mothers may be referred for prenatal karyotyping due to an abnormal ultrasound or other screening (MINY *et al.* 1995).

A number of studies have attempted to look at the parental origin of triploidy at different gestational ages. McFadden and Robinson (2006) were involved in two separate studies that further illustrated that digynic triploidy predominates in the early embryonic period. These studies totaled 47 triploid conceptuses of which 32 were digynic and only 15 of diandric origin. These observations also serve to further illustrate the rather complicated relationship between parental origin and gestational age. Another study found that 19/23 triploid embryos of greater than 10 weeks gestational age were of digynic

origin (BAUMER *et al.* 2000). A study by Jacobs et al. (1979) reported that digynic triploids originating from a maternal meiosis II error often had a reduced gestational age compared to other types of digynic triploidy. The authors suggested that homozygosity for such a large number of genes may be deleterious even in the presence of another haploid set of heterozygous genes. McFadden and Langlois (2000) used DNA polymorphisms to examine the parental origins of triploid conceptuses during the embryonic and fetal periods. They found that 11/14 fetal triploids ranging from 11-34 weeks gestational age were of digynic origin. The proportions of diandric (n = 11) and digynic (n = 13) triploids in conceptuses of less than 10 weeks gestation were much closer. However, there was a significant difference in parental origin depending on whether or not the gestation had a recognizable embryo or embryo parts. Embryos or embryo parts were present in 20 cases with 13 of them being digynic whereas 4/5 cases that lacked embryo parts were of diandric origin. The remaining cases were uninformative.

The relationship between parental origin of the extra haploid set of chromosomes and gestational age of the conceptus appears to be quite complex (ZARAGOZA *et al.* 2000). Digynic triploids abort relatively early compared to diandric cases and account for a higher proportion of early triploid gestation but decline in frequency as gestational age increases. This trend appears to then reverse later in pregnancy as the majority of second and third trimester triploid gestations are often found to be of digynic origin. Overall, most diandric triploids abort at 10-20 weeks of gestation while digynic triploids either abort very early or survive until relatively late in gestation (ZARAGOZA *et al.* 2000). It is known that the majority of triploid gestations with cystic placentas abort in the first trimester (MCFADDEN and KALOUSEK 1991). This suggests that the cytogenetic makeup of the trophoblast may be more important than placental function in the sense that digynic triploids often have smaller placentas that would seem to be more likely to suffer from insufficiency. It has been suggested that confined placental mosaicism may help to explain this discrepancy (MCFADDEN and KALOUSEK 1991). There is evidence that the trophoblast is 2n/3n in at least some triploid fetuses with the presence of cytogenetically normal trophoblast possibly allowing for longer survival. It is not currently known if the presence of a diploid cytotrophoblast is more common in diandric or digynic triploidy (MCFADDEN and KALOUSEK 1991).

This pattern can be illustrated by noting the gestational ages and parental origins of all cases of triploidy from a total of six studies. Among these studies, there were a total of 238 cases in which the gestational age and parental origin were known. Of these cases, 141 were diandric and 97 digynic. As can be seen in Figure 1, digynic triploidy predominates at gestational ages less than 10-11 weeks and greater than 20-21 weeks while diandric triploidy predominates from approximately 10-20 weeks. Since there were far fewer digynic cases than diandric cases, the number of digynic cases in each age group were multiplied by a factor of approximately 1.45 in order to adjust the values to those expected had there been 141 digynic triploids. The data used to construct this chart can be found in appendix D, Tables 17-19.

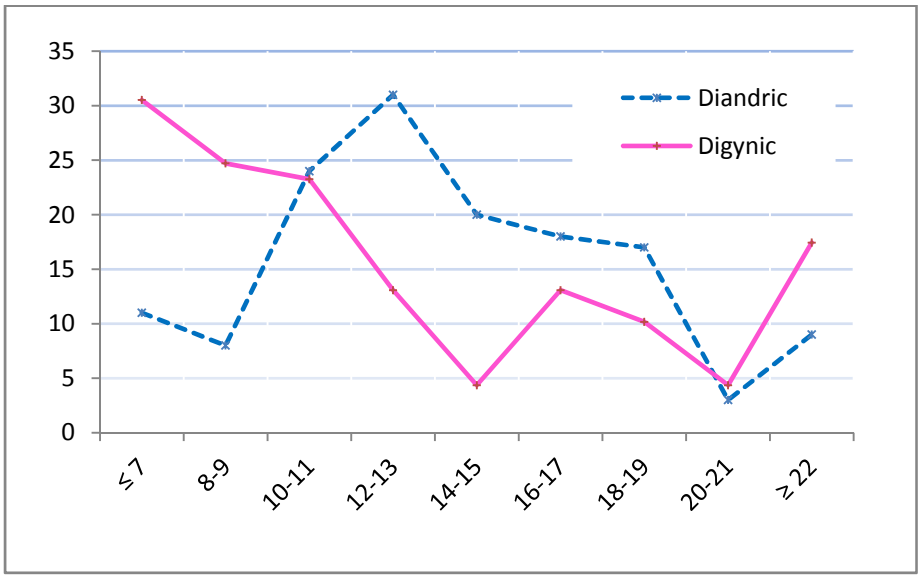

Figure 1. Prevalence of diandric versus digynic triploidy with respect to gestational age

The reasons for this complex pattern remain somewhat speculative at best (McFADDEN and ROBINSON 2006). The small digynic placenta implies less likelihood of intrauterine survival and may explain their predominance in early abortions. Conversely, partial molar placentas may be more likely to survive into the fetal period. However, their increased volume and associated elevated hCG levels may lead to an earlier clinical presentation and miscarriage. The precise reasoning for the predominance of

digynic triploidy in later gestation is not clear, however the genetic background may play a role (MCFADDEN and ROBINSON 2006).

8.0 LITERATURE REVIEW

8.1 OVERVIEW

An extensive search of the literature turned up total of 63 cases of diploid triploid mixoploidy that were published in English. The ages of these cases ranged from late first trimester terminations of pregnancy to adult. The amount of detail provided regarding phenotypic characteristics was also highly variable ranging from very detailed to almost no information. Many cases including most of those describing older children or adults provided no information on placental morphology or histology. Only 28/63 cases provided mechanisms of origin with 19 being of digynic origin and nine being of diandric origin. A detailed table describing the genotypes, parental origin, and phenotypes of all case can be found in appendix A, tables 10 and 11. Table 5 summarizes the genotype and parental origin distribution of these cases.

Table 5. Genotype and parent-of-origin distribution among 2n/3n mixoploid cases

	46,XX/69,XXX	**46,XX/69,XXY**	**46,XY/69,XXY**	**46,XY/69,XYY**	**Totals**
Diandric	4	2	3	0	9
Digynic	9	0	10	0	19
Unknown	15	6	8	1	30
Totals	28	8	21	1	58
- Exclusions					
4 (4)	- Gropp et al., 1964	- Karyotype of 3n line not indicated – Possibly restricted to palatal defect			
10b (11)	- Fulton et al., 1977	- Karyotype not indicated			
33 (36)	- Lin et al., 1998	- No karyotype, 2n/3n by flow cytometry			
35 (38)	- Hsieh et al., 1999	- Fetus 2n, Placental karyotype unknown but assume 3n based on PHM			
37 (40)	- Zhang et al., 2000	- Fetus 46,XX – Placenta 3n but karyotype not mentioned			

The numbers in the first column refer to the cases as they are listed in appendix A, tables 10 and 11 with the first number being the article in chronological order and the second referring to the overall total number of cases, again in chronological order. There were no cases with 46,XX/69,XYY or

46,XY/69,XXX genotypes. Both of these situations could only result from chimeric fusion of two separate embryos or some other unusual mechanism. The 46,XX/69,XXY column also included two cases with 45,X/69,XXY genotypes, one of diandric origin and the other of undetermined origin. Finally, five cases were not included in the distribution table due to incomplete karyotype data and are listed separately. The parental origin of the extra haploid set of chromosomes was not determined in either of these latter five cases

Additionally, a sample of 67 cases of complete triploidy was reviewed for comparison to diploid/triploid mixoploidy. This likely represents only a fraction of the total number of published cases of complete triploidy. The age range of these cases ranges from first trimester terminations of pregnancy to 10 ½ months old, the longest known surviving liveborn infant with complete triploidy. As with diploid/triploid mixoploidy, the phenotypic details of these cases were also highly variable ranging from very good to essentially none. Also like the diploid/triploid mixoploid cases, only a fraction of the complete triploid cases provided information regarding the parental origin of the extra haploid set. A total of 26/67 cases provided data on parental origin with 11 being of diandric origin and 15 being of digynic origin (Table 6). The 69,XXX column also includes two cases of 68,XX triploidy of undetermined parental origin. Three cases were not included in the table due to not providing karyotype data and are listed separately. Parental origin was not determined in these three cases. Detailed data on genotype, phenotype, and parental origins can be found in appendix B tables 12 and 13.

Table 6. Genotype and parent-of-origin distribution among complete triploidy cases

	69,XXX	**69,XXY**	**69,XYY**	**Total**
Diandric	5	5	1	11
Digynic	10	5	0	15
Unknown	24	14	0	38
Totals	39	24	1	64
- Exclusions				
37 (44) - Frates & Feinberg, 2000		- No karyotype		
41 (48) - Stefos et al., 2002		- No karyotype		
52 (63) - Madeiros et al., 2008		- No karyotype		

8.2 ASCERTAINING PARENTAL ORIGIN

A number of different methods have been used to ascertain the parental origin of the extra haploid set of chromosomes over the years. During the 1960's through 1980's, investigators usually relied on cytogenetic polymorphism analysis or blood group typing of the parents and proband to ascertain parental origin. A few investigators simply relied on observations of phenotypic characteristics and the available body of knowledge on triploidy to surmise a theoretical origin in some cases. Starting in the 1990's, the use of DNA polymorphisms to identify the parental origin of the extra haploid set of chromosome became much more prevalent. Table 7 summarizes the differing modes of ascertainment used to ascertain the parental origin of the extra haploid set of chromosomes in various case reports and studies from the 1960's through 2000's and listed in chronological order.

Table 7. Historical trends in ascertaining parental origin of the extra haploid set of chromosomes

Author	Type of 3n	Type of Report	Origin	Ascertained
Book et al., 1962	2n/3n	Case report	Digynic	Theory
Ellis et al., 1962	2n/3n	Case report	Digynic	Blood group analysis
Ferrier et al., 1964	2n/3n	Case report	Digynic	Cytogenetic polymorphisms
Schmid & Vischer, 1967	2n/3n	Case report	Digynic	Cytogenetics/Reasoning
Sparrevohn et al., 1971	3n	Case report	Digynic	Blood group analysis
Niebuhr et al., 1972	3n	Case report	Digynic	Blood group analysis
Dewald et al., 1975	2n/3n	Case report	Diandric	Cytogenetic polymorphisms
Bocian et al., 1978	3n	Case report	Digynic	Cytogenetic polymorphisms
Deligdisch et al., 1978	3n	Case report	Diandric	Presence of 2 Y chromosomes
Bieber et al., 1981	3n (2n twin)	Case report	Digynic	Multiple methods
Graham et al., 1981	2n/3n	Case report	Diandric	Cytogenetic polymorphisms
Page et al., 1981	3n	Case report	Diandric	Cytogenetic polymorphisms
Jacobs et al, 1982	3n	Study	Both	Cytogenetic polymorphisms
Maraschio et al., 1984	3n	Case report	Diandric	Cytogenetic polymorphisms
Procter et al., 1984	3n	Study	Diandric	Cytogenetic polymorphisms
Uchida and Freeman, 1985	3n	Study	Both	Cytogenetic polymorphisms
Sherrard et al., 1986	3n	Case report	Digynic	Blood group typing
Vejerslev et al., 1986	3n (3 cases)	Case reports	Diandric	Cytogenetic polymorphisms
Royston & Bannigan, 1987	3n	Case report	Diandric	Cytogenetic polymorphisms
Rochon & Vekemans, 1990	3n	Case report	Digynic	Cytogenetic polymorphisms
Galan et al., 1991	3n	Case report	Digynic	Cytogenetic polymorphisms
Kennerknecht et a., 1993	2n/3n	Case report	Digynic	DNA fingerprinting
Muller et al., 1993	2n/3n (triplet)	Case report	Digynic	DNA polymorphisms
Niemann-Seyde & Zoll, 1993	3n	Case report	Diandric	Cytogenetic polymorphisms
Tuerlings et al., 1993	2n/3n	Case report	Diandric	Logic and probability
Miny et al., 1995	3n	Study	Both	DNA polymorphisms
Ikeda et al., 1996	2n/3n	Case report	Diandric	DNA polymorphisms
Hasegawa et al., 1999	3n	Case report	Digynic	Cytogenetic and DNA polymorphisms
Baumer et al., 2000	3n	Study	Both	DNA polymorphisms
English et al., 2000	2n/3n	Case report	Digynic	Reasoning
McFadden and Langlois, 2000	3n	Study	Both	DNA polymorphisms
Zaragoza et al., 2000	3n	Study	Both	DNA polymorphisms
Chang et al., 2001	3n	Case report	Digynic	DNA polymorphisms
Phelan et al., 2001	2n/3n	Case report	Digynic	Reasoning
Ban et al., 2002	3n	Case report	Digynic	DNA polymorphisms
van de Laar et al., 2002	2n/3n (3 cases)	Case reports	Digynic	DNA polymorphisms
Brems et al., 2003	2n/3n (3 cases)	Case reports	Digynic	DNA polymorphisms
Daniel et al., 2003	2n/3n (4 cases)	Case reports	Both	DNA polymorphisms
Flori et al., 2003	2n/3n	Case report	Digynic	DNA polymorphisms
Lim et al., 2003	3n	Case report	Diandric	Reasoning
Billeaux et al., 2004	3n	Case report	Diandric	DNA polymorphisms
Dalmia et al., 2005	3n	Case report	Diandric	Phenotype
Quigley et al., 2005	2n/3n	Case report	Diandric	DNA polymorphisms
Giurgea et al., 2006	2n/3n	Case report	Diandric	DNA polymorphisms
McFadden and Robinson (2006)	3n	Study	Both	DNA polymorphisms

Table 7 (continued)

Shafi et al., 2007*	2n/3n	Case report	Digynic	Cytogenetic Markers
Chen et al., 2008	3n (5 cases)	Study/Case reports	Digynic	DNA polymorphisms
Rittinger et al., 2008	2n/3n	Case report	Digynic	DNA polymorphisms
Wegner et al., 2009	2n/3n	Case report	Diandric	DNA polymorphisms
*This case was actually first reported by Wulfsberg et al. (1991) with these authors using cytogenetic polymorphisms to determine the parental origin of the extra haploid set.				

During the 1960's and early 1970's blood group analysis was a common means of ascertaining parental origin. Cytogenetic polymorphism analysis was also used during the 1960's and throughout the 1970's and 1980's. DNA polymorphism analysis began to appear during the 1990's and is now the preferred method for determining the parental origin of the extra haploid set of chromosomes. The first report of human triploidy in a young boy with a 46,XY/69,XXY karyotype was published in 1960 with further studies published two years later (BOOK *et al.* 1962; BOOK and SANTESSON 1960). These authors did not do any studies to determine the parental origin of the extra haploid set of chromosomes, but suggested it arose through a maternal meiosis error or incorporation of the second polar body into a blastomere following the first cleavage division.

The earliest attempt to ascertain the parental origin of the extra haploid set of chromosomes was published in 1963 (ELLIS *et al.* 1963). The authors used ABO blood group analysis to determine a digynic origin of triploidy in this case. The proband's mother was BO while her father was AO. The proband was found to be OO in her blood lymphocytes, but did not have anti-B antigen which should be present in type O individuals. However, B antigen was found in saliva and buccal epithelium leading to the conclusion that the proband's diploid cells were OO while her triploid cells were OOB. This mechanism implies incorporation of the second polar body into a blastomere as a likely mechanism. Though the second polar body chromatids are the sister chromatids to those found in the ovum, meiotic recombination can explain the presence of different ABO alleles on the two maternally inherited homologues in the triploid cell line. Several other cases have utilized various types of blood typing to determine parental origin including Rhesus alleles (Rh) and human lymphocyte antigen (HLA) typing (NIEBUHR *et al.* 1972; SHERARD *et al.* 1986; SPARREVOHN *et al.* 1971).

Cytogenetic techniques relied on the various methods of chromosome banding to identify polymorphisms that could be used to help determine the parental origin of different haploid sets of chromosomes. These polymorphisms include pericentric inversions, duplications, unusually prominent or dull bands, and unusually sized satellites and secondary constrictions on the acrocentric chromosomes. The affected parts of chromosomes are generally areas of non-coding constitutive heterochromatin or ribosomal RNA genes, thus these variants are of no pathological significance to the individuals who may carry them. Ferrier et al. (1964) used such a method to determine that the extra haploid set of chromosomes in the triploid line of a 46,XY/69,XXY mixoploid child was of maternal origin. The proband was found to have a single chromosome 13 with an unusually large satellite in the diploid cell line which was duplicated in the triploid cell line. Though the authors attempted to obtain peripheral lymphocytes for karyotyping from both parents, apparently only the paternal lymphocytes produced satisfactory slides. However, neither paternal chromosome 13 showed these large satellites thus it was concluded that the unusual chromosome 13 and extra haploid set of chromosomes were derived from the mother (FERRIER *et al.* 1964).

Bieber et al. (1981) combined several different methods to determine the parental origin in an unusual case of monochorionic diamnionic twins with discordant sex chromosomes. One twin was a healthy boy with a normal 46,XY karyotype while the other was a holoacardiac fetus with a 69,XXX karyotype. The sex chromosome discordance indicate two separate fertilization events, however the single chorion is indicative of monozygotic twinning. Cytogenetic studies were used to determine that the extra haploid set in the triploid twin was of maternal origin. In the father, neither chromosome 13 showed visible silver staining of the nucleolar organizing region (AgNOR), while both maternal 13's showed staining. The diploid twin had one chromosome 13 with staining and one without as expected. The triploid twin showed two chromosome 13's with silver staining and one without indicating a digynic origin. Blood group typing also revealed that each twin received a different paternal haplotype confirming two separate fertilization events. Putting the data together, the authors surmised that the triploid twin arose through the fertilization of the first polar body. At least one attempt has been made to

determine the parental origin of triploidy using DNA footprinting analysis (KENNERKNECHT *et al.* 1991). These authors were able to determine a digynic origin based on the observation that some bands present in the mother were found in the triploid genome of the fetus but not in the diploid fetal genome.

The use of molecular DNA markers began to become more prominent in the early 1990's. Muller et al. (1993) used short tandem repeat polymorphism (STRP) analysis to determine the digynic origin of a 46,XX/69,XXX mixoploid infant. This particular case was also of particular interest because the infant was one of a set of triplets conceived by way of clomiphene induced ovulation (MULLER *et al.* 1993). The authors attempted to test one STRP marker per chromosome, though seven chromosomes either didn't provide informative results or didn't have any suitable markers to test. By comparing maternal and paternal alleles with those present in the diploid and triploid cell lines in the infant, the authors were able to determine that the extra haploid set was of maternal origin. For example, the authors used the STRP marker MFD 60 for the D1S322 locus on chromosome 1. The father was 102/118 and the mother was 96/102. The infants blood, which was diploid, had the 102/118 alleles while triploid fibroblasts were 96/102/118 (MULLER *et al.* 1993). Though both parents had the 102 allele, it can be concluded that it is of maternal origin in both of the infant's cell lines since it is paired with the 118 allele in diploid lymphocytes which is of paternal origin.

Microsatellite marker analysis has become the preferred method of ascertainment. Specifically, the use of pericentromeric microsatellite markers allows for more precise determination of the meiotic stage during which the error leading to triploidy occurred. During anaphase I, the homologous pairs of chromosomes separate leaving each daughter cell with a haploid set of chromosomes with each chromosome consisting of two sister chromatids. These chromatids then divide during anaphase II to produce the haploid gametes. Thus if an error occurs during meiosis I and the homologous chromosomes don't divide, the resultant daughter cells will essentially be tetraploid with both homologues of each chromosome being present and each consisting of two sister chromatids. After the chromatids divide during meiosis I, the resultant gamete will be diploid and have both parental homologues. In this scenario, pericentromeric microsatellite marker analysis of a triploid conceptus that incorporates a diploid

gamete resulting from meiosis I error will reveal that the conceptus has inherited both copies of any allele for which the parent is heterozygous. A meiosis II error will result in the sister chromatids failing to separate and thus a diploid gamete that will be homozygous at all pericentromeric loci. More distal loci will not always be homozygous in this case due to meiotic crossing over.

A number of cases have been ascertained solely based on what is known about triploidy and meiosis. The single case of 69,XYY triploidy reported by Deligdisch et al. (1978) can be inferred to have been of diandric origin solely based on the presence of two Y chromosomes. The fact that the placenta in this case was reported to be a partial mole also adds support to the diandric origin. Diandric triploidy arising from dispermy was definitively concluded in a case of a triploid fetus in which the father carried a balanced translocation (LIM *et al.* 2003). These authors reported on a product of conception carrying a 69,XXY,t(2;6)(p12;q24)der6,t(2;6)(p12;q24)pat karyotype. The father was found to carry the balanced t(2;6)(p12;q24) translocation. It can thus be inferred that this conceptus arose through dispermic fertilization with one sperm carrying the balanced t(2;6)(p12q24) karyotype by way of alternate 2:2 segregation while the other sperm carried the unbalanced der(6),t(2;6)(p12;q24) karyotype by way of adjacent 1 segregation.

Similarly, Tuerlings et al. (1993) used logic and probability to infer diandric origin in a fetus with a 47,XX,+18/70,XXX,+18 mixoploid karyotype. The authors suggest that the most probable mechanism was dispermic fertilization of an initially 24,X,+18 oocyte with the second male pronucleus remaining in the cytoplasm until after the first cleavage division at which point it was incorporated into a blastomere. Incorporation of the second polar body could not have occurred because it would also be aneuploid and thus the triploid cell line would have had a different aneuploid karyotype. If a disomy 18 ovum had arisen from a nondisjunction event during meiosis I, then the secondary oocyte would be 48,XX,+18,+18 while the first polar body would be 44,XX,-18,-18. The second meiotic division would then produce a 24,X,+18 ovum and a 24,X,+18 second polar body. Had this second polar body been incorporated, the resultant mixoploid genotype would have been 47,XX,+18/71,XXX,+18,+18. Such a case of 2n/3n mixoploidy with an autosomal trisomy in the diploid line and an autosomal tetrasomy in the triploid line

has not been reported. Had this aberrant oocyte arisen from a meiosis II nondisjunction, then the second polar body would have a 22,X,-18 karyotype. Incorporation of this second polar body would have resulted in a 47,XX,+18/69,XXX karyotype. This latter scenario in which a trisomic cell line coexists with an apparently balanced triploid cell line has been reported on a number of occasions (DANIEL *et al.* 2003; DEAN *et al.* 1997; ENGLISH *et al.* 2000; PHELAN *et al.* 2001; POST and NIJHUIS 1992). Daniel et al. (2003) actually proposed that the triploid line of their 47,XY,+16/69,XXY embryo was of a simple digynic origin, but then suggest that this embryos underwent chimeric fusion with a second 47,XY,+16 embryo. Microsatellite analysis did unequivocally prove digynic origin for the triploid cell line, but the trisomy 16 cell line was not analyzed and there was no evidence to suggest two separate fertilization events were involved. Post and Nijhuis also proposed a chimeric origin for their 46,XX/47,XX,+16/69,XXX case of which no further studies were performed to elucidate the true parental origin. This case can also be explained by incorporation of a 22,X,-16 second polar body into a 47,XX,+16 blastomere to generate the 69,XXX line. The normal 46,XX line can be explained by trisomy rescue in a cell descended from the 47,XX,+16 blastomere.

There have been 2 reported cases of 45,X/69,XXY mixoploidy (BETTS *et al.* 1989; QUIGLEY *et al.* 2005). These cases are somewhat harder to reconcile. Quigley et al (2005) used microsatellite marker analysis to determine that the extra haploid set in the triploid cell line was of diandric origin and suggested delayed incorporation of a second male pronucleus into a blastomere as the origin. They suggested that the 45,X cell line originated from a secondary nondisjunction event resulting in chromosome loss in the diploid blastomere. This mechanism seems plausible, but one would expect to find some remaining 46,XX or 46,XY cells depending on the initial sex chromosome complement of the diploid blastomere especially when considering the reduced viability of 45,X cells.

There have also been two reported cases of apparent diploid/triploid/tetraploid mixoploidy (KARTESZI *et al.* 2006; TOPALOGLU *et al.* 1998). When tetraploidy is present in an embryo or fetus, it is usually assumed to have arisen from a failure of cytokinesis during the first cleavage division of an initially diploid zygote or at a slightly later stage in the case of 2n/4n mixoploidy (SCHLUTH *et al.* 2004).

This is supported by the observation that all reported cases of human tetraploidy have had either XXXX or XXYY sex chromosome complements. The case reported by Karteszi et al. (2006) had a 46,XX(24%)/69,XXX(60%)/92,XXXX(14%) genotype. Though no cytogenetic studies were performed, it can be inferred that the 69,XXX cell line was derived from the inclusion of an additional X bearing gamete into a blastomere after the first cleavage division. The tetraploidy line could have then arisen from a failed cytokinesis in a diploid cell at some stage very early in development. This case is also interesting because the child exhibited a progeroid phenotype resembling that seen in Wiedemann-Rautenstrauch syndrome during early infancy. This condition is usually progressive and fatal during childhood, however by the time the patient was 2 ½ years old, she had shown a significant improvement with most of the progeroid features having largely disappeared (KARTESZI *et al.* 2006).

The second case of 2n/3n/4n mixoploidy is much more fascinating and much more difficult to explain. Topaloglu et al. (1998) reported a child with cryptogenic cirrhosis, membranous glomerulonephritis, and other minor dysmorphic features. The patients lymphocyte karyotype was found to be 46,XY(58%)/69,XXY(7%)/92,XXXY(35%). The presence of a single Y chromosome in each cell line rules out a simple failed cytokinesis as the origin for the tetraploid cell line. Unfortunately, the authors did not perform any cytogenetic or molecular studies nor did they attempt to elucidate a possible mechanism for this unique case. Considering the relatively mild phenotype shown by the patient and the low proportion of triploid cells, it seems reasonable to assume that the tetraploid cell line is digynic/diandric thus resulting in a balanced genome with respect to imprinting. This situation would require a multistep process to occur. Initially, there may have been a double fertilization of a normal 23,X zygote by a 23,X sperm and a 23,Y sperm with the zygote subsequently failing to extrude the second polar body. This would have resulted in a tetrapronuclear zygote with two maternal and two paternal pronuclei. Assuming the 23,Y male pronucleus unites with one of the 23,X female pronuclei, normal cleavage could have occurred with both extra pronuclei being segregated to the same blastomere. At the two-cell stage, one of the additional pronuclei is incorporated into a blastomere nucleus while the other continues to remain in the cytoplasm. Cleavage of this two-cell embryo will result in a four-cell

embryo with two 46,XY blastomeres and two 69,XXY blastomeres. One of the 3n blastomeres will contain the final pronucleus which will then merge with the nucleus before the next round of division. The end result is an eight-cell embryo containing four 46,XY blastomeres, two 69,XXY blastomeres, and two 92,XXXY blastomeres. The triploid blastomeres may be either diandric or digynic while the tetraploid blastomeres will have two maternal and two paternal haploid sets. The low proportion of triploid cells in the patient's peripheral lymphocytes may also be a result of the same mechanism that seemingly excludes triploid cells from the peripheral lymphocytes in other 2n/3n cases.

Table 8 summarizes all of the complete triploidy and diploid/triploid mixoploidy cases for which the origin of the extra haploid set of chromosomes was determined as well as several interesting mixoploid cases for which the parental origin was not determined. The numbers in the first column are in reference to the table listing the complete details of all cases of triploidy and diploid/triploid mixoploidy used in this review and which can be found in appendices A and B, tables 10-13. Additionally, this table only lists overall karyotype of each case. Detailed information on what tissues were karyotyped and the proportion of cells in each cell line can be found in appendix A, table 10 and appendix B, table 12.. The first number refers to the article in which the case(s) was reported in chronological order while the second number refers to the overall case number, again in chronological order. The complete details of the triploid cases and diploid/triploid mixoploid cases are listed in separate tables and are thus numbered separately.

Table 8. Details on ascertaining parental origin of the extra haploid set of chromosomes in individual cases

Complete Triploidy		
Digynic Cases		
3 (4)	**Author:**	Sparrevohn et al., 1971
	Genotype:	69,XXX
	Age:	Born at 37 weeks gestation, died at 93 hours old
	Ascertained:	Blood group analysis: Proband received both maternal rhesus alleles – Showed double dose affect to anti-M. Father type N, mother type M
	Mechanism:	None proposed
4 (5)	**Author:**	Niebuhr et al., 1972
	Genotype:	69,XXX
	Age:	Born at 37 weeks gestation, died at 92 hours old
	Ascertained:	Rh constellation showed 3 alleles: Proband showed double dose reaction against anti-M and single-dose against anti-N – Patient = M/M/N, Mother = M, father = N
	Mechanism:	Suggested maternal meiosis failure
11(13)	**Author:**	Bocian et al., 1978
	Genotype:	69,XXY
	Age:	TOP at 24 weeks gestation
	Ascertained:	Cytogenetic polymorphisms: 2 fetal #3's had identical prominent bright markers just below the centromere and identical to 1 maternal #3 – 2 fetal #13's have identical prominent bright p-arms identical to 1 maternal #13 – 2 fetal #21's identical with very faint satellites that could only come from mother as both paternal #21's had medium bright satellites
	Mechanism:	Meiosis II error – Other maternal #21 had medium-bright satellites
14(16)	**Author:**	Bieber et al., 1981
	Genotype:	69,XXX (holoacardiac twin), 46,XY (normal twin)
	Age:	SB – Unknown gestational age – Had normal LB twin
	Ascertained:	MC/DA placenta – QFC and C-banding gave results consistent with 2n maternal contribution – Father contributed different leukocyte histocompatibility antigen to each twin supporting 2 fertilization events
	Mechanism:	Fertilization of 1st polar body
18(20)	**Author:**	Sherrard et al., 1986
	Genotype:	69,XXY
	Age:	Born at 37 weeks gestation, died at 312 days old
	Ascertained:	HLA typing – No further information given
	Mechanism:	None proposed
21(26)	**Author:**	Rochon & Vekemans, 1990
	Genotype:	69,XXY,t(6;14)(p23;q24) – Mother carried balanced t(6;14)
	Age:	SA at 8 weeks gestation
	Ascertained:	Cytogenetics: Comparison of chromosome heteromorphisms on parental and fetal chromosomes 13, 14, and 21
	Mechanism:	Maternal meiosis I nondisjunction
23(28)	**Author:**	Galan et al., 1991
	Genotype:	69,XXX
	Age:	Born at 37 weeks gestation, died at 7 days old
	Ascertained:	Cytogenetic polymorphism: Proband inherited 2 copies of #'s 1, 15, & 21 with polymorphisms seen in 1 copy in mother
	Mechanism:	Fertilization of 2n ovum by 1n sperm

Table 8 (continued)

35(42)	**Author:**	Hasegawa et al., 1999
	Genotype:	69,XXX
	Age:	Born at 31 weeks gestation, died at 46 days old
	Ascertained:	Cytogenetics: Q-band polymorphisms, later confirmed by microsatellite analysis
	Mechanism:	None proposed
39(46)	**Author:**	Chang et al., 2001
	Genotype:	69,XXX
	Age:	Live birth at 33 weeks gestation, died almost immediately
	Ascertained:	Molecular studies: STRP analysis
	Mechanism:	Maternal meiosis I nondisjunction
40(47)	**Author:**	Ban et al., 2002
	Genotype:	69,XXX
	Age:	Stillbirth at 31 weeks gestation
	Ascertained:	Molecular studies: STRP analysis
	Mechanism:	None proposed
51a(58)	**Author:**	Chen et al., 2008
	Genotype:	69,XXX
	Age:	Termination of pregnancy at 16 weeks gestation
	Ascertained:	Molecular: QF-PCR and STRP analysis
	Mechanism:	Maternal meiosis II error
51b(59)	**Author:**	Chen et al., 2008
	Genotype:	69,XXX
	Age:	Termination of pregnancy at 15 weeks gestation
	Ascertained:	Molecular: QF-PCR and STRP analysis
	Mechanism:	Maternal meiosis II error
51c(60)	**Author:**	Chen et al., 2008
	Genotype:	69,XXX
	Age:	TOP 13 weeks
	Ascertained:	Molecular: QF-PCR and STRP analysis
	Mechanism:	Maternal meiosis II error
51d(61)	**Author:**	Chen et al., 2008
	Genotype:	69,XXY
	Age:	TOP 14 weeks
	Ascertained:	Molecular: QF-PCR and STRP analysis
	Mechanism:	Maternal meiosis II error
51e(62)	**Author:**	Chen et al., 2008
	Genotype:	69,XXY
	Age:	TOP 14 weeks
	Ascertained:	Molecular: QF-PCR and STRP analysis
	Mechanism:	Maternal meiosis II error
Diandric Cases		
12(14)	**Author:**	Deligdisch et al., 1978
	Genotype:	69,XYY
	Age:	Born at 22 weeks gestation, died immediately
	Ascertained:	Presence of 2 Y chromosomes, partial molar placenta
	Mechanism:	None proposed, probably dispermy

Table 8 (continued)

15(17)	**Author:**	Page et al., 1981
	Genotype:	69,XXX
	Age:	Born at 35 weeks gestation, died at 17 hours old
	Ascertained:	Serological studies: Showed 2 paternally inherited alleles Cytogenetic markers: Presence of 2 fetal #22's with markers identical to those present in 1 paternal #22
	Mechanism:	Diplospermy II
17(19)	**Author:**	Maraschio et al., 1984
	Genotype:	69,XXX,inv(15)(q15q26) – inv(15) inherited from mother
	Age:	Born at term, died at 45 days old
	Ascertained:	Cytogenetics: 2 of proband's #15's showed markers present on 1 paternal #15
	Mechanism:	Dispermy
19a(21)	**Author:**	Vejerslev et al., 1986
	Genotype:	69,XXY
	Age:	Born at 28 weeks gestation, died within 1 hour
	Ascertained:	Cytogenetics: Chromosome heteromorphisms
	Mechanism:	Dispermy
19b(22)	**Author:**	Vejerslev et al., 1986
	Genotype:	69,XXY
	Age:	Intrauterine fetal demise before 14 weeks gestation
	Ascertained:	Cytogenetics: Chromosome Heteromorphisms
	Mechanism:	Dispermy
19c(23)	**Author:**	Vejerslev et al., 1986
	Genotype:	69,XXY
	Age:	Termination of pregnancy at 18 weeks gestation
	Ascertained:	Cytogenetics: Chromosome heteromorphisms
	Mechanism:	Dispermy
20b(25)	**Author:**	Royston & Bannigan, 1987
	Genotype:	69,XXY
	Age:	Born at 30 weeks gestation, died at 45 minutes old
	Ascertained:	Cytogenetic polymorphisms: Presence of 2 unusually large #9's in proband identical to that present in single copy in father
	Mechanism:	None proposed
26(31)	**Author:**	Niemann-Seyde and Zoll, 1993
	Genotype:	69,XXX
	Age:	Born at 34 weeks gestation, died at 10 ½ weeks old
	Ascertained:	Cytogenetics: Chromosome polymorphisms
	Mechanism:	None proposed
43(50)	**Author:**	Lim et al., 2003
	Genotype:	69,XXY,t(2;6)(p12;q24)der(6)t(2;6)(p12;q24)pat
	Age:	Not indicated: Early spontaneous abortion
	Ascertained:	Reasoning
	Mechanism:	Dispermy: 1 sperm carried balanced t(2;6) while 2nd sperm carried a der(6) chromosome
45(52)	**Author:**	Billieaux et al., 2004
	Genotype:	69,XXX
	Age:	Termination of pregnancy at 18 weeks gestation
	Ascertained:	Molecular: Microsatellite marker polymorphism analysis
	Mechanism:	None proposed

Table 8 (continued)

46(53)	**Author:**	Dalmia et al., 2005
	Genotype:	69,XXX
	Age:	Termination of pregnancy at 16 weeks gestation
	Ascertained:	Phenotype – Large cystic placenta, mild IUGR
	Mechanism:	Diplospermy? – Conceived post-ICSI
Diploid/Triploid Mixoploidy		
Digynic Cases		
1 (1)	**Author:**	Book et al., 1962
	Genotype:	46,XY/69,XXY
	Age:	Born at term, Diagnosis established at 3 ½ years old
	Ascertained:	Cytogenetic studies
	Mechanism:	Suggested maternal meiosis error but provided no real evidence
2 (2)	**Author:**	Ellis et al., 1963
	Genotype:	46,XX/69,XXX
	Age:	6 years old
	Ascertained	ABO blood group typing: Father AO, Mother BO, Patient OO in lymphocytes but didn't contain Anti-A antibody – B antigen found in saliva (BOO)
	Mechanism	2nd polar body incorporation into blastomere
3 (3)	**Author:**	Ferrier et al., 1964
	Genotype:	46,XY/69,XXY
	Age:	10 years old
	Ascertained:	Cytogenetics: #13 with large satellites in 2n line & 2 #13's with large satellites in 3n line, paternal karyotype lacked large satellited #13 so must have been maternally derived Molecular studies: Showed both X's of maternal origin
	Mechanism:	Maternal meiotic error
5 (5)	**Author:**	Schmid & Vischer, 1967
	Genotype:	48,XXYY/71,XXXYY
	Age:	11 months old at time of diagnosis
	Ascertained:	Cytogenetics, reasoning
	Mechanism:	Fertilization by aberrant 25,XYY sperm and incorporation of 2nd PB into blastomere
25(28)	**Author:**	Kennerknecht et al., 1993
	Genotype:	46,XY/69,XXY
	Age:	Stillborn at 41 weeks gestation
	Ascertained:	DNA fingerprinting: Each band in 2n villi also present in 3n fetus indicating both originated from same zygote. 3n fetus has additional maternal bands indicating digynic origin. Mother has bands not found in fetus indicative of M-II error. Father shows bands not present in villi or fetus
	Mechanism:	Maternal M-II error (2nd PB incorporation into a blastomere) to form 2n placenta & 3n fetus
26(29)	**Author:**	Muller et al., 1993
	Genotype:	46,XX/69,XXX
	Age:	9 months old
	Ascertained:	STRP analysis
	Mechanism:	2nd polar body incorporation into blastomere
36(39)	**Author:**	English et al., 2000
	Genotype:	46,XX/47,XX,+6/69,XXX
	Age:	Termination of pregnancy at 18 weeks gestation
	Ascertained:	STRP analysis
	Mechanism:	Digynic: Fertilization of 24,X,+6 ovum and later incorporation of 22,X,-6 2nd polar body into blastomere

Table 8 (continued)

39(42)	**Author:**	Phelan et al., 2001
	Genotype:	47,XY,+13/69,XXY
	Age:	died at 22 hours old
	Ascertained:	PCR amplified microsatellite marker analysis
	Mechanism:	Suggested 2nd PB incorporation into blastomere with later nondisjunction
40a(43)	**Author:**	van de Laar et al., 2002
	Genotype:	46,XY/69,XXY
	Age:	6 years old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Digynic
40b(44)	**Author:**	van de Laar et al., 2002
	Genotype:	46,XY/69,XXY
	Age:	6 years old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Digynic
40c(45)	**Author:**	van de Laar et al., 2002
	Genotype:	46,XX/69,XXX
	Age:	21 months old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Digynic
41a(46)	**Author:**	Brems et al., 2003
	Genotype:	46,XY/69,XXY
	Age:	Not reported
	Ascertained:	PCR amplified DNA marker analysis
	Mechanism:	2nd polar body incorporation into blastomere
41b(47)	**Author:**	Brems et al., 2003
	Genotype:	46,XX/69,XXX
	Age:	Not reported
	Ascertained:	Polymorphic marker analysis
	Mechanism:	2nd polar body incorporation into blastomere
41c(48)	**Author:**	Brems et al., 2003
	Genotype:	46,XX/69,XXX
	Age:	Not reported
	Ascertained:	Polymorphic marker analysis
	Mechanism:	2nd polar body incorporation into blastomere
42b(50)	**Author:**	Daniel et al., 2003
	Genotype:	46,XY/69,XXY
	Age:	8 years old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	2nd polar body incorporation into blastomere
42c(51)	**Author:**	Daniel et al., 2003
	Genotype:	46,XY/47,XY,+16/69,XXY
	Age:	Not reported: Presumed termination of pregnancy
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Chimera: Fertilization of 2n ovum resulting from M-II error followed by fusion with a 2nd trisomy 16 embryo
43 (53)	**Author:**	Flori et al., 2003
	Genotype:	46,XX/69,XXX
	Age:	5 years old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	2nd PB incorporation into blastomere

Table 8 (continued)

51 (61)	**Author:**	Shafi et al., 2007
	Genotype:	46,XX/69,XXX
	Age:	25 years old
	Ascertained:	Cytogenetic polymorphisms
	Mechanism:	2^{nd} polar body incorporation into blastomere
52 (62)	**Author:**	Rittinger et al., 2008
	Genotype:	46,XX/69,XXX
	Age:	14 years old
	Ascertained:	Microsatellite analysis
	Mechanism:	Digynic
Diandric Cases		
9 (9)	**Author:**	Dewald et al., 1975
	Genotype:	46,XX/69,XXY
	Age:	13 years old
	Ascertained:	Cytogenetics: Proband had 2 #13's with large satellites & 1 #22 with unusually bright region, both inherited from father where they were present in 1 copy
	Mechanism:	Delayed dispermy
13 (14)	**Author:**	Graham et al., 1981
	Genotype:	46,XY/69,XXY
	Age:	19 months old
	Ascertained:	Cytogenetics: C-band analysis indicated diandric origin more likely than digynic origin but results not definitive
	Mechanism:	None proposed
28 (31)	**Author:**	Tuerlings et al., 1993
	Genotype:	47,XX,+18/70,XXX,+18
	Age:	Termination of pregnancy at 10 weeks gestation
	Ascertained:	Logic & probability: Assuming initial 24,X,+18 ovum, 2^{nd} PB would either be 22,X,-18 or 24,X,+18 so couldn't get 70,XXX,+18 by 2^{nd} PB incorporation
	Mechanism:	Delayed incorporation of 2^{nd} sperm nucleus into 47,XX,+18 blastomere
31 (34)	**Author:**	Ikeda et al., 1996
	Genotype:	46,XX/67,XX,-3,-4,+11,+13,-14,-X (Most likely broken 4n cell) (Placenta)
	Age:	Termination of pregnancy at 18 weeks gestation
	Ascertained:	Molecular methods showed excess of paternally inherited alleles. Densitometry gave ratio of 1.4 from molar placenta indicative of 2n/3n
	Mechanism:	None proposed
42a(49)	**Author:**	Daniel et al., 2003
	Genotype:	46,XX/69,XXX
	Age:	Termination of pregnancy, gestational age not reported
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Delayed dispermy
42d(52)	**Author:**	Daniel et al., 2003
	Genotype:	46,XX/69,XXX
	Age:	3 months old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Delayed dispermy
47 (57)	**Author:**	Quigley et al., 2005
	Genotype:	45,X/69,XXY
	Age:	11 weeks old
	Ascertained:	Molecular marker analysis
	Mechanism:	Authors suggested delayed dispermy with 2n cell undergoing 2^0 loss of sex chromosome

Table 8 (continued)

48(58)	**Author:**	Giurgea et al., 2006
	Genotype:	46,XY/69,XXY (presumed), 3n line apparently restricted to pancreatic lesion
	Age:	6 years old
	Ascertained:	Microsatellite marker analysis
	Mechanism:	Delayed dispermy
53(63)	**Author:**	Wegner et al., 2009
	Genotype:	46,XX/69,XXY
	Age:	Intrauterine fetal demise at 25 weeks gestation
	Ascertained:	Microsatellite analysis
	Mechanism:	Diandric
- Interesting Cases with Unknown Parental Origin		
8 (8)	**Author:**	Sellyei et al., 1971
	Genotype:	46,XY/69,XYY
	Age:	39 years old
	Note:	3n cells found in very low levels in blood of normal male. May be remnant of 2n/3n mixoploidy or result of tripolar division of rare 4n 92,XXYY cell
19(22)	**Author:**	Dahl et al., 1988
	Genotype:	46,XY,+2p/69,XXY
	Age:	Born at 33 weeks gestation (emergency C-section), Died at 5 weeks old
	Note:	No known cases of liveborn infant with complete trisomy 2p
21(24)	**Author:**	Callen et al., 1991
	Genotype:	Placenta 46,XX/69,XXY
	Age:	Normal liveborn infant
	Note:	Significant part of placenta derived from vanished 69,XXY twin as evidenced by remains of 2nd gestational sac
22(25)	**Author:**	Post & Nijhuis, 1992
	Genotype:	46,XX/47,XX+16/69,XXX
	Age:	Termination of pregnancy at 25+2 weeks gestation
	Note	Chimera: Placenta largely from vanished 47,XX,+16 twin with 2n line derived from trisomy rescue. Surviving fetus entirely 69,XXX with some 3n cells in placenta
27(30)	**Author:**	Sarno et al., 1993
	Genotype:	46,XX/68,XXX,-11
	Age:	Diagnosis established at 14 weeks gestation
	Note:	3n PHM with surviving normal 2n fetus
32(35)	**Author:**	Dean et al., 1997
	Genotype:	46,XX/47,XX,+15,69,XXX
	Age:	Diagnosis at 2 ½ years old, died at 3 8/12 years old
	Note	46,XX present in very low numbers and couldn't be definitively proven. Suggested delayed inclusion of additional 1n set into 1 blastomere and mitotic nondisjunction in other resulting in trisomy 15
34(37)	**Author:**	Topaloglu et al., 1998
	Genotype:	46,XY/69,XXY/92,XXXY
	Age:	7 years old
	Note	4n line could not have arisen from simple failed cytokinesis of 2n cell
49(59)	**Author:**	Karteszi et al., 2006
	Genotype:	46,XX/69,XXX/92,XXXX (3n & 4n genotypes presumed)
	Age:	2 ½ years old
	Note:	Transient progeroid phenotype present at birth but largely disappeared by age of 2 ½.

8.3 PHENOTYPE DISTRIBUTION

It was difficult to discern any real phenotypic trends with regard to genotype or parent of origin due to the wide range of ages and amount of details provided in case reports. The nine cases of 2n/3n mixoploidy determined to be of diandric origin seemed to be particularly lacking in phenotype information. Two of these cases may have been confined placental mosaicism while a third was an elective abortion at 10 weeks gestation with no phenotypic data provided. The dearth of phenotypic data on the diandric cases combined with the fact that digynic cases outnumbered diandric cases 19-9 makes it impractical to draw any conclusions regarding any parent-of-origin specific patterns. Of the traits known have a parent-of-origin effect, macrocephaly was more predominant in digynic triploids by a 2-0 count, IUGR was more predominant in digynic cases by a 6-2 count, adrenal hypoplasia was more predominant in digynic cases by a 2-0 count, and partial mole was more common among diandric cases by a 1-0 count. There were an additional four cases of partial mole among those cases where the parental origin was not conclusively determined, but these could probably be assumed to be diandric.

Parent-of-origin specific traits appeared to show a more distinct pattern among the complete triploid cases. Intrauterine growth retardation and macrocephaly were each present in 10/15 and 8/15 digynic triploids respectively, but in only 3/11 and 0/11 diandric triploids respectively. Strangely, adrenal hypoplasia was reported in only 2/15 digynic triploids, but in 5/11 diandric triploids. Only 5/11 diandric triploids were reported to have a partial molar placenta, though 13/41 cases of undetermined parental origin were reported to have partial molar placentas. The differences in prevalence of parent-of-origin dependent traits between complete triploids and diploid/triploid mixoploids can likely be attributed to the diploid cell line in the latter group diminishing the severity of congenital anomalies. This theory is supported by the observation that these parent-of-origin specific traits are all present in higher numbers in complete triploidy despite fairly similar numbers of digynic and diandric triploidy in each group (19/9 versus 15/11). Table 9 provides a comparison of the parent-of-origin specific traits between diandric and digynic triploidy in both mixoploid and complete triploid cases.

Table 9. Comparison of parent-of-origin specific traits in complete triploidy and 2n/3n mixoploidy

Diandric Triploidy			Digynic Triploidy	
2n/3n (n = 9)	3n (n = 11)	Trait	2n/3n (n = 19)	3n (n = 15)
2	3	IUGR	6	10
0	0	Macrocephaly	2	8
0	5	Adrenal Hypoplasia	2	2
1	5	PHM	0	0

A number of phenotypic traits generally accepted to not show any parent-of-origin effects showed a rather large discrepancy between digynic and diandric cases of diploid/triploid mixoploidy, though considering the aforementioned dearth of information on diandric cases and the fact that there were 10 more digynic cases than diandric, this was probably not significant. Among the more notable examples were low-set or dysplastic ears which were present in 8 digynic and 0 diandric cases. Micro(retro)gnathia was present in 10 digynic cases but only 1 diandric case while syndactyly of the fingers and of the toes were more prevalent in digynic triploidy by 13-3 and 11-1 margins respectively. This phenomenon was not apparent among complete triploidy cases, probably because the total number of digynic cases over diandric cases was a much closer 15/11 compared to the 19-9 seen in the mixoploid cases. Not including those traits that are known to have a distinct parent-of-origin effect, the largest discrepancy between digynic and diandric triploidy was five cases of holoprosencephaly noted among digynic triploids compared to only one among diandric triploids. It should however be noted that all five of these digynic triploids with holoprosencephaly came from a single study that was specifically examining chromosomal abnormalities associated with this defect (CHEN *et al.* 2008).

Overall, the most common traits seen in diploid/triploid mixoploidy were IUGR (21/62), syndactyly of the fingers (27/62), syndactyly of the toes (22/62), and mental or psychomotor retardation (29/62). Among complete triploids, the most prevalent characteristics were IUGR (35/67), low-set/dysplastic ears (29/67), and syndactyly of the fingers (23/67). Additionally, syndactyly of the toes, renal abnormalities, and adrenal hypoplasia were each reported in 20 cases. A table with the complete breakdown of phenotypic abnormalities by parental origin and genotype can be found in the appendix C, Table 14 for 2n/3n mixoploidy and appendix C, table 15 for complete triploidy..

When comparing the overall distribution of phenotypic traits between complete triploidy and diploid triploid mixoploidy, large discrepancies can be observed between the two groups. This is in agreement with the observation that complete triploidy presents with a greater number and increased severity of congenital anomalies than mixoploid individuals. Additionally, body asymmetry was present in 11 mixoploid cases but wasn't seen at all in the cases of complete triploidy. As asymmetry is thought to be a result of unequal distributions of diploid and triploid cells on either side of the body in mixoploid individuals, this is not surprising. Abnormal curvature of the spine was also seen exclusively in mixoploid individuals and can probably be considered secondary to body and/or lower limb asymmetry. Finally, pigmentary anomalies were present in 16 mixoploid cases but were not seen in any cases of complete triploidy. As pigmentary anomalies, particularly patches or streaks of hypo or hyperpigmented skin, are considered a hallmark of mosaicism; this is also not surprising.

The most striking differences between complete triploidy and diploid/triploid mixoploidy was the much higher frequency of internal anomalies seen in complete triploidy, a phenomenon which has been well documented. Holoprosencephaly (12 versus 1) and myelomeningocele (7 versus 1) were both much more common in complete triploidy. It should however be noted that five of the cases of holoprosencephaly in complete triploidy were reported in a single study examining chromosome abnormalities associated with the defect. Thus this figure cannot be considered to accurately reflect the prevalence of holoprosencephaly in complete triploidy, but rather it merely indicates that triploidy is potential underlying cause of holoprosencephaly. Additionally, other general defects of the cerebral hemispheres such as abnormal gyral patterns were also more prevalent in complete triploidy by an 11 to 3 margin. Though the occurrence of septal defects (8 versus 10) and patent ductus arteriosus or patent foramen ovale (4 versus 3) were fairly similar among mixoploids and complete triploidy, there were 10 instances of more complex heart defects among complete triploids compared to only 3 among 2n/3n mixoploids. Abnormal lobation of the lungs (6 versus 1) and pulmonary hypoplasia (16 versus 2) were also much more common in complete triploidy.

Among deformities of the digestive system, hypoplasia or agenesis of the gallbladder and hepatomegaly were more common in complete triploidy by 11/1 and 6/1 margins respectively. Ventral wall defects including omphalocele, exomphalos, umbilical hernia, and a single case of ectopia cordis were also more prevalent in complete triploidy by an 11/1 margin. When comparing defects of the genito-urinary tract between complete triploidy and diploid triploid mixoploidy, the most striking difference was the presence of renal anomalies which were more prevalent in complete triploids by a 20/4 margin. Most other abnormalities of the genitalia were fairly evenly distributed between the two groups. The one major exception was the prevalence of ovarian anomalies in 7 cases of complete triploidy compared to only a single case of 2n/3n mixoploidy. This could possibly be explained by considering that there were 39 cases of XXX complete triploidy compared to 28 cases of XX/XXX mixoploidy.

Abnormalities of the endocrine glands were also strikingly more common in complete triploidy. Adrenal hypoplasia was observed in 20 complete triploids but only six mixoploids. Additionally, hypoplasia of the thymus and of the thyroid were observed in six and three cases of complete triploidy respectively, but were absent from 2n/3n mixoploids. Finally, there were also significant differences in the rates of abnormal placental morphology between complete triploidy and 2n/3n mixoploidy. Among complete triploids, 18 were reported as being partial moles with an abnormal fetus compared to a single case for 2n/3n mixoploidy. Among 2n/3n mixoploids, four cases were reported as apparent confined placental mosaicism characterized by a partial molar placenta with a normal fetus. A total of 10 complete triploid placentas were reported as being small and noncystic compared to only one mixoploid placenta. At first, this may seem surprising considering that there were more digynic 2n/3n mixoploids than digynic complete triploids. However, when considering that the mixoploid digynic placentas would likely also contain large populations of normal diploid cells, this is not surprising since this latter population will allow for more normal placental development. A complete side-by-side comparison of the phenotypic traits seen in diploid/triploid mixoploidy and complete triploidy can be found in appendix C, Table 16.

9.0 CONCLUSION

Much has been learned about triploidy in humans since the first case of diploid/triploid mixoploidy was documented nearly 50 years ago. The methods used to investigate triploidy have evolved over the decades from the comparatively simple cytogenetic and cytological techniques used in the 1960's to the much more advanced molecular techniques in use now. However, as the technology improved, the mystery surrounding triploidy only seemed to deepen and become increasingly complex. While early studies suggested that most triploids were of diandric origin and associated with partial mole, later studies suggested digyny was more prevalent and that a smaller proportion of triploids were associated with partial mole. A significant portion of these differences can be attributed to varying degrees of between study and ascertainment bias. Early cytogenetic studies ascertained mostly spontaneous abortions regardless of the presence or absence of a fetus. On the other hand, later molecular studies often sampled only cases with a discernable embryo or fetus which biases towards digyny and nonmolar placentas. Overall, studies that collected their samples from consecutive series of spontaneous abortions such as Jacobs et al. (1982), Warburton et al. (1991), and Redline et al. (1998) can be considered the least biased. It has become increasingly apparent that to fully understand triploidy, many factors including parental origin, genomic imprinting, placental and fetal phenotypes, and gestational age must be looked at together.

Though dispermy and retention of the second polar body are regarded as being the two most common mechanisms leading to triploidy, a number of additional mechanisms have been proposed and documented. Diandric triploidy has been shown to arise from diplospermy I or II and could also potentially arise through abnormal endoreduplication of the male pronucleus. Several scenarios involving abnormal division of the oogonium, primary oocyte, or secondary oocyte can lead to digynic triploidy.

Additionally, it is thought that assisted reproduction technology may increase the risk of triploidy in certain cases.

A number of studies have revealed some of the unique characteristics of triploid cells. Perhaps as a direct result of their increased DNA content, the proliferative capacity of triploid cells is different than that of their diploid counterparts. X chromosome inactivation behaves in an unusual manner in triploid individuals with populations of cells having anywhere from zero to two inactive X chromosomes. The meiotic behavior of triploid cells, though as yet poorly understood, appears to be characterized by the formation of unusual structures during synapsis and random changes in which two of the three homologous chromosomes are paired. Triploid cells also show some degree of tissue specificity. The primary example of this is their near total absence in the peripheral lymphocytes of diploid/triploid mixoploid individuals. The leading explanation for this phenomenon is a selective growth advantage of 2n cells over their 3n counterparts.

The phenotypic characteristics of complete triploidy are quite broad with every major organ system being affected to some degree. It has been noted that the triploid phenotype often mimics that of individual trisomies, particularly trisomy 18. The few triploid infants who are born alive generally do not survive longer than a few hours to days with the longest reported survival being 10 ½ months. Death is usually ascribed to respiratory problems in these rare cases. Genital abnormalities are a near constant feature of triploidy and may be related to the highly variable nature of X inactivation and dosage affects of the *DAX1* gene in cases of 69,XXY males. Among diandric triploids, partial hydatidiform mole is a very common finding, though it may be likely to go undiagnosed in some cases. Though less severe than complete moles, PHM can lead to severe complications for both mother and fetus. On rare occasions, a triploid partial mole may coexist with a normal diploid fetus through either twinning or confined placental mosaicism.

The phenotypic spectrum of diploid/triploid mixoploidy is comparable to complete triploidy in breadth, but milder in terms of severity. The longer survival of mixoploid individuals is largely attributed to the absence of severe anomalies of the heart and central nervous system that are seen in complete

triploidy. The phenotype of this syndrome often mimics certain genomic imprinting disorders such as Prader-Willi syndrome, Beckwith-Wiedemann syndrome, and maternal UPD(14). There have been a number of reported cases of diploid/triploid mixoploidy in which the diploid line contains an additional aneuploidy. It has been noted that in such cases, the phenotype is often less severe than that seen when triploidy or trisomy are seen alone. This phenomenon is best exemplified in a case of a 47,XX,+15/69,XXX child surviving 3 2/3 years when neither complete triploidy nor complete trisomy 15 are compatible with survival.

One of the more interesting avenues of investigation into triploidy is the parent-of-origin effect on phenotype. This phenomenon is thought largely the result of differential imprinting effects that are dependent on the parental origin of the additional haploid set of chromosomes. Diandric triploidy is characterized by a relatively well grown fetus with proportionate head size or relative microcephaly along with a large cystic placenta. Conversely, digynic triploidy is characterized by severe asymmetric IUGR, relative macrocephaly, and an unusually small, non-cystic placenta. It remains unclear if the effects on fetal morphology are the result of a direct imprinting effect or are secondary to imprinting effects on the placenta. The parent-of-origin effects generally only become apparent during the second trimester of pregnancy or during the fetal period.

Additionally, diandric and digynic triploidy show an unusual distribution with respect to gestational age. Digynic triploids usually either abort early in the first trimester or survive well into the fetal period while diandric triploids tend to predominate from 10-20 weeks of gestation. The underlying cause of this phenomenon is currently not well understood, but may be related to imprinting effects on placental morphology and function. As a side effect of this complex pattern, many if not all comprehensive studies attempting to ascertain the parental origin of the extra haploid set of chromosomes suffer from sampling bias related to the gestational ages of their specimens. Most of these studies look at triploid conceptuses over a very broad range of gestational ages and rarely if ever provide specific gestational ages for each case. The increasing prevalence of routine prenatal screening also adds a degree of bias since most triploids that are detected in this manner will be aborted.

A review of the literature revealed that there have been more reported cases of digynic triploidy than diandric triploid in both the complete and mixoploid groups. When considering the triploid cell line of 2n/3n mixoploids there were 28 XXX cases compared to 29 XXY cases. However, among complete triploids, there were 39 69,XXX cases compared to 24 69,XXY cases. Many different methods have been used to ascertain the parental origin of the extra haploid set of chromosomes over the years. Most early reports relied on blood group analysis and cytogenetic polymorphisms while later reports almost exclusively rely on molecular DNA polymorphism analysis. A few reports of 2n/3n mixoploidy were able to ascertain the parental origin simply by observing the karyotypes of the different cell lines. IUGR, macrocephaly, and adrenal hypoplasia were more common in digynic 2n/3n mixoploids while PHM was more common in diandric mixoploids and complete triploids. Though IUGR and macrocephaly were more common in digynic complete triploids, adrenal hypoplasia was more common in diandric complete triploids. Most other traits did not show large differences between diandric and digynic triploidy and those that did can largely be attributed to sample size and the completeness of phenotype reports. Overall, syndactyly and low-set ears were among the most common traits in both complete triploidy and 2n/3n mixoploidy. There were generally fewer anomalies overall among 2n/3n mixoploids and significantly fewer central nervous system, cardiopulmonary, and renal anomalies among mixoploids compared to complete triploidy.

This comprehensive review of the literature provides an in depth look at what is currently known about human triploidy and diploid/triploid mixoploidy. The findings of this review could be used to help design future studies into the origins and characteristics of human triploidy that are free of the bias that has plagued earlier studies. From a public health standpoint, such studies could provide insight into the management and perhaps prevention of triploid gestation. In order to unravel the mysteries surrounding triploidy, a couple more detailed studies will have to be done. It may be necessary to combine the results of many studies examining the parental origin of triploids in an effort to obtain a better view of the gestational age effect. It is also imperative to provide a gestational age for each case rather than a broad range for the whole study. Additional studies will need to be carried out to examine how imprinted genes

affect early embryonic development and the development of the trophoblast. It may also be prudent to combine these imprinting studies with dosage-effect studies. Only by conducting these studies and paying close attention to detail will the answers to the many questions surrounding human triploidy be found.

APPENDIX A

COMPLETE DATA FOR ALL CASES OF 2N/3N MIXOPLOIDY

The following tables contain the complete case information for all cases of diploid/triploid mixoploidy cited within this paper and used for the literature review. The cases are numbered in chronological order, with the exception of one case, and alphabetical order in the case of multiple publications from the same year. There are a total of 63 cases from 53 published reports. Case 51(61) had been published previously, but only the later publication is indicated in the table. Table 10 contains detailed information of the karyotype and tissue distribution of diploid and triploid cell lines. The parental origin of the extra haploid set of chromosomes and its mode of ascertainment are also noted when available. The age listed refers to the age of the proband at the time the 2n/3m mixoploidy was ascertained or at the time of the patient's final assessment or death prior to the publication of the case report.

Table 11 lists the morphological data of all cited cases of diploid/triploid mixoploidy. The first three columns are the same as in Table 10. The phenotypic characteristics of the placenta as well as the proband are listed when available. The phenotypic characteristics of the proband may be divided into external and internal findings when appropriate. The final column lists any additional notes that may be of relevance to that particular case.

Table 10. Complete genetic and molecular data for all cases of 2n/3n mixoploidy

Authors	Case #	Age	Genotype	Origin
(BOOK and SANTESSON 1960)	1 (1)	3 1/2 y/o	- Skin fibroblasts: 46,XY(16%)/69,XXY(84%) - Fascia lata: 46,XY(51%)/69,XXY(49%) - Bone marrow & Leukocytes: 46,XY - Many 2n cells grossly unbalanced	- Suggest meiotic error during oogenesis but don't provide any supporting evidence
(ELLIS *et al.* 1963)	2 (2)	6 y/o	- Skin fibroblasts: 46,XX/69,XXX in about equal proportions at 2 sites from opposite sides of body - Leukocytes: Entirely 46,XX	- Digynic based on ABO blood group analysis
(FERRIER *et al.* 1964)	3 (3)	10 y/o	- Leukocytes: 46,XY(50) - Right fascia lata: 46,XY(15)/69,XXY(4) - Fibroblasts (Right forearm): 46,XY(156)/69,XXY(11) - Fibroblasts (Left forearm #1): 46,XY(85)/69,XXY(9) - Fibroblasts (Left forearm #2): 46,XY(176)/69,XXY(13) - Large satellited chromosome 13 in 2n line, duplicated in 3n line	- Digynic based on finding of paternal #13's with no large satellites - Molecular studies also showed both X's maternally derived
(GROPP *et al.* 1964)	4 (4)	3 1/2 m/o	- Palatal mucosa in area of defect: 72 chromosomes with extra F group - Lymphocytes: 46,XY	- ? - Possibly restricted to malformation
(SCHMID and VISCHER 1967)	5 (5)	11 m/o	- Lymphocytes: 48,XXYY(63) - Fibroblasts: 48,XXYY(243)/71,XXXYY(88) - Labeling studies: 2n cells consistently showed 1 late replicating X	- Fertilization by abnormal sperm followed by 2nd polar body incorporation into blastomere
(VAN DEN BERGHE and VERRESEN 1970)	6 (6)	d 8 h/o.	- Blood: 46,XX(17)/69,XXX(24) - Also 4 hypodiploid (45) and 14 6n cells	- ?
(JENKINS *et al.* 1971)	7 (7)	10 1/2 y/o	- Peripheral lymphocytes: 46,XX - Skin fibroblasts: 46,XX/69,XXX - X-chromatin studies showed single polar body	- ?
(SELLYEI *et al.* 1971)	8 (8)	39 y/o	- 322 lymphocyte mitotic plates revealed some 69,XYY among 1st 30 cells analyzed - Also showed 2 4n and 1 polytrisomic (57 chromosomes) cell	- Puzzling, Remnants of 2n/3n mosaicism?
(DEWALD *et al.* 1975)	9 (9)	13 y/o.	- Blood (initial): 46,XX - Blood (repeat): 46,XX(93)/69,XXY(5)/92,XXXX(2) - Skin (initial): 46,XX(40%)/69,XXY60%) after 5 passages - Skin (repeat): showed 46,XX(34%)/69,XXX(66%)	- Dispermy: Delayed incorporation of 2nd male pronucleus into blastomere
(FULTON *et al.* 1977)	10a (10)	11 y/o.	- Blood: 46,XX - Fibroblasts: 46,XX/69,XXX - 2n/3n ratio: 1:1 at 5 years and 4:1 at 11 years	- ?
	10b (11)	13 y/o.	- Karyotype not indicated	- ?

Authors	Case #	Age	Genotype	Origin
(FRYNS *et al.* 1980)	11 (12)	21 y/o	- Lymphocytes: 46,XX - Skin fibroblasts (right forearm): 46,XX(75)/69,XXX(36) - Skin fibroblasts (left forearm): 46,XX(88%)/69,XXX(12%) - Buccal smear showed Barr bodies in 20% of cells	- ?
(GINSBERG *et al.* 1981)	12 (13)	d 3 h/o	- Lymphocytes: 69,XXY(102)/46,XY(1)	- ?
(GRAHAM JR. *et al.* 1981)	13 (14)	19 m/o	- Lymphocyte (1 d/o & 3 m/o): 46,XY - Skin (R arm, 1 d/o): 46,XY(94%)/69,XXY(6%) - Skin (L arm, 1 d/o): 46,XY(79%)/69,XXY(21%) - Skin (R leg) - 1 d/o: 46,XY(67%)/69,XXY(33%) - 9 m/o: 46,XY(78%)/69,XXY(22%) - Skin (L leg) - 1 d/o: 46,XY(66%)/69,XXY(34%) - 9 m/o: 46,XY(87%)/69,XXY(13%)	- Suggested diandric but couldn't be proved
(THARAPEL *et al.* 1983)	14a (15)	d 40 h/o	- Lymphocytes: 46,XY - Skin fibroblasts: 46,XY(61%)/69,XXY(39%) - Lung fibroblasts: 46,XY(46%)/69,XXY(54%) - Reevaluation of lymphocytes showed 1 of 50 cells was 68,XXY,-17 suggesting low level mosaicism	- ?
	14b (16)	8 1/2 y/o	- Lymphocytes: Entirely 46,XX at 4 days and 1 yr. - 2 skin biopsies at 1 yr – site 1: 46,XX(40%)/69,XXX(60%) - site 2: 46,XX(34%)/69,XXX(66%) - Buccal smear showed 44% of cells had 1Barr body and no cells with 2	- ?
(DONNAI *et al.* 1986)	15a (17)	12 y/o	- Blood: 46,XX - Fibroblasts:46,XX(16%/ 69,XXX(84%)	- ?
	15b (18)	1 y/o	- Blood: 46,XX - Fibroblasts: 46,XX(59%/69,XXX(41%)	- ?
(PETTENATI *et al.* 1986)	16 (19)	d 2 d/o	- Bone marrow: 46,XX(41%)/69,XXX(59%) - Peripheral lymphocytes: 46,XX(96%)/69,XXX(4%)	- ?
(TANTRAVAHI *et al.* 1986)	17 (20)	3 y/o	- Initial blood lymphocytes: 46,XX(15) - Additional lymphocytes: 46,XX(292)/69,XXY(8) - Skin fibroblasts: 46,XX(887)/69,XXY(3) - Buccal smear for X-chromatin studies: 5/100 cells positive	- ?
(BENDON *et al.* 1988)	18 (21)	TOP 20 wks	- Liver and skin: 46,XY(50%)/69,XXY(50%) - Placenta: Entirely 69,XXY	- ?

Authors	Case #	Age	Genotype	Origin
(DAHL *et al.* 1988)	19 (22)	d 5 w/o	- Lymphocytes (63 cells): 69,XXY(20%)/46,XY,+2p(80%) - Skin fibroblasts (3 cells): 46,XY,+2p - Parents and patient negative for fra(2)(q13)	- ?
(BETTS *et al.* 1989)	20 (23)	TOP, 20 wks.	- Fibroblasts: 45,X(35)/69,XXY(115) - Gonad: 45,X(4)/69,XXY(7)	- ?
(CALLEN *et al.* 1991)	21 (24)	N/A	- Cord blood, amnion, child: entirely 46,XX - 3 separate macroscopically normal areas of placenta: 46,XX/69,XXY - Chorion and grossly abnormal placenta: Entirely 69,XXY	- Chimera: Major contribution of placenta from resorbed 69,XXY twin
(POST and NIJHUIS 1992)	22 (25)	TOP 25+2 wks	- LT-CVS: 46,XX(4)/47,XX,+16(12) - Cordocentesis entirely 69,XXX - Total of 4 placental samples: 46,XX(24)/47,XX,+16(103)/69,XXX(19) - All 3 cell types found in placenta with proportions varying by site - Skin fibroblasts entirely 3n	- Chimera: Trisomy 16 placenta from vanishing twin + surviving 3n fetus - 2n cells from trisomy rescue
(DAUBENEY *et al.* 1993)	23 (26)	3 y/o	- Lymphocytes: 46,XX with 22p+ - Skin fibroblasts: 46,XX/69,XXX/69,XXX,+22p+ - Father also possessed 22p+, probably normal polymorphism	- ?
(JARVELA *et al.* 1993)	24 (27)	20 m/o	- Cord blood at 30 wk gestation: 46,XX - Postnatal blood: 46,XX - Skin fibroblasts: 69,XXX(28)/46,XX(2)	- ?
(KENNERKNECHT *et al.* 1993)	25 (28)	SB 41 wks	- CVS direct prep: 46,XY - Peri-umbilical blood: 69,XXY	- Digynic: Likely maternal M-II non-disjunction
(MULLER *et al.* 1993)	26 (29)	9 m/o	- Lymphocytes: 46,XX - Fibroblasts: 69,XXX(46)/46,XX(4)	- Digynic
(SARNO JR. *et al.* 1993)	27 (30)	Dx 14 wks GA	- AF: 46,XX - Villous core mesenchyme: 68,XXX,-11 - Term placenta and amnion: 46,XX - Chorionic plate: 46,XX(50%)/68,XXX,-11(50%) - Chorionic villi: 100% 3n - Neonatal blood: 46,XX	- Suggest postzygotic loss of 1n set from originally 3n conceptus
(TUERLINGS *et al.* 1993)	28 (31)	TOP, 10 wks.	- Skin: 47,XX,+18 CVS at 9 1/2 wks. and after TOP: 70,XXX,+18 - LT-CVS of mesenchymal core cells: 47,XX,+18(3)/70,XXX,+18(3)	- Dispermy: Delayed incorporation of 2nd male pronucleus
(CARAKUSHANSKY *et al.* 1994)	29 (32)	4 1/2 y/o	- Blood lymphocytes: 46,XX(57%)/69,XXX(43%)	- ?
(WOODS *et al.* 1994)	30 (33)	d 15 y/o	- Lymphocytes: Repeatedly normal 46,XX (?, probably typo in paper) - Skin fibroblasts: 69,XXY(29)/45,XY,-15(1) - Maternal lymphocytes = 46,XX(42)/45,X(3)/47,XXX(4)/48,XXXX(1)	- ?

Authors	Case #	Age	Genotype	Origin
(IKEDA *et al.* 1996)	31 (34)	TOP 18 wks	- Normal appearing placenta: 46,XX - Hydropic placenta: 46,XX(273)/67,XX,-3,-4,+11,+13,-14,-X(1) (May have been broken 4n cell) - Molecular analysis confirmed 2n/3n in placenta - Permission not granted for fetal karyotyping	- Diandric based on molecular analysis showing excess of paternal alleles
(DEAN *et al.* 1997)	32 (35)	d 3 2/3 y/o	- AF (35 wks): 46,XX(2)/47,XX,+15(7)/69,XXX(4) - 13 cells - AF (subculture): 47,XX,+15(14)/69,XXX(22) - 36 cells - Cord blood (birth): 47,XX,+15(5)/69,XXX(80) - 85 cells - Cord (birth): 47,XX/+15(5)/69,XXX(20) - 25 cells - Amnion (birth): 46,XX(2)/47,XX,+15(3)/69,XXX,(20) - 25 cells - Chorion (birth): 46,XX(1)/47,XX,+15(4)/69,XXX(20) - 25 cells - Blood (1.5 y/o): 47,XX,+15(2)/69,XXX(358) - 360 cells - Muscle (1.5 y/o): 47,XX,+15(10)/69,XXX(90) - 100 cells - Skin (1.5 y/o): 47,XX,+15(9)/69,XXX(91) - 100 cells - Bone Marrow (1.5 y/o): 69,XXX(163) - 163 cells	- Suggest delayed inclusion of additional 1n set into blastomere followed by mitotic nondisjunction in second blastomere creating trisomy 15 cell line
(LIN *et al.* 1998)	33 (36)	IUFD 22 wks.	- Flow cytometry of heart sections: 32% 3n - Chromosome analysis not done due to macerated condition of fetus	- ?
(TOPALOGLU *et al.* 1998)	34 (37)	7 y/o	- Peripheral blood lymphocytes: 46,XY(58%)/69,XXY(7%)/92,XXXY(35%)	- ?
(HSIEH *et al.* 1999)	35 (38)	18 m/o	- Amniocentesis: 46,XX - Placenta: N/A (Assume 3n based on Dx of PHM)	- ?
(ENGLISH *et al.* 2000)	36 (39)	TOP 18 wks.	- CVS & placenta: 46,XX/47,XX,+6/69,XXX - Skin & muscle: 69,XXX - 3n cell line had 2 maternal genomes	- Maternal M-II nondisjunction produces 24,X,+6 ovum fertilized by normal sperm with later mitotic trisomy rescue. 3n line originates from incorporation of 22,X,-6 polar body into blastomere
(ZHANG *et al.* 2000)	37 (40)	IUFD 20 wks	- Amniocentesis at 15 weeks: 46,XX - Normal placental villi 2n - Cystic placental villi 3n	- Loss of 1n set from 3n conceptus - Fertilization of 4n oocyte creating 5n zygote which splits into 2n & 3n components

Authors	Case #	Age	Genotype	Origin
(LAMBERT *et al.* 2001)	38 (41)	8 y/o	- Blood: 46,XY(99.5%)/69,XXY(0.5%) (200 cells) - Fibroblasts (right arm): 46,XY(59%)/69,XXY(41%) (70 cells) - Fibroblasts (left arm): 46,XY (15 cells)	- ?
(PHELAN *et al.* 2001)	39 (42)	d 22 h/o	- Amniocytes: 47,XY,+13(12)/69,XXY(4) - 16 cells - Cord blood: 47,XY,+13(16)/69,XXY(4) - 20 cells - Fibroblasts: 47,XY,+13(7)/69,XXY(18) - 25 cells - Amnion: 69,XXY(32) - 32 cells - Chorionic villi: 47,XY,+13(15) - 15 cells	- Fusion of blastomere with 2nd polar body with later chromosome 13 nondisjunction
(VAN DE LAAR *et al.* 2003)	40a (43)	6 y/o	- Lymphocytes: 46,XY - Fibroblasts: 69,XXY(22)/46,XY(10)	- Digynic
	40b (44)	6 y/o	- Lymphocytes: 46,XY - Fibroblasts: 69,XXY(33%)/46,XY(67%)	- Digynic
	40c (45)	21 m/o	- Lymphocytes: 46,XX - Fibroblasts: 69,XXX(45)/46,XX(5)	- Digynic
(BREMS *et al.* 2003)	41a (46)	N/A	- Lymphocytes: 46,XY - Skin fibroblasts: 46,XY/69,XXY	- Digynic: 2nd polar body incorporation into blastomere
	41b (47)	N/A	- Lymphocytes: 46,XX - Skin fibroblasts: 46,XX/69,XXX	- Digynic: 2nd polar body incorporation into blastomere
	41c (48)	N/A	- Lymphocytes: 46,XX - Skin fibroblasts: 46,XX/69,XXX	- Digynic: 2nd polar body incorporation into blastomere
(DANIEL *et al.* 2003)	42a (49)	N/A	- ST-CVS: 46,XX(23) - LT-CVS: 69,XXX(50)	- Diandric: delayed incorporation of 2nd sperm into blastomere
	42b (50)	8 y/o	- Blood: 46,XY(20) - Skin: 69,XXY(45)/46,XY(5)	- Digynic: delayed incorporation of 2nd polar body into blastomere
	42c (51)	N/A	- AF: 69,XXY(28)/47,XY,+16(4)	- Chimera: Digyny from maternal M-II error resulting in 2n ovum and fertilization by normal sperm + Fusion with 2nd trisomy 16 embryo
	42d (52)	3 m/o	- AF: 46,XX(50) - LT-CVS: 69,XXX(14)/46,XX(2) - ST-CVS = 46,XX(25) - Postnatal blood = 46,XX	- Diandric: delayed incorporation of 2nd sperm into blastomere
(FLORI *et al.* 2003)	43 (53)	5 y/o	- Amniocytes, fetal and postnatal lymphocytes: 46,XX - Skin fibroblasts (1 y/o): 69,XXX(30)/46,XX(70) (5 y/o): 69,XXX(298)/46,XX(2)	- Digynic: Incorporation of 2nd polar body into blastomere

Authors	Case #	Age	Genotype	Origin
(DEVRIENDT *et al.* 2004)	44 (54)	8 y/o	- Lymphocytes: 46,XY - Scrotal skin biopsy during surgery: 69,XXY (n = 4) - Buccal smear: Interphase FISH revealed 46,XY86%)/69,XXY(14%)	- ?
(VATISH *et al.* 2004)	45 (55)	b 26 wks d ? h/o	- Lymphocytes: 69,XXY/46,XX - Skin fibroblasts: 69,XXY(30%)/46,XX(70%)	- ?
(WRIGHT and WALES 2004)	46 (56)	N/A	- AF: 46,XX - Blood lymphocytes: 46,XX - Skin fibroblasts and gonadal tissue: 46,XX/69,XXY	- Chimera: Authors couldn't think of mechanism leading to XX/XXY from single zygote
(QUIGLEY *et al.* 2005)	47 (57)	11 w/o	- Lymphocytes: 45,X - FISH studies showed no evidence of SRY - 197/200 cells showed pattern consistent with 1 X chromosome while 3/200 consistent with 2 X chromosomes - Fibroblasts: 69,XXY - Repeat fibroblasts showed 3/60 cells 45,X	- Diandric: Delayed dispermy with 2n cell undergoing secondary loss of sex chromosome
(GIURGEA *et al.* 2006)	48 (58)	6 y/o	- Almost entirely 46,XY except for pancreatic lesions which were 3n	- Diandric: Postzygotic diploidization of triploid or delayed incorporation of 2nd sperm into 1 of 2 blastomeres
(KARTESZI *et al.* 2006)	49 (59)	2 1/2 y/o	- Peripheral lymphocytes: 46,XX - Skin biopsy: 2n(26%)/3n(60%)/4n(14%)	- ?
(OKTEM *et al.* 2007)	50 (60)	8 y/o	- Lymphocytes: 46,XX - Skin: 46,XX/69,XXY or 46,XX/69,XX,+mar (mar later identified as Y) - 20% of ovarian tissue contained Y chromosome	- ?
(SHAFI *et al.* 2007)	51 (61)	25 y/o	- Lymphocytes: 46,XX - Skin fibroblasts: 46,XX(65%)/69,XXX(35%)	-Digynic: Incorporation of 2nd polar body into blastomere
(RITTINGER *et al.* 2008)	52 (62)	14 y/o	- Lymphocytes: 46,XX - Cultured fibroblasts: 69,XXX(15)/46,XX(3) - Interphase FISH fibroblasts: 69,XXX(200)/46,XX(13)/92,XXXX(6) - 4n cells likely culture artifact	- Digynic
(WEGNER *et al.* 2009)	53 (63)	IUFD 25 wks	- Native amniocytes: 46,XX(70%)/69,XXY(30%) - 2n/3n confirmed by FISH on 2nd amniocentesis - Fetal WBC showed 1 (uncultured) & 3 (cultured) 3n cells - Fetal urine cells: 8.8 3n cells (n = 80)	- Diandric based on microsatellite analysis

Table 11. Complete phenotype data and additional notes for all cases of 2n/3n mixoploidy

Author	Case #	Age	Phenotype	Notes
(BOOK and SANTESSON 1960)	1 (1)	3 ½ y/o	- Placenta: N/A - Child: BW 2100 g, psychomotor delay, occasional feeding difficulty, localized lipomatosis, thin lower legs, small for age, micrognathia, bony and cutaneous syndactyly of hands/feet, some abnormal ataxic movements, porencephaly	- First reported case of 2n/3n mixoploidy
(ELLIS *et al.* 1963)	2 (2)	6 y/o	- Placenta: N/A - Child: Mild MR, right sided hemiatrophy, zygodactyly	- Mother had slight congenital asymmetry but normal karyotype
(FERRIER *et al.* 1964)	3 (3)	10 y/o	- Placenta: N/A - Child: BW 1850 g, body asymmetry, dolicho-oxycephaly, feeding difficulties, psychomotor delay, enuria, partial 3-4 syndactyly of hands, complete 3-4 syndactyly of left foot, abnormal pigmentation on right side, small penis/scrotum, cryptorchidism, decreased bone age, thin long bones, hypoplastic right pelvis, very low urinary gonadotrophin secretion	
(GROPP *et al.* 1964)	4 (4)	3 1/2 m/o	- Placenta: N/A - Child: Harelip, cleft palate	
(SCHMID and VISCHER 1967)	5 (5)	11 m/o	- Placenta: N/A - Child: Severe developmental and mental delay, thin limbs, prominent forehead, peculiar facies, low-set abnormal ears, coloboma, cutaneous abnormalities, muscular atrophy, 3-4 syndactyly of fingers, 2-3 syndactyly of toes	
(VAN DEN BERGHE and VERRESEN 1970)	6 (6)	d 8 h/o.	- Placenta :N/A - External: Asymmetric head, low-set malformed ears, joint contractures, cutaneous syndactyly of hands and feet, normal appearing genitalia with testes in scrotum - Internal = N/A	
(JENKINS *et al.* 1971)	7 (7)	10 1/2 y/o	- Placenta: N/A - Child: Asymmetric growth (right side larger), psychomotor delay, MR, heart murmur, downturned corners of mouth, thoracic scoliosis, clinodactyly with single crease of left 5th finger, EEG showed slowed activity bilaterally	
(SELLYEI *et al.* 1971)	8 (8)	39 y/o	- Proband: Apparently normal	- Screening due to genetic disorder in son
(DEWALD *et al.* 1975)	9 (9)	13 y/o.	- Placenta : N/A - Child: Ambiguous genitalia, urogenital anomalies, feminine appearance, severe mental and developmental delay, bilateral clubfoot, small gonad in left scrotum - Internal: small vagina, no prostate, small right gonad in pelvis	

Author	Case #	Age	Phenotype	Notes
(FULTON *et al.* 1977)	10a (10)	11 y/o.	- Placenta: N/A - Child: Motor and developmental retardation, left hemiatrophy, facial and body asymmetry, pigmentary abnormalities of legs, left sided grand mal seizures, kyphoscoliosis, 2-3-4 syndactyly of left toes and fingers, generalized weakness	- Sister with grand mal seizures
	10b (11)	13 y/o.	- Placenta: N/A - Child: Severe MR, truncal obesity, dorsal scoliosis, bilateral blepharoptosis	
(FRYNS *et al.* 1980)	11 (12)	21 y/o	- Placenta: N/A - Proband: Severe psychomotor retardation, "oldish appearance" with facial lipodystrophy, peculiar facies, mandibular prognathism, , facial asymmetry, truncal obesity, left hemihypotrophy, , lumbar lordosis, finger syndactyly, unusual feet with 2-3 syndactyly, VSD murmur, generalized dysrythmy on EEG	
(GINSBERG *et al.* 1981)	12 (13)	d 3 h/o	- Placenta: N/A - Child: Generalized edema, unusual facies, low-set ears, ocular anomalies, ambiguous genitalia, rocker bottom feet,, dysplastic kidneys, adrenal hypoplasia, Leydig cell hyperplasia, partial cerebellar agenesis	- Maternal oral contraceptive use until 20 weeks gestation
(GRAHAM JR. *et al.* 1981)	13 (14)	19 m/o	- Placenta: N/A - Child: BW 2480 g, transverse palmar crease, short 1st and 5th metacarpals, 5th finger clinodactyly, partial 2-3-4 syndactyly of fingers, asymmetric growth, hemihypoplasia, decreased muscle strength, mild developmental delay, facial and body asymmetry (right side structures smaller)	- Maternal proteinuria and hypertension during 3rd trimester
(THARAPEL *et al.* 1983)	14a (15)	d 40 h/o	- Placenta: Reported normal - Child: IUGR, cyanotic at birth, neurologically depressed, brachycephaly, blepharophimosis, low-set ears, micrognathia, peculiar facies, short neck, bell-shaped thorax with wide set nipples, weak heart tones, small genitalia with bilateral hydrocele, hypotonia, wrinkled skin with little subcutaneous tissue, flexion deformities of knees and elbows, clinodactyly of fingers, left transverse palmar crease, bilateral clubfoot, syndactyly of toes	
	14b (16)	8 1/2 y/o	- Placenta: Normal - Child: decreased fetal movement, hypotonia, unusual facies, micrognathia, deficient muscle mass in limbs, clinodactyly of fingers, abnormal dermatoglyphics, hypoplastic 4^{th} and 5^{th} toes, psychomotor delay, body asymmetry, seizure disorder developed around 3 yrs, pigmentary anomalies becoming more pronounced with age	- Paternal great aunt with sever MR & severe spastic CP - Mother took antibiotics early in pregnancy
(DONNAI *et al.* 1986)	15a (17)	12 y/o	- Placenta: N/A - Child :Severe MR, face and body asymmetry, truncal obesity, unusual hands and feet, sandal gap	

Author	Case #	Age	Phenotype	Notes
	15b (18)	1 y/o	- Placenta: N/A - Child: Body asymmetry, diffuse retinal pigmentary disturbance, obesity, unusual feet, sandal gap	
(PETTENATI *et al.* 1986)	16 (19)	d 2 d/o	- Placenta: N/A - Child: BW 1969 g @ 43 wks, IUGR, hypoglycemia, depressed nasal bridge, telecanthus, low set posteriorly rotated ears, facial asymmetry, bulbous nasal tip, micrognathia, right cutaneous 3-4 finger syndactyly, 5th finger clino/camptodactyly, hypoplastic right thumb, hypoplastic right hallux, short toes, sandal gap, hypoplastic toes 4-5 and 2-3 toe syndactyly, metatarsus adductus, talipes equinovarus - Necropsy: Adrenal hypoplasia, partial agenesis of corpus callosum, heart defect, incompletely pulmonary lobation, multiple hemorrhages in lungs and cerebellum	
(TANTRAVAHI *et al.* 1986)	17 (20)	3 y/o	- Placenta: N/A - Child: Ambiguous genitalia, hermaphroditism, skin pigmentary dysplasia, right foot larger than left	
(BENDON *et al.* 1988)	18 (21)	TOP 20 wks	- Placenta: Thick with small echolucencies, characteristic changes of PHM - Fetus: Hydrocephaly, lumbosacral myelomeningocele, IUGR - Autopsy: Bulbous nose, microstomia, 3-4 syndactyly, small adrenals, thickened tricuspid valve, macrocephaly, hydrocephaly, micropenis, hypospadias, gonads consisting of central small testicular region and peripheral rim of immature ovarian tissue, abnormally large utricle/mullerian structure in place of prostate	
(DAHL *et al.* 1988)	19 (22)	d 5 w/o	- Placenta: N/A - External: IUGR, respiratory insufficiency, high forehead, micrognathia, peculiar facies, asymmetric funnel chest, slender pelvis, thin extremities, 3-4 syndactyly of hands, sandal gap, flexion deformities of multiple joints, convex thoracic scoliosis - Internal: Horseshoe kidney, dextroposition of lower descending & sigmoid colon, mesocolon not attached to cecum and ascending colon	
(BETTS *et al.* 1989)	20 (23)	TOP 20 wks	- Placenta: N/A - External: Incompletely masculinized genitalia, slight hypertelorism, prominent forehead, receding jaw, malformed ears, single palmar crease, sandal gap - Internal: Grossly male gonads, adrenal hypoplasia	

Author	Case #	Age	Phenotype	Notes
(CALLEN *et al.* 1991)	21 (24)	N/A	- Placenta: 670 g, bulky, strikingly abnormal, numerous vesicular villi scattered throughout parenchyma and intermixed with macroscopically normal villous tissue, grossly enlarged hydropic villi covered with thin layer of trophoblast showing focal hyperplasia and containing central cisterns without normal fetal vessels, flat sac at one edge consisting of 2 adherent amnions and degenerate chorion with no apparent fetal remnants - Child: Normal 2.3 kg female born at 35 weeks gestation	
(POST and NIJHUIS 1992)	22 (25)	TOP 25+2 wks	- Placenta: 122 g with normal appearance - Fetus (external): IUGR, hypertelorism, coloboma, camptodactyly, other minor dysmorphic features - Fetus(internal): Transposition of great vessels, VSD, intestinal malrotation, agenesis of gallbladder	
(DAUBENEY *et al.* 1993)	23 (26)	3 y/o	- Placenta: N/A - Child: Plagiocephaly, hypotelorism, depressed nasal bridge, 4-5 clinodactyly of fingers, pigmentary anomalies on chest, developmental delay, hypotonia, precocious puberty at 3 months, seizures, ventriculomegaly	
(JARVELA *et al.* 1993)	24 (27)	20 m/o	- Placenta: 420 g, no abnormalities - External: BW 1410 g, narrow skull, hypertelorism, micrognathia, high narrow palate, low-set ears, complete 3-4 finger syndactyly, partial 2-3 toe syndactyly, facial asymmetry, streaky pigmentary anomalies on legs and wrists - Internal: Agenesis of septum pellucidum and posterior corpus callosum, very delayed neurological development, hypotonia, areflexia, feeding difficulties for 1st 5 months, hypothyroidism, precocious puberty Dx at 5 months, Infantile seizures with hypsarrythmia on EEG,	
(KENNERKNECHT *et al.* 1993)	25 (28)	SB 41 wks	- Placenta: N/A - Fetus: BW 760 g, severe IUGR, dysmorphic brain	
(MULLER *et al.* 1993)	26 (29)	9 m/o	- Placenta = N/A - Child: Cerebral anomalies, precocious puberty at 6 months, intractable myoclonic seizures, sensorineural hearing loss, intestinal malrotation	One of set of triplets (others normal) conceived with fertility drugs
(SARNO JR. *et al.* 1993)	27 (30)	Dx 14 wks GA	- Placenta: Unusually thickened with diffuse multi-cystic appearance - Child: Apparently normal female, BW 1935 g	
(TUERLINGS *et al.* 1993)	28 (31)	TOP 10 wks.	-Placenta: N/A - Fetus: N/A	

Author	Case #	Age	Phenotype	Notes
(CARAKUSHANSKY *et al.* 1994)	29 (32)	4 1/2 y/o	- Placenta: N/A - Child: BW 2900 g, craniosynostosis, microcephaly, poor suck reflex, severe psychomotor delay, peculiar facies, microstomia, micrognathia, facial and body asymmetry, single transverse palmar crease on left, 5th finger clinodactyly, soft tissue 3-4 syndactyly of toes, proximally positioned halluces, pigmentary dysplasia on lower body, marked hypotonia, microophthalmia, coloboma, ovaries not seen on ultrasound	
(WOODS *et al.* 1994)	30 (33)	d 15 y/o	- Placenta: N/A - Child: Severe MR, short stature, asymmetry, failure to thrive, apparent macrocephaly, peculiar facies, bossed forehead, micrognathia, abnormal ears, 3-4 syndactyly of left hand, 2-3 syndactyly of left foot, undescended right testis, severe developmental delay, moderate hypotonia, generalized osteoporosis, cotton reel shaped vertebrae, grand mal epilepsy, flexion contractures of large joints, lumbar scoliosis	
(IKEDA *et al.* 1996)	31 (34)	TOP 18 wks	- Placenta: PHM, areas of hydropic & normal villi, capillary formation in hydropic villi - Fetus: Grossly normal, 248 g, appropriate for dates	
(DEAN *et al.* 1997)	32 (35)	2 1/2 y/o	- Placenta: N/A - Child: IUGR, fetal akinesia persisting throughout life, macrocephaly , small palpebral fissures, 3-4 syndactyly of fingers, 2-3 syndactyly of toes, severe developmental and intellectual delay	Died at 3 y 8 mo.
(LIN *et al.* 1998)	33 (36)	IUFD 22 wks.	- Placenta: 74g, apparently normal - Fetus: IUGR, omphalocele, radial agenesis, 4-5 syndactyly right hand, 2-3 syndactyly left hand	
(TOPALOGLU *et al.* 1998)	34 (37)	7 y/o	- Placenta: N/A - Child: Hepatomegaly, hypertension, flat occiput, short palpebral fissures, low-set ears, transverse palmar crease, short thumbs, heart murmur, moderate ascites, pedal edema, cryptogenic cirrhosis, membranous glomerulonephritis	- Parents 1st degree cousins
(HSIEH *et al.* 1999)	35 (38)	18 m/o	- Placenta: Huge, hydropic and multicystic at 18 weeks; evidence of molar areas invading normal areas at birth - Infant: BW 1551 g, IUGR, respiratory distress at birth, complete recovery within 2 weeks & healthy at 18 months	
(ENGLISH *et al.* 2000)	36 (39)	TOP 18 wks.	- Placenta: very small, 23 g (expected 130 g at 18 weeks) - Fetus: Severe IUGR, abnormal ears, poor limb muscle development, oligohydramnios, 3-4 syndactyly of right hand & left foot, bilateral talipes equinovarus, adrenal hypoplasia	

Author	Case #	Age	Phenotype	Notes
(ZHANG *et al.* 2000)	37 (40)	IUFD 20 wks	- Placenta: 500 g with cystic molar villi scattered throughout and intermixed with normal villi - Fetus: 500 g, delivered at 23 wks, severe maceration precluded further examination	
(LAMBERT *et al.* 2001)	38 (41)	8 y/o	- Placenta: N/A - Child external: MR, developmental. delay, seizures, obesity, lordosis, single palmar crease, 5th finger campto/clinodactyly, 2-3 toe syndactyly, calcaneovalgus, asymmetry Child Internal: Epileptic activity on EEG, vermis hypoplasia	
(PHELAN *et al.* 2001)	39 (42)	d 22 h/o	- Placenta: Very small 154.3 g, small diameters, hypoplastic decidua but no parenchymal cysts - Infant: Severe IUGR, abnormal ears, cleft palate, syndactyly of fingers and toes	
(VAN DE LAAR *et al.* 2003)	40a (43)	6 y/o	- Placenta: N/A - Prenatal: IUGR, oligohydramnios, decreased movement - Child: Unusual facies, body asymmetry, marked hypotonia, joint contractures, 2-3 syndactyly of toes, small phallus, bifid scrotum, severe developmental delay	
	40b (44)	6 y/o	- Placenta: N/A - Prenatal: IUGR - Child: Growth retardation, failure to thrive, hypotonia, dysmorphic features, syndactyly, small underdeveloped genitalia, severe psychomotor delay	
	40c (45)	21 m/o	- Placenta: N/A - Child: Peculiar facies, small ASD, rocker bottom feet, 3-4 syndactyly of left hand, long digits, anteriorly placed anus, bilateral cochlear hearing loss, thyroid agenesis, developmental delay	
(BREMS *et al.* 2003)	41a (46)	N/A	- Placenta: N/A - Child: N/A	
	41b (47)	N/A	- Placenta: N/A - Child: N/A	
	41c (48)	N/A	- Placenta: N/A - Child: N/A	
(DANIEL *et al.* 2003)	42a (49)	N/A	- Placenta: N/A - Fetus: Dandy-Walker hydrocephalus, severe oligohydramnios, cardiac anomalies (single ventricle), small right VSD	- Hydrocephalus detected at 19 wks, no further details on pregnancy outcome
	42b (50)	8 y/o	- Placenta: N/A - Child: Globally delayed, microcephaly, microstomia, micrognathia, short stature, osteoporosis, truncal obesity, controlled diabetes, 3-4 syndactyly of hands and feet	

Author	Case #	Age	Phenotype	Notes
	42c (51)	N/A	- Placenta: Non-cystic - Fetus: Severe IUGR, wasted, holoprosencephaly, complete arhinia, large midline cleft palate, syndactyly of fingers and toes, hypoplastic genitalia, adrenal hypoplasia, sex reversal with normal uterus, ovaries, and fallopian tubes	- Pregnancy terminated but date not given
	42d (52)	3 m/o	- Placenta: N/A - "Child: Normal female	
(FLORI *et al.* 2003)	43 (53)	5 y/o	- Placenta: N/A - Child external: IUGR, polyhydramnios, unusual facies, micrognathia, low-set posteriorly rotated ears, truncal obesity, club hands and feet, 3-4 syndactyly of left hand, pigmentary dysplasia along Blaschko's lines on legs, severe psychomotor delay - Child internal: Fronto-parietal atrophy, focal pachygyria, hypsarythmia	
(DEVRIENDT *et al.* 2004)	44 (54)	8 y/o	- Placenta: N/A - Child: BW 2.5 kg at 37 wks, IUGR, hypospadias, ring-shaped skin creases on all 4 limbs, abundant connective tissue, right preauricular pit, asymmetric leg circumference, hyperpigmented areas of skin, mild developmental delay, tapering fingers, weight > 97th percentile @ 8 y/o	- Conceived through ICSI
(VATISH *et al.* 2004)	45 (55)	b 26 wks d ? h/o	- Placenta: 406 g, circumscribed area with small vesicles, hypoplastic terminal villi, hydropic villi with abnormal contours and trophoblastic pseudoinclusions but no trophoblast proliferation, overall features of PMD and PHM - Child: Increased leg muscle bulk, bulbous toes	Mother: Severe early onset preeclampsia at 26 wks - Emergency C-section due to fetal distress
(WRIGHT and WALES 2004)	46 (56)	N/A	- Placenta: 2.0 kg, large, pale - Child: BW 2.84 kg, ambiguous genitalia, true hermaphroditism, micrognathia, macroglossia, microcephaly, sloping forehead, wide simian crease, bilateral ovotestes	- Age of child not indicated
(QUIGLEY *et al.* 2005)	47 (57)	11 w/o	- Placenta: N/A - Child: Ambiguous genitalia, 3-4 syndactyly of left hand, CHD, pigmentary mosaicism, showed normal development at 11 weeks old	Mom 36 y/o
(GIURGEA *et al.* 2006)	48 (58)	6 y/o	- Placenta: N/A - Child: Hypoglycemia, unusual facies, abnormal pancreas, liver hamartoma	

Author	Case #	Age	Phenotype	Notes
(KARTESZI *et al.* 2006)	49 (59)	2 1/2 y/o	- Placenta: N/A - Child External: Deep set eyes, prominent forehead, beaked nose, thin wrinkled skin, prominent veins, left sided inguinal hernia, partial 3-4 finger syndactyly, arachnodactyly, narrow feet, cutis laxa on trunk, muscle hypotonia, truncal ataxia, strabismus, gluteal lipodystrophy, developmental delay - Child internal: Subependymal cyst, ASD	- Neonatal phenotype matched Dx criteria for Wiedemann-Rautenstrauch syndrome but progeroid features markedly diminished by 2 1/2 yrs of age
(OKTEM *et al.* 2007)	50 (60)	8 y/o	- Placenta: N/A - Child: Pigmentary dysplasia following Blaschko's lines, early developmental delay, 2-3 soft tissue syndactyly of toes, 5th finger clinodactyly, growth retardation, otherwise phenotypically normal with normal internal and external genitalia	
(SHAFI *et al.* 2007)	51 (61)	25 y/o	- Placenta: N/A - Patient: Psychomotor delay, MR, facial asymmetry, truncal obesity, syndactyly, transverse palmar crease, pigmentary dysplasia, neonatal polycythemia - Adult onset: Back pain, kyphosis, skin lesions, weakness of distal hand muscles	MZ twin with similar phenotype but no evidence of 3n cell line
(RITTINGER *et al.* 2008)	52 (62)	14 y/o	- Placenta: N/A - Child: BW 2400 g, prominent forehead, broad nasal tip, small chin, clino/camptodactyly of fingers, soft tissue 2-3 syndactyly of right foot and 3-4 of left, bulbous tip of 2^{nd} toes, calcaneovalgus, psychomotor delay, seizures, truncal obesity, lumbarization of S1, elongation of metacarpals 2-3, ankylosis of proximal interphalangeal joint of 5^{th} fingers, patchy or streaky hyperpigmentation, precocious puberty, scoliosis, growth retardation	
(WEGNER *et al.* 2009)	53 (63)	IUFD 25 wks	- Placenta: Hypertrophic - Fetus: Polyhydramnios, tricuspid regurgitation, pericardial effusion, mild pyelectasia - Autopsy: Microgenia, macroglossia, hypertelorism, 3-4 finger syndactyly, hypoplastic right lung, short right arm, mild dilation of ureters, unambiguously female external genitalia despite 69,XXY line (internal organs not examined due to autolysis)	

APPENDIX B

COMPLETE DATA FOR ALL CASES OF COMPLETE TRIPLOIDY

Table 12 provides complete karyotype details for all cases of complete triploidy cited in this paper as well as those used in the literature review. The cases are listed and numbered in the same manner as for the diploid/triploid mixoploid cases. There were a total of 67 cases collected from 56 different published articles. Case 51a(58) had been published separately in a previous article, but only the more recent article is listed in the table. Information regarding the parental origin of the extra haploid set of chromosomes and the mode by which they were ascertained is also included when available. Table 13 provides the complete phenotype data for all cases of complete triploidy as well as any relevant notes. These tables are set up in the same way as Tables 10 and 11.

Table 12. Complete genetic and molecular data for all cases of complete triploidy

Authors	Case #	Age	Genotype	Origin
(BUTLER *et al.* 1969)	1 (1)	d 23 h/o	- Peripheral blood and skin: 69,XXX - Fibroblast sex chromatin analysis: 67 (32.5%) with single Barr body, 134 (65%) X-chromatin negative, 5 (2-5%) with 2 Barr bodies though 2 may have been 6n cells based on size	- ?
(PATTERSON *et al.* 1971)	2a (2)	SB 29 wks	- Placental vesicles: 69,XXX - Thymus, skin, spleen: 69,XXX	- ?
	2b (3)	SA 25 wks	- Skin fibroblasts: 69,XXX	- ?
(SPARREVOHN *et al.* 1971)	3 (4)	d 93 h/o	- Lymphocytes: 69,XXX - Autoradiography: 2 late-replicating X's in 12/22 cells & 1 in 1/22 cells	- Digynic: Blood group analysis showed both maternal rhesus alleles
(NIEBUHR *et al.* 1972)	4 (5)	d 93 h/o	- Lymphocytes: 69,XXX	- Suggestive of maternal meiosis failure
(SIMPSON *et al.* 1972)	5 (6)	d 3 d/o	- Lymphocytes: Entirely 69,XXY	- ?
(HENRIKSSON *et al.* 1974)	6 (7)	d 9 h/o	- Leukocytes: 69,XXY	- ?
(LEISTI *et al.* 1974)	7 (8)	d 7 d/o	- Karyotype from multiple tissues: 69,XXY - No evidence of X-chromatin in 1500 buccal cells	- ?
(GOSDEN *et al.* 1976)	8 (9)	b 26 wks d < 1 hr	- Cardiac blood, skin fibroblasts, muscle: 69,XXX	- ?
(DUDAKOV *et al.* 1977)	9a (10)	SA 4th month	- Skin, amnion, placenta: 69,XXX	- ?
	9b (11)	b 37 wks d 4 d/o	- Peripheral lymphocytes: 69,XXX	- ?
(FULTON *et al.* 1977)	10 (12)	d 50 min	- Karyotype: 69,XXY	- ?
(BOCIAN *et al.* 1978)	11 (13)	TOP 24 wks	- Q-band karyotype: 69,XXY in all 25 cells scanned	- Digynic based on presence of 2 fetal homologues with polymorphism present in 1 copy in mother
(DELIGDISCH *et al.* 1978)	12 (14)	LB 22 wks d < 1 min	- Cord blood, fetal fibroblasts, Wharton's jelly: 69,XYY	- Diandric based on presence of 2 Y chromosomes
(LUCIANI *et al.* 1978)	13 (15)	TOP 17 wks	- Fetal blood and fibroblasts: 69,XXX	- ?
(BIEBER *et al.* 1981)	14 (16)	SB	- Gut fibroblasts: 69,XXX	- Digynic: 1st polar body fertilization
(PAGE *et al.* 1981)	15 (17)	d 17 h/o	- Karyotype: Entirely 69,XXX	- Diandric: Diplospermy II
(BROEKHUIZEN *et al.* 1983)	16 (18)	TOP 24 wks	- Karyotype: 69,XXY	- ?

Authors	Case #	Age	Genotype	Origin
(MARASCHIO *et al.* 1984)	17 (19)	d 45 d/o	- Lymphocytes & fibroblasts: Entirely 69,XXX - Karyotype: 69,XXX,inv(15)(q15q26) - inv(15) of maternal origin	- Diandric: Probably dispermy
(SHERARD *et al.* 1986)	18 (20)	d 312 d/o	- Bone marrow, lymphocytes, fibroblasts: 69,XXY - Repeat lymphocytes at 9 months old showed no evidence of mosaicism	- Digynic: HLA typing
(VEJERSLEV *et al.* 1986)	19a (21)	b 28 wks d < 1 hr	- Karyotype: 69,XXY	- Diandric: dispermy
	19b (22)	IUFD < 14 wks	- Karyotype: 69,XXY	- Diandric: dispermy
	19c (23)	TOP 18 wks	- Karyotype: 69,XXY	- Diandric: dispermy
(ROYSTON and BANNIGAN 1987)	20a (24)	d 3 h/o	- Peripheral leukocytes: 69,XXX	- ?
	20b (25)	d 45 min	- Peripheral leukocytes & skin fibroblasts: 69,XXY - Paternal heteromorphism with 1 #9 noticeably larger than other	- Diandric: infant had 2 unusual #9's similar to that seen in father
(ROCHON and VEKEMANS 1990)	21 (26)	SA 8 wks	- Products of conception: 69,XXY,t(6;14)(p23;q24) - Mother balanced carrier 46,XX,t(6;14)(p23;q24)	- Digynic: M-I non-disjunction based on comparison of parental & fetal chromosome heteromorphisms on #'s 13, 14, & 21
(SCHWAIBOLD *et al.* 1990)	22 (27)	d 20 h/o	- Karyotype: 69,XXX in 30 metaphases - RBA staining showed 2 late-replicating X chromosomes	- Could not be determined due to insufficient FISH signal
(GALAN *et al.* 1991)	23 (28)	d 7 d/o	- Lymphocytes: 69,XXX	- Digynic: Fertilization of 2n ovum by 1n sperm
(MERLOB *et al.* 1991)	24 (29)	d 6 d/o	- Bone marrow, skin fibroblasts: 68,XX	- ?
(PETIT *et al.* 1992)	25 (30)	TOP 20 wks	- Q-banding of chorionic villi, skin fibroblasts & peripheral blood: 69,XXY - No evidence of Barr bodies in 200 cells	- ?
(NIEMANN-SEYDE and ZOLL 1993)	26 (31)	d 10 1/2 w/o	- Peripheral blood & skin fibroblasts: 69,XXX	- Diandric: Cytogenetic polymorphisms
(SEPULVEDA *et al.* 1994)	27 (32)	TOP 12 wks	- CVS, fetal skin, placenta: 69,XXY	- ?
(PIETRANTONI *et al.* 1995)	28 (33)	TOP 18+3 wks	- Fetal blood and placenta: 69,XXY	- ?
(SMETS *et al.* 1995)	29 (34)	d 38 h/o	- Peripheral blood and skin fibroblasts: 69,XXY	- ?
(SOREM and SHAH 1995)	30 (35)	TOP 26 wks	- Cordocentesis: 69,XXY	- ?
(DE RAVEL *et al.* 1996)	31a (36)	SB 31 wks	- Fetal blood: 69,XXX	- ?

Authors	Case #	Age	Genotype	Origin
	31b (37)	TOP 26 wks	- Cordocentesis: 69,XXX	- ?
	31c (38)	TOP 32 wks	- Fetal blood: 69,XXY	- ?
(JOHNSON *et al.* 1997)	32 (39)	TOP 17 wks	- Fetus: 69,XXX	- ?
(LUDWIG *et al.* 1998)	33 (40)	TOP 15 wks	- CVS and amniocentesis: Entirely 69,XXX	- ?
(RAMSEY *et al.* 1998)	34 (41)	TOP 14 wks	- Fetus: 69,XXX	- ?
(HASEGAWA *et al.* 1999)	35 (42)	b 31 wks d 46 d/o	- Amniocentesis: 69,XXX - Postnatal cord blood, skin fibroblasts, peripheral lymphocytes: 69,XXX	- Digynic based on Q-band heteromorphisms and confirmed by microsatellite marker analysis
(KAFFE *et al.* 1989)	36 (43)	TOP 22 wks	- Amniocentesis and fetal tissue: 68,XX	- ?
(FRATES and FEINBERG 2000)	37 (44)	TOP 14+5 wks	- Both fetuses 3n	- ?
(MCFADDEN *et al.* 2000)	38 (45)	d. < 1 hr	- Amnion & chorion: 69,XXY - FISH studies found no definitive evidence of mosaicism	- ?
(CHANG *et al.* 2001)	39 (46)	LB 33 wks d < 1 min	- Fetal karyotype: 69,XXX	- Digynic: Maternal M-II non-disjunction based on STRP marker analysis
(BAN *et al.* 2002)	40 (47)	SB 31 wks	- CVS (due to severe oligohydramnios): 69,XXX	- Digynic: STRP analysis
(STEFOS *et al.* 2002)	41 (48)	TOP 18 wks	- Triploid	- ?
(GASSNER *et al.* 2003)	42 (49)	SF 20+3 wks	- Karyotype: 69,XXX	- Probably digynic based on phenotype
(LIM *et al.* 2003)	43 (50)	N/A	- Karyotype: 69,XXY,t(2;6)(p12;q24)der(6)t(2;6)(p12;q24)pat	- Diandric: Dispermy, 1st sperm carried balanced t(2;6) and 2nd carried der(6)
(BIANCA *et al.* 2004)	44 (51)	TOP 22 wks	- Amniocentesis: 69,XXX	- ?
(BILLIEUX *et al.* 2004)	45 (52)	TOP 18 wks	- Amniocentesis and fetal biopsy: 69,XXX	- Diandric: Microsatellite marker analysis
(DALMIA *et al.* 2005)	46 (53)	TOP 16 wks	- Amniocytes: 69,XXX - Post-TOP skin and placenta confirm 3n	- Diandric based on pattern of malformations
(ILIOPOULOS *et al.* 2005)	47 (54)	b 39 wks d 164 d/o	- Peripheral blood: 69,XXX(50)	- ?
(KOS *et al.* 2005)	48 (55)	TOP 26 wks	- Cordocentesis: 69,XXY,inv(9)(p11q13) in all lymphocytes	- ?

Authors	Case #	Age	Genotype	Origin
(BARSOOM *et al.* 2006)	49 (56)	TOP 20 wks	- Amniocentesis: 69,XXX	- ?
(MENDILCIOGLU *et al.* 2006)	50 (57)	SF 19 wks	- Amniocentesis: 69,XXX (growth discordant fetus); 46,XX (normal fetus)	- ?
(CHEN *et al.* 2008)	51a (58)	TOP 16 wks	- TA-CVS: 69,XXX	- Digynic: Maternal M-II by QF-PCR and STRP analysis
	51b (59)	TOP 15 wks	- Karyotype: 69,XXX	- Digynic: Maternal M-II error
	51c (60)	TOP 13 wks	- Karyotype: 69,XXX	- Digynic: Maternal M-II error
	51d (61)	TOP 14 wks	- Karyotype: 69,XXY	- Digynic: Maternal M-II error
	51e (62)	TOP 13 wks	- Karyotype: 69,XXY	- Digynic: Maternal M-II error
(MEDEIROS *et al.* 2008)	52 (63)	TOP 22 wks	- 3n by flow cytometry	- ?
(TAKABACHI *et al.* 2008)	53 (64)	d 221 d/o	- Lymphocytes: 69,XXX	- ?
(BEKDACHE *et al.* 2009)	54 (65)	SB 33 wks	- Amniocentesis: 69,XXY	- ?
(FALKERT *et al.* 2009)	55 (66)	TOP 16+2 wks	- CVS: 69,XXX	- ?
(SOLOMON *et al.* 2009)	56 (67)	SA 8 wks	- Fetal chromosomes: 69,XXX	- ?

Table 13. Complete phenotype data and additional notes for all cases of complete triploidy

Author	Case #	Age	Phenotype	Notes
(BUTLER *et al.* 1969)	1 (1)	d 23 h/o	- Placenta: Large 945 g (normal 450 g), scattered small calcification foci - Child: BW 1825 g (< 10th centile), flat face, hypertelorism, coloboma, long upper lip, underdeveloped low-set ears, short neck, single palmar crease, Absent distal flexion creases on fingers 2-4, proximally placed thumbs, unusual dermatoglyphics, short halluces, sandal gap, long 2nd and 3rd toes, hypoglycemia, areflexia, heart murmur, congestive heart failure - Necropsy: Dilated right heart with osteum secundum defect, VSD, bicuspid aortic & pulmonary valves, hydronephrotic right kidney, dysplastic left kidney, hypoplastic ovaries, adrenal hypoplasia, small brain, hepatosplenomegaly, poorly developed eyes	- Possibly first reported case of liveborn complete triploidy
(PATTERSON *et al.* 1971)	2a (2)	SB 29 wks	- Placenta: Large, 817 g, diffuse hydatidiform degeneration - Child: Hydramnios, severe hare-lip, bilateral 3-4 syndactyly, long 5th fingers, flexion deformity of toes 2-4, exomphalos containing most of small intestine, ASD, large left kidney, cystic right kidney	
	2b (3)	SA 25 wks	- Placenta: 281 g, diffuse hydatidiform degeneration - Fetus: 789 g, high arched palate, 3-4 syndactyly of left hand, long 5th fingers, splayed toes, umbilical hernia containing large portion of intestine, protrusion of part of liver into chest through diaphragmatic defect	
(SPARREVOHN *et al.* 1971)	3 (4)	d 93 h/o	- Placenta: N/A - Child: BW 1600 g at 37 wks, very immature, macrocephaly, small malformed low-set ears, micrognathia, blepharophimosis, long thick upper lip, arachnodactyly, irregular finger insertion, webbing between fingers, knee contractures, foot/ankle deformities, esophageal atresia - Necropsy: agenesis of corpus callosum, esophageal atresia, tracheo-esophageal fistula, alobar left lung, agenesis of gallbladder/cystic ducts, adrenal hypoplasia	
(NIEBUHR *et al.* 1972)	4 (5)	d 93 h/o	- Placenta: N/A - Child: Large head, asymmetric dysmorphic face, trachea-esophageal fistula, hand and foot malformations, 3-4 syndactyly of left hand, agenesis of corpus callosum, agenesis of gallbladder, persistent urachus	
(SIMPSON *et al.* 1972)	5 (6)	d 3 d/o	- Placenta: N/A - Child: BW 2500 g, myelomeningocele, icterus, prominent occiput, soft fontanelles, low-set ears, broad nasal bridge, bulbous nose, epicanthal folds, upslanted palpebral fissures, macroglossia, arachnodactyly, bilateral transverse palmar crease, 5th finger camptodactyly, small penis - Autopsy: Small brain, occipital polygyria, dilated lateral ventricles, coloboma, slightly enlarged heart, fenestrated septum primum, fusion of pulmonary valve commissure, small scrotum, small testes with immature tubules and few interstitial cells	

Author	Case #	Age	Phenotype	Notes
(HENRIKSSON *et al.* 1974)	6 (7)	d 9 h/o	- Placenta: Large, 1400 g - Child: Extreme hypotonia, neonatal areflexia, 3-4 finger syndactyly, 2-3-4 toe syndactyly, omphalocele, large LV, PFO, atelectatic lung disease with erythropoietic cells in capillaries, atrophic thymus, small bile ducts, hypoplastic gallbladder, adrenal hypoplasia, Leydig cell hyperplasia	
(LEISTI *et al.* 1974)	7 (8)	d 7 d/o	- Placenta: Large, edematous, 1350 g - Child: BW 2800 g at 41 wks, Hypotonia, weak reflexes, numerous target-like erythrocytes in peripheral blood, peculiar facies, hypertelorism, beaked nose with shallow bridge, ocular asymmetry, small vertically ovoid corneas, high arched palate, micrognathia, large posterior fontanelle, edema of hands and feet, soft tissue 2-3-4 syndactyly of hands, Retroflexed thumbs, flexion contractures of proximal interphalangeal joints of 5th finger, single transverse palmar crease, unusual dermatoglyphics, Partial 2-3-4-5 soft tissue syndactyly of toes, ambiguous external genitalia, severe micropenis, bifid scrotum with no palpable gonads, perineal urethral opening - Autopsy: Atelectatic lungs, small intraabdominal gonads attached to rudimentary epididymus, rudimentary uterus, gonads consisted of testicular tissue with Leydig cell hyperplasia, histologically normal fallopian tubes, some renal dysplasia, severe adrenal hypoplasia, microophthalmia, optic atrophy, coloboma	
(GOSDEN *et al.* 1976)	8 (9)	b 26 wks d < 1 hr	- Placenta: 750 g, diffuse hydatidiform change - Fetus: BW 860 g, prominent forehead, depressed nasal bridge, low-set malformed ears, long upper lip, flared ribcage, wide set aplastic nipples, flexion deformities of fingers, 3-4 finger syndactyly, hyperconvex nails, single transverse palmar crease, overdeveloped thigh muscles, talipes equinovarus, 3-4 toe syndactyly, sandal gap - Autopsy: Cardiomegaly, small hemorrhagic lungs, cystic right kidney, adrenal hypoplasia, ovarian hypoplasia, large abnormal brain with dilated ventricles, Dandy-Walker malformation	
(DUDAKOV *et al.* 1977)	9a (10)	SA 4th month	- Placenta: 114 g, macroscopically normal areas along with areas with cystic villi, microscopic features of transitional mole - Fetus: 27 g, low-set ears, 3-4 finger syndactyly, 2-3 toe syndactyly, VSD	
	9b(11)	b 37 wks d 4 d/o	- Placenta: N/A - Fetus: IUGR, oligohydramnios, BW 1020 g, large posteriorly rotated ears, hypertelorism, broad nasal bridge, peculiar facies, hypoplastic mandible, cleft soft palate, overlapping fingers, radial deviation of fingers 3-5, pes varus, rocker bottom feet, 2-3 toe syndactyly, small chest, respiratory distress, cardiomegaly, small lungs, jaundice, bleeding - Autopsy: Agenesis of gallbladder and bile ducts, VSD, small lungs, hypoplastic and cystic kidneys, very small but histologically normal adrenals, bicornuate uterus, subarachnoid hemorrhage over left cerebellum	

Author	Case #	Age	Phenotype	Notes
(FULTON *et al.* 1977)	10 (12)	d 50 min	- Placenta: N/A - Child: Cebocephaly, holotelencephaly, severe ocular anomalies, retinal dysplasia, single midline nostril, low-set ears, meningomyelocele, bilateral single transverse palmar crease, 3-4 syndactyly of left toes, thymus hypoplasia, agenesis of gallbladder, ambiguous genitalia, extramedullary hepatic hematopoiesis, adrenal hyperplasia, undescended testes, Leydig cell hyperplasia	
(BOCIAN *et al.* 1978)	11 (13)	TOP 24 wks	- Placenta: Fragmented, 10 cm diameter, 1000 g - Fetus: Relative macrocephaly, IUGR, abnormally shaped skull, large fontanelles, hypoplastic occipital and parietal bones, malar hypoplasia, prominent glabella, bulbous beaked nose, large VSD, 3-4 syndactyly of all limbs, single transverse palmar crease, positional deformities of legs, soft tissue constrictions about thighs, vertebral anomalies, radioulnar synostosis	
(DELIGDISCH *et al.* 1978)	12 (14)	LB 22 wks d < 1 min	- Placenta: Large (450 g), PHM degeneration, mostly vesicular with trophoblastic hyperplasia, some fleshy normal areas - Fetus: BW 200 g at 22 wks, cyclopia, complete 2-3 (finger) & 2-3-4 (toe) syndactyly - Necropsy: 2 medially fused eyeballs, supraorbital proboscis, absent philtrum, microstomia, frontal porencephaly, agenesis of corpus callosum/septum pellucidum/optic chiasma, holoprosencephaly, thyroid/adrenal agenesis, intraabdominal testes, hypoplastic Leydig cells, absent scrotum, micropenis, polycystic kidneys	- Maternal grandparents 1st cousins
(LUCIANI *et al.* 1978)	13 (15)	TOP 17 wks	- Placenta: Pseudomolar cystic degeneration - Fetus: No apparent external anomalies	
(BIEBER *et al.* 1981)	14 (16)	SB	- Placenta: Extensive vascular anastomoses between small area supplying acardiac twin and larger area supplying normal twin - Fetus: Holoacardia, grossly malformed	- Normal 46,XY MC/DA co-twin
(PAGE *et al.* 1981)	15 (17)	d 17 h/o	- Placenta: 120 g, extensive squamous metaplasia around cord insertion, keratinization of amnion with underlying dense fibrosis - Infant: IUGR, BW 920 g, triangular face, flattened nose, low-set ears, mild jaundice, syndactyly of fingers & toes, slight hepatomegaly, agenesis of gallbladder	
(BROEKHUIZEN *et al.* 1983)	16 (18)	TOP 24 wks	- Placenta: 683 g, hydrops and cystic changes consistent with PHM - Fetus: 361 g, Polyhydramnios, hydranencephaly, polycystic kidneys, myelomeningocele	
(MARASCHIO *et al.* 1984)	17 (19)	d 45 d/o	- Placenta: Normal - Child: BW 1600 g, hypotonia, hyporeactive, rounded head, hypertelorism, high forehead, low nasal bridge, large low-set posteriorly rotated ears, micrognathia, short neck, slender thorax, malposed 2nd finger, single transverse palmar crease, tetradactyly of left foot, long 2nd and 3rd toes, severe jaundice, hepatomegaly, atrophic areas of skin, slight atrophy of corpus callosum, severe adrenal hypoplasia, hypoplastic ovaries	

Author	Case #	Age	Phenotype	Notes
(SHERARD *et al.* 1986)	18 (20)	d 312 d/o	- Placenta: small; thin, hypoplastic villi with scalloped outlines and central edema, minimal trophoblastic hyperplasia consistent with PHM - Child: BW 1417 g at 37 wks, IUGR, hypotonia, prominent occiput, triangular face, hypertelorism, large thin ears, thin abdominal muscles, undescended testes, hydrocele, beaked nose, cleft lip/palate, micrognathia, flexed wrists, ulnar deviation of hands, 2-3 syndactyly of left hand, clino/camptodactyly, bowed right tibia, rocker bottom feet, VSD, hypsarrhythmia, feeding difficulties, psychomotor delay	
(VEJERSLEV *et al.* 1986)	19a (21)	b 28 wks d < 1 hr	- Placenta: 760 g, central vesicles, edema, fibrous degeneration, did not meet criteria for PHM - Fetus: BW 1050 g, webbed neck, single transverse palmar crease, dysplastic 5th fingers, hypospadias, tracheo-esophageal fistula, adrenal hypoplasia, hydronephrosis, hydroureters	
	19b (22)	IUFD < 14 wks	- Placenta: 145 g, PHM - Fetus: 8 g when delivered at 20 wks, moderate maceration but no apparent gross abnormalities	
	19c (23)	TOP 18 wks	- Placenta: PHM - Fetus: 16 cm CRL, no apparent gross abnormalities	
(ROYSTON and BANNIGAN 1987)	20a (24)	d 3 h/o	- Placenta: small (948 g sans cord and membranes), grossly and microscopically normal - Fetus: BW 1286 g at 31 wks, epicanthal folds, hypertelorism, micrognathia, flattened nose, macroglossia, generalized edema, cutaneous 2-3-4 syndactyly of hands and feet, cystic adenomatoid malformation of lung, adrenal hypoplasia, extramedullary hematopoiesis, small thyroid/thymus, reduced number of primary follicles in ovaries	
	20b (25)	d 45 min	- Placenta: 880 g, grossly normal - Fetus: Epicanthal folds, microophthalmia, opacified corneas, flattened nasal bridge, cleft palate, macrocephaly, small fontanelles, small low-set ears, exomphalos micropenis, bifid scrotum, single transverse palmar crease, cutaneous 2-3-4 syndactyly of hands and feet, hydrocephalus, partial agenesis of corpus callosum, malformed basal ganglia, complete absence of cerebellar Purkinje cells, right ventricular hypotrophy, infandibular pulmonary stenosis, VSD, immature lungs (appeared ~20 wks), adrenal hypoplasia, extramedullary hematopoiesis, small thymus/thyroid, intraabdominal testes with Leydig cell hyperplasia, aniridia, coloboma, retinal dysplasia	
(ROCHON and VEKEMANS 1990)	21 (26)	SA 8 wks	- Placenta: Non-hydropic - Embryo: N/A	

Author	Case #	Age	Phenotype	Notes
(SCHWAIBOLD *et al.* 1990)	22 (27)	d 20 h/o	- Placenta: Hypoplastic, 214 g, immature terminal villi, single flat continuous trophoblast - Child: BW 1050 g, triangular face, microstomia, hypertelorism, low-set malformed ears, microretrognathia, 3-4 finger syndactyly, proximally positioned thumbs, short toes, symmetrical bilobar hypoplastic lungs, ASD, VSD, splenomegaly, agenesis of gallbladder, adrenal/renal hypoplasia, ovarian hilum cell hyperplasia	
(GALAN *et al.* 1991)	23 (28)	d 7 d/o	- Placenta: N/A - Child: IUGR, macrocephaly, microstomia, micrognathia, beaked nose, low set ears, ocular asymmetry, finger syndactyly, club feet, incipient genitalia, hydrocephaly, cerebral atrophy, partial agenesis of corpus callosum	
(MERLOB *et al.* 1991)	24 (29)	d 6 d/o	- Placenta: N/A - Child: BW 2000 g at 39 wks (small), microcephaly, large posterior fontanelle, small underdeveloped ears, proptosis, hypotelorism, coloboma, depressed nasal bridge, prominent columnella, microstomia, short philtrum, cleft palate, low set nipples, ulnar deviation of thumbs, transverse palmar crease, fusiform digits, large feet, 2-3 syndactyly of toes, large halluces, 5^{th} toe clinodactyly, prominent clitoris absent fourchette, persistent fetal circulation	
(PETIT *et al.* 1992)	25 (30)	TOP 20 wks	- Placenta: Grossly enlarged, focal hydropic changes, persistent immature stromal cells, hypoplastic trophoblast - Fetus: Hydrocephaly, hepatomegaly, relative macrocephaly, small flat facies, malar hypoplasia, microophthalmia, microstomia, micrognathia, low-set poorly lobulated ears, short neck with low hairline and abundant skin, narrow thorax, clinodactyly, 3-4 finger syndactyly, ambiguous external genitalia (hypospadias, urogenital blind slit) Autopsy: Triventricular hydrocephaly, agenesis of corpus callosum, agenesis of formix, ASD, hepatomegaly, adrenal hypoplasia, rudimentary small gonads in internal inguinal position, testes had reduced number of seminiferous tubules and were surrounded by rim of immature ovarian tissue	
(NIEMANN-SEYDE and ZOLL 1993)	26 (31)	d 10 ½ w/o	- Placenta: Placental insufficiency - Child: BW 800 g at 34 wks, IUGR, respiratory distress, dolichocephaly, microcephaly, blepharedema, hypertelorism, short upturned nose, short philtrum, microstomia, microretrognathia, low-set dysmorphic ears, short neck, macro/camptodactyly of hands and feet, maldeveloped external genitalia, CHD - Autopsy: Pulmonary hypoplasia with absent lobation, multicystic horseshoe kidney, small bladder, adrenal hypoplasia, ovarian hypoplasia, thyroid cyst, aplasia of gallbladder, hepatic degeneration, cerebral cyst in septum pellucidum	
(SEPULVEDA *et al.* 1994)	27 (32)	TOP 12 wks	- Placenta: Enlarged, thickened, parenchymal cysts, villous hydrops, no trophoblastic hyperplasia - Fetus: Ectopia cordis, ventral wall defect, increased nuchal translucency	Authors note similarity to pentalogy of Cantrell

Author	Case #	Age	Phenotype	Notes
(PIETRANTONI *et al.* 1995)	28 (33)	TOP 18+3 wks	- Placenta: hydropic, irregular, gelatinous, hydropic villous changes but not consistent with PHM, small chorioangioma - Fetus: IUGR, omphalocele, probable NTD, polyhydramnios	
(SMETS *et al.* 1995)	29 (34)	d 38 h/o	- Placenta: Large (1800 g), macroscopically consistent with PHM - Child: Polyhydramnios, BW 1434 g at 30+2 wks, cyanosis, edema, severe hypotonia, large posterior fontanelle, low-set malformed ears, microophthalmia, corneal opacities, coloboma, microstomia, cleft palate, left intraabdominal mass, ambiguous genitalia, micropenis, cryptorchidism, multicystic kidneys, macrocytosis	
(SOREM and SHAH 1995)	30 (35)	TOP 26 wks	- Placenta: Large, PHM - Fetus: BW 557 g, polyhydramnios, omphalocele, cleft lip/palate, severe IUGR, ambiguous genitalia, single transverse palmar crease, low-set ears	
(DE RAVEL *et al.* 1996)	31a (36)	SB 31 wks	- Placenta: Normal - Fetus: BW 477 g, oligohydramnios, asymmetric IUGR, relative macrocephaly, micrognathia, low-set malformed ears, 2-3-4 syndactyly of all limbs, malformed external genitalia, poorly formed labia minora, absent clitoris - Autopsy: Hypoplastic lungs with absent lobation, aplasia of gallbladder, agenesis of right kidney, ureter, and adrenal, poor development of cerebral gyri	
	31b (37)	TOP 26 wks	- Placenta: Small - Fetus: Severe IUGR, hypertelorism, bulbous nose, malformed ears, micrognathia, 3-4 finger and 2-3 toe syndactyly - Autopsy: Cleft palate, pulmonary hypoplasia, distended ileum ending in blind pouch, hypoplastic and collapsed colon	
	31c (38)	TOP 32 wks	- Placenta: Edematous with large immature villi - Fetus: IUGR, aplasia cutis of posterior scalp, 3-4 syndactyly of all limbs, talipes equinovarus - Autopsy: Astomia, mandibular aplasia, low-set posteriorly angulated ears, pulmonary hypoplasia, gastric hypoplasia, gallbladder hypoplasia, renal hypoplasia, adrenal hypoplasia, ambiguous external genitalia, cryptorchidism, scant seminiferous tubules, prominent Sertoli cells, abundant Leydig cells, arhinencephaly, hypoplasia of corpus callosum	
(JOHNSON *et al.* 1997)	32 (39)	TOP 17 wks	- Placenta: Normal - Fetus: Vertebral anomalies, renal dysplasia, single flexion crease on index fingers	
(LUDWIG *et al.* 1998)	33 (40)	TOP 15 wks	- Placenta: Swiss cheese-like appearance on ultrasound, PHM - Fetus: Nuchal edema, IUGR	- Complicated by maternal OHSS
(RAMSEY *et al.* 1998)	34 (41)	TOP 14 wks	- Placenta: Thickened, PHM, focal areas of hydropic trophoblastic villi - Fetus: Gastroschisis, abdominal wall defect	

Author	Case #	Age	Phenotype	Notes
(HASEGAWA *et al.* 1999)	35 (42)	b 31 wks d 46 d/o	- Placenta: Small (152 g), non-cystic - Child: IUGR, BW 650 g at 31 wks), oligohydramnios, hypotonia, respiratory distress, relative macrocephaly, blepharophimosis, microophthalmia, hypertelorism, low-set malformed ears, short neck, micrognathia, asymmetric funnel chest, cutaneous 3-4 (finger) and 2-3 (toe) syndactyly, slight ventriculomegaly, bilateral absence of 5^{th} ribs - Autopsy: Thymic hypoplasia, ovarian dysgenesis	
(KAFFE *et al.* 1989)	36 (43)	TOP 22 wks	- Placenta: 40 g, normal fetal vasculature, focal microscopic calcification - Fetus: 210 g, IUGR, relative macrocephaly, hydrocephaly, dysmorphic facies, hypoplastic mandible, broad nasal bridge, short philtrum, low-set ears, eye anomalies, handlebar clavicles, cervical rib, medial deviation of ribs, flexion deformities of fingers, proximal placement of thumbs, talipes equinovarus, bicuspid aortic valve, aortic stenosis, anomalous origin of left subclavian artery, cystic horseshoe kidney, hypoplastic lungs without lobation, ovarian hypoplasia, extramedullary hematopoiesis, adrenal hypoplasia	
(FRATES and FEINBERG 2000)	37 (44)	TOP 14+5 wks	- Placenta: Large, multiple cysts, thin membrane separating individual amnions - Presenting twin: Severe hydrops, excessive skin thickening, ascites, holoprosencephaly, endocardial cushion defect - Non-presenting twin: similar but less severe	- Twin 3n gestation
(MCFADDEN *et al.* 2000)	38 (45)	d. < 1 hr	- Placenta: Large, 3 vessel cord, normal villous architecture, no signs of PHM - Child: Born at 32 wks, IUGR - Autopsy: Protuberant eyes, flattened nasal bridge, small alae nasi, occipital encephalocele, lumbar meningomyelocele, microcephaly, abnormal gyri, low set ears, mild nuchal webbing, 2-3 syndactyly of hands & feet, left talipes equinovarus, omphalocele, perimembranous VSD, multivalvular dysplasia, hypoplastic aortic isthmus, right renal agenesis, small phallus, very small labioscrotal folds, perineal urethral opening, internal genitalia consisting of mullerian derivatives and uterus-like structure, dysgenetic gonads consisting of immature testicular tissue	
(CHANG *et al.* 2001)	39 (46)	LB 33 wks d < 1 min	- Placenta: small, non-cystic - Fetus: IUGR, BW 1100 g, oligohydramnios, cleft lip, relative macrocephaly, each lung missing lobe	
(BAN *et al.* 2002)	40 (47)	SB 31 wks	- Placenta: N/A - Child: BW 1200 g, oligohydramnios, hypoplastic LV, asymmetric IUGR, pulmonary hypoplasia, renal hypoplasia, adrenal hypoplasia, limb abnormalities	
(STEFOS *et al.* 2002)	41 (48)	TOP 18 wks	- Placenta: PHM - Fetus: Hydrocephaly, severe IUGR	- Maternal HELLP syndrome

Author	Case #	Age	Phenotype	Notes
(GASSNER *et al.* 2003)	42 (49)	SF 20+3 wks	- Placenta: Abnormally small - Fetus: Asymmetric IUGR, relative macrocephaly, cleft lip/palate/ CHD	-Selective feticide, normal 46,XY DC co-twin
(LIM *et al.* 2003)	43 (50)	? - Early SA	- POC: Initially described as blighted ovum but later reclassified as 3n PHM	
(BIANCA *et al.* 2004)	44 (51)	TOP 22 wks	- Placenta: Smaller than normal - Fetus: Symmetrical IUGR, diaphragmatic hernia, peculiar facies, cutaneous 2-3 toe syndactyly, pulmonary hypoplasia, herniation of stomach and large portion of intestines into thorax	
(BILLIEUX *et al.* 2004)	45 (52)	TOP 18 wks	- Placenta: Large (480 g), features consistent with PHM - Fetus: 159 g, abnormalities of limbs, CNS, heart, and kidneys	- Maternal peripartum cardiomyopathy
(DALMIA *et al.* 2005)	46 (53)	TOP 16 wks	- Placenta: large, cystic - Fetus: Echogenic bowel and kidneys, dilated renal pelvis, open sacral spina bifida, micrognathia, low set ears, talipes, 3-4 syndactyly of left foot, ambiguous external genitalia, intestinal malrotation, cystic kidneys, adrenal/thymus hypoplasia, small spleen/liver	- Conceived through ICSI
(ILIOPOULOS *et al.* 2005)	47 (54)	b 39 wks d 164 d/o	- Placenta: N/A - Child: BW 1850 g, IUGR, relative macrocephaly, oligohydramnios, asymmetric skull, small palpebral fissures, small fontanelles, low-set ears, flat nasal bridge, small tongue, right hand hexadactyly, overlapping 3rd and 4th fingers, single transverse palmar crease, overlapping 2nd and 3rd toes, tonic-clonic convulsions, partial aplasia of occipital lobe, partial aplasia of corpus callosum, hypotonia, respiratory problems	
(KOS *et al.* 2005)	48 (55)	TOP 26 wks	- Placenta: 70% approximately normal, 30% consisted of large and edematous villi - Fetus: Spina bifida, microcephaly, left JGCT of testis, female external genitalia, agenesis of corpus callosum, pulmonary hypoplasia, stenosis of pulmonary ostium, right Sertoli cell adenoma, hypoplastic uterus	- JCGT = juvenile granulosa cell tumor of testis
(BARSOOM *et al.* 2006)	49 (56)	TOP 20 wks	- Placenta: Subchorionic hemorrhage, some hydropic change - Fetus: 229 g, grossly normal, some webbing of fingers & toes	- Possible undetected mixoploid?
(MENDILCIOGLU *et al.* 2006)	50 (57)	SF 19 wks	- Placenta: Smaller than normal - Fetus : IUGR, hydrocephaly - Selective feticide precluded further examination following delivery of co-twin at 38 wks	- Healthy co-twin delivered @ 38 wks
(CHEN *et al.* 2008)	51a (58)	TOP 16 wks	- Placenta: Small, non-cystic - Fetus: IUGR, anhydramnios, alobar holoprosencephaly, relative macrocephaly, cyclopia, thin small trunk	Initially reported separately, (CHEN *et al.* 2002)
	51b (59)	TOP 15 wks	- Placenta: N/A - Fetus: Alobar holoprosencephaly, asymmetric IUGR, midfacial cleft	

Author	Case #	Age	Phenotype	Notes
	51c (60)	TOP 13 wks	- Placenta: Single umbilical artery - Fetus: Alobar holoprosencephaly, proboscis, oligohydramnios, asymmetric IUGR, relative macrocephaly	
	51d (61)	TOP 14 wks	- Placenta: N/A - Fetus: Alobar holoprosencephaly, oligohydramnios, asymmetric IUGR, absence of urinary bladder, relative macrocephaly	
	51e (62)	TOP 13 wks	- Placenta: N/A - Fetus: Alobar holoprosencephaly, oligohydramnios, asymmetric IUGR	
(MEDEIROS *et al.* 2008)	52 (63)	TOP 22 wks	- Placenta: Grossly normal, weight 295 g (> 95th percentile for gestational age), features typical of PHM, admixture of normal and markedly enlarged villi with mild trophoblastic hyperplasia, microscopic foci of severely atypical trophoblastic cells consistent with intraplecental choriocarcinoma - Fetus: Spina bifida	
(TAKABACHI *et al.* 2008)	53 (64)	d 221 d/o	- Placenta: Very small, 71 g, no cystic villi, short cord - Child: BW 556 g, severe IUGR, relative macrocephaly, marked hypotonia, frontal bossing, apparent hypertelorism, blepharophimosis, microstomia, micrognathia, low-set ears, bell-shaped thorax, syn/clino/camptodactyly, malposition of fingers, thoracic hypoplasia, decreased lung permeability, skeletal anomalies, PDA, ASD, VSD, pulmonary hypertension, hyperbillirubinemia, postnatal growth deficiency, significant psychomotor delay	
(BEKDACHE *et al.* 2009)	54 (65)	SB 33 wks	- Placenta: Large, Multicystic, 895 g at delivery (> 95th percentile), chorionic cysts, scalloping, villous and extravillous trophoblastic inclusions, no features of molar change - Fetus: Alobar holoprosencephaly, proboscis, severe hypotelorism, severe hydrocephalus, BW 1185 g	– Described as female but no further info, post mortem declined
(FALKERT *et al.* 2009)	55 (66)	TOP 16+2 wks	- Placenta: Thickened with multiple cysts, pathology consistent with PHM - Fetus: Symmetric IUGR, small omphalocele	- Maternal HELLP syndrome
(SOLOMON *et al.* 2009)	56 (67)	SA 8 wks	- Placenta: N/A - Embryo: Probable alobar holoprosencephaly, severe hypotelorism, proboscis, no evidence of nasal pits or mouth, webbed but distinct fingers, no toe rays, measurements consistent with 30-34 days gestational age, level of maceration precluded further examination	

APPENDIX C

PHENOTYPE DATA FOR ALL CASES OF COMPLETE TRIPLOIDY AND 2N/3N MIXOPLOIDY

Tables 14-16 provide a breakdown of the different congenital anomalies seen in cases of diploid/triploid mixoploidy and complete triploidy respectively. The different congenital abnormalities are largely grouped by organ system or region. The list of abnormalities listed is by no means exhaustive, but rather includes those that are somewhat to very common either in triploidy as a whole or in a particular subgroups of triploids. Table 14 lists the phenotypic characteristics of diploid/triploid mixoploidy according to parental origin, genotype, and total. In this case, genotype only refers to the sex chromosome constitution of the diploid and triploid lines and any cases in which additional aneuploidies were present were included under the group corresponding to their sex chromosome constitution. The cases of 45,X/69,XXX were included under XX/XXX sex chromosome constitution. Similarly, the cases of 68,XX triploidy were included in the column for 69,XXX in Table 15 which provides the breakdown of phenotypic characteristics for complete triploidy. Table 16 provides a side-by-side comparison of these traits between diploid/triploid mixoploidy and complete triploidy without regard to parent-of-origin or genotype.

Table 14. Phenotypic traits of 2n/3n mixoploid cases according to parent-of-origin and genotype

	Digynic			Diandric				Unknown Origin					
	46,XX/69,XXX	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Unknown	Total	**Total**
Class Totals	9	10	**19**	4	2	3	**9**	15	5	8	6	**34**	62
Prenatal													
Polyhydramnios	1	0	**1**	0	0	0	**0**	0	0	0	0	**0**	**1**
Oligohydramnios	1	1	**2**	1	0	0	**1**	0	1	1	0	**2**	**5**
IUGR	1	5	**6**	0	1	1	**2**	5	1	5	2	**13**	**21**
Premature birth (< 37 weeks)	1	1	**2**	0	0	0	**0**	3	0	2	1	**6**	**8**
Craniofacial													
Cranium - Asymmetric/Dysplastic	0	3	**3**	0	0	0	**0**	3	0	2	0	**5**	**8**
Ears - Low set/Dysplastic	4	4	**8**	0	0	0	**0**	3	0	4	2	**9**	**17**
Epicanthal folds ?	1	1	**2**	0	0	0	**0**	0	0	0	0	**0**	**2**
Facies - Peculiar/Other	0	2	**2**	0	0	1	**1**	5	0	1	0	**6**	**9**
Fontanelles - Abnormal size	1	0	**1**	0	0	0	**0**	0	0	1	0	**1**	**2**
Forehead - Bossed/Prominent	3	3	**6**	0	0	0	**0**	3	0	3	1	**7**	**13**
Hypertelorism/Telecanthus	3	1	**4**	0	1	0	**1**	3	0	1	1	**5**	**10**
Hypotelorism	0	0	**0**	0	0	0	**0**	1	0	0	0	**1**	**1**
Macrocephaly	1	1	**2**	0	0	0	**0**	0	0	1	0	**1**	**3**
Macroglossia	1	1	**2**	0	1	0	**1**	0	1	0	0	**1**	**4**
Microcephaly	0	0	**0**	0	0	0	**0**	2	1	1	0	**4**	**4**
Micro(retro)gnathia	4	6	**10**	0	1	0	**1**	3	1	3	1	**8**	**19**
Microstomia	0	4	**4**	0	0	0	**0**	2	0	2	0	**4**	**8**
Nose - Unusual shape	4	3	**7**	0	0	1	**1**	6	0	4	0	**10**	**18**
Ocular anomalies	0	2	**2**	0	1	0	**0**	5	0	2	1	**8**	**10**
Palate/Lip - Cleft	0	3	**3**	0	0	0	**0**	0	0	1	1	**2**	**5**
Palate - High Arched	0	1	**1**	0	0	0	**0**	1	0	1	0	**2**	**3**
Palpebral Fissures - Abnormal	1	1	**2**	0	0	0	**0**	4	0	1	1	**6**	**8**
Upper Limbs													
Thin/Hypoplastic	1	3	**4**	0	0	0	**0**	2	0	1	0	**3**	**7**
Fingers - Arachnodactyly	1	0	**1**	0	0	0	**0**	1	0	1	0	**2**	**3**
Fingers - Clino/Camptodactyly	2	2	**4**	0	0	1	**1**	7	1	2	0	**10**	**15**
Fingers - Syndactyly	6	7	**13**	0	2	1	**3**	6	0	4	1	**11**	**27**
Hands/Digits - Aberrant placement	0	1	**1**	0	1	0	**0**	0	0	1	0	**1**	**2**
Joint Deformities	1	3	**4**	0	0	0	**0**	0	0	4	0	**4**	**8**
Palmar crease - Single transverse	4	1	**5**	0	1	1	**2**	2	1	3	2	**9**	**16**
Lower Limbs													
Thin/Hypoplastic	1	4	**5**	0	0	0	**0**	2	0	1	0	**3**	**8**
Feet - Rocker bottom/Talipes	4	1	**5**	0	1	0	**1**	3	0	3	0	**6**	**12**
Joint Deformities	0	2	**2**	0	0	0	**0**	0	0	4	0	**4**	**6**
Toes - Sandal Gap	0	0	**0**	0	0	0	**0**	3	0	1	1	**5**	**5**
Toes - Syndactyly	3	8	**11**	0	0	1	**1**	6	1	3	0	**10**	**22**
Trunk/Other General Malformations													
Abdominal wall defects	0	0	**0**	0	0	0	**0**	0	0	0	1	**1**	**1**

	Digynic			Diandric				Unknown Origin					
	46,XX/69,XXX	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Unknown	Total	**Total**
Asymmetry - Body	1	2	**3**	0	0	0	**0**	7	0	1	0	**8**	**11**
Asymmetry - Face	2	1	**3**	0	0	1	**1**	7	0	0	0	**7**	**11**
Asymmetry - Limbs	2	0	**2**	0	0	0	**0**	2	1	2	0	**5**	**7**
Dermatoglyphics - Abnormal		0	**0**	0	0	0	**0**	1	0	1	0	**2**	**2**
Hematopoietic abnormalities	1	0	**1**	0	0	0	**0**	1	1	0	0	**2**	**3**
Hypotonia/Dyskinesia	2	4	**6**	0	1	1	**2**	6	0	3	0	**9**	**17**
Kyphosis/Lordosis/Scoliosis	2	1	**3**	0	0	0	**0**	5	0	3	1	**9**	**12**
Nipples - Abnormal/Supernumerary	1	2	**3**	0	0	0	**0**	0	0	1	0	**1**	**4**
Pigmentary anomalies	3	2	**5**	0	1	0	**1**	7	2	1	0	**10**	**16**
Truncal obesity	3	2	**5**	0	1	0	**1**	4	0	1	1	**6**	**12**
Developmental/Neurological Abnormalities													
Feeding difficulty/Dysphagia	1	3	**4**	0	0	0	**0**	2	0	0	0	**2**	**6**
Hearing Loss	2	0	**2**	0	0	0	**0**	1	0	0	0	**1**	**3**
Mental/Psychomotor Retardation	6	6	**12**	0	1	1	**2**	10	1	3	1	**15**	**29**
Neonatal Areflexia/Dysreflexia	0	0	**0**	0	0	1	**1**	3	0	0	0	**3**	**4**
Neonatal Respiratory Distress	0	1	**1**	0	0	0	**0**	1	0	4	0	**5**	**6**
Postnatal growth deficiency	1	4	**5**	0	0	1	**1**	1	1	0	0	**2**	**8**
Seizures/Abnormal EEG	3	3	**6**	0	0	0	**0**	5	0	2	0	**7**	**13**
Central Nervous System Abnormalities													
Cerebellum - Abnormalities	0	0	**0**	0	0	0	**0**	0	0	2	0	**2**	**2**
Cerebrum - General/Gyral Anomalies	1	2	**3**	0	0	0	**0**	0	0	0	0	**0**	**3**
Corpus Callosum - Agenesis	0	0	**0**	0	0	0	**0**	2	0	0	0	**2**	**2**
Holoprosen/telencephaly	0	1	**1**	0	0	0	**0**	0	0	0	0	**0**	**1**
Hydrocephaly/Ventriculomegaly	2	1	**3**	1	0	0	**1**	1	0	2	0	**3**	**7**
Myelomeningocele/Spina bifida	0	0	**0**	0	0	0	**0**	0	0	1	0	**1**	**1**
Cardiovascular & Pulmonary Abnormalities													
Atrial/Ventricular septal defect	1	1	**2**	1	1	0	**2**	3	0	1	0	**4**	**8**
PDA/PFO	0	0	**0**	0	1	0	**1**	3	0	0	0	**3**	**4**
Complex heart disease	0	0	**0**	1	0	0	**1**	2	0	0	0	**2**	**3**
Valvular defects	0	0	**0**	0	0	0	**0**	1	0	1	0	**2**	**2**
Lungs - Abnormal lobation	0	0	**0**	0	0	0	**0**	1	0	0	0	**1**	**1**
Lungs - Hypoplastic/Atelectatic	0	0	**0**	0	1	0	**1**	0	0	1	0	**1**	**2**
Gastrointestinal Abnormalities													
Esophagus - Atresia/TE fistula	0	0	**0**	0	0	0	**0**	0	0	0	0	**0**	**0**
Gallbladder - A/Dysgenesis	0	0	**0**	0	0	0	**0**	1	0	0	0	**1**	**1**
Hepatomegaly	0	0	**0**	0	0	0	**0**	0	0	0	1	**1**	**1**
Intestinal Malrotation	1	0	**1**	0	0	0	**0**	1	0	0	0	**1**	**2**
Splenomegaly	0	0	**0**	0	0	0	**0**	0	0	0	0	**0**	**0**
Genito-Urinary Abnormalities													
Cryptorchidism	0	1	**1**	0	0	0	**0**	0	2	3	0	**5**	**6**
Genitalia - Ambiguous	0	0	**0**	0	1	0	**1**	0	2	2	1	**5**	**6**
Genitalia - Hypoplastic/Small	1	4	**5**	0	1	0	**1**	0	2	3	1	**6**	**12**
Genitalia - Normal female - XX/XXY	0	0	**0**	0	1	0	**1**	0	1	0	0	**1**	**2**

	Digynic			Diandric				Unknown Origin					Total
	46,XX/69,XXX	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Total	46,XX/69,XXX	46,XX/69,XXY	46,XY/69,XXY	Unknown	Total	
Leydig Cell Hyperplasia	0	0	**0**	0	0	0	**0**	0	0	1	0	**1**	**1**
Ovarian abnormalities	0	0	**0**	0	0	0	**0**	1	0	0	0	**1**	**1**
Ovotestes	0	0	**0**	0	0	0	**0**	0	2	1	0	**3**	**3**
Precocious puberty	2	0	**2**	0	0	0	**0**	2	0	0	0	**2**	**4**
Renal abnormalities	0	1	**1**	0	1	0	**1**	0	0	2	0	**2**	**4**
Endocrine/Metabolic Disorders													
Adrenal hypoplasia	1	1	**2**	0	0	0	**0**	1	0	2	1	**4**	**6**
Thymus - A/Dysgenesis	0	0	**0**	0	0	0	**0**	0	0	0	0	**0**	**0**
Thyroid - A/Dysgenesis	0	0	**0**	0	0	0	**0**	0	0	0	0	**0**	**0**
Hypobilirubinemia/Jaundice	0	0	**0**	0	0	0	**0**	0	0	0	0	**0**	**0**
Placental Abnormalities													
PHM with Abnormal Fetus	0	0	**0**	0	0	0	**0**	0	0	1	0	**1**	**1**
PHM with Normal Fetus	0	0	**0**	1	0	0	**1**	1	0	0	2	**3**	**4**
Other/Non-molar	0	1	**1**	0	0	0	**0**	0	0	0	0	**0**	**1**
Small/Hypoplastic	0	1	**1**	0	0	0	**0**	0	0	0	0	**0**	**1**
Apparent CPM	0	0	**0**	0	1	0	**1**	0	1	0	0	**0**	**1**

Table 15. Phenotypic traits of complete triploidy cases according to parent-of-origin and genotype

	Digynic			Diandric				Unknown			Total	
	69,XXX	69,XXY	Total	69,XXX	69,XXY	69,XYY	Total	69,XXX	69,XXY	Unknown	Total	
Class Totals	10	5	**15**	5	5	1	**11**	24	14	3	**41**	**67**
Prenatal												
Polyhydramnios	0	0	**0**	0	0	0	**0**	1	3	0	**4**	**4**
Oligohydramnios	5	2	**7**	0	0	0	**0**	3	0	0	**3**	**10**
IUGR	6	4	**10**	3	0	0	**3**	16	4	2	**22**	**35**
Premature birth (< 37 weeks)	3	0	**3**	2	0	0	**2**	7	5	0	**12**	**17**
Craniofacial												
Cranium - Asymmetric/Dysplastic	0	2	**2**	2	0	0	**2**	1	1	0	**2**	**6**
Ears - Low set/Dysplastic	3	1	**4**	3	1	0	**4**	12	9	0	**21**	**29**
Epicanthal folds ?	0	0	**0**	0	0	0	**0**	1	2	0	**3**	**3**
Facies - Peculiar/Other	0	2	**2**	1	0	0	**1**	5	4	0	**9**	**12**
Fontanelles - Abnormal size	0	1	**1**	0	0	0	**0**	1	3	1	**5**	**6**
Forehead - Bossed/Prominent	0	0	**0**	1	0	0	**1**	2	0	0	**2**	**3**
Hypertelorism/Telecanthus	1	1	**2**	1	0	0	**1**	6	1	0	**7**	**10**
Hypotelorism	0	0	**0**	0	0	0	**0**	1	0	0	**1**	**1**
Macrocephaly	6	2	**8**	0	0	0	**0**	6	2	8	**4**	**16**
Macroglossia	0	0	**0**	0	0	0	**0**	1	1	0	**2**	**2**
Microcephaly	0	1	**1**	1	0	0	**1**	1	2	0	**3**	**5**
Micro(retro)gnathia	3	1	**4**	2	1	0	**3**	8	2	0	**10**	**17**
Microstomia	1	0	**1**	2	0	1	**3**	3	3	0	**6**	**10**
Nose - Unusual shape	2	2	**4**	2	0	0	**2**	7	4	0	**11**	**17**
Ocular anomalies	2	0	**2**	0	0	0	**0**	3	6	0	**9**	**11**
Palate/Lip - Cleft	0	1	**1**	0	0	0	**0**	5	4	0	**9**	**10**
Palate - High Arched	0	0	**0**	0	0	0	**0**	1	1	0	**2**	**2**
Palpebral Fissures - Abnormal	2	0	**2**	0	0	0	**0**	3	3	0	**6**	**8**
Upper Limbs												
Thin/Hypoplastic	0	0	**0**	0	0	0	**0**	1	0	0	**1**	**1**
Fingers - Arachnodactyly	1	0	**1**	0	0	0	**0**	1	1	0	**2**	**3**
Fingers - Clino/Camptodactyly	0	1	**1**	1	0	0	**1**	1	2	0	**3**	**5**
Fingers - Syndactyly	3	2	**5**	1	0	1	**2**	11	5	0	**16**	**23**
Hands/Digits - Aberrant placement	1	1	**2**	1	0	0	**1**	6	0	0	**6**	**9**
Joint Deformities	0	0	**0**	1	0	0	**1**	2	1	0	**3**	**4**
Palmar crease - Single transverse	0	1	**1**	1	1	0	**2**	3	5	1	**9**	**12**
Lower Limbs												
Thin/Hypoplastic	0	0	**0**	0	0	0	**0**	1	0	0	**1**	**1**
Feet - Rocker bottom/Talipes	2	1	**3**	0	1	0	**1**	4	2	0	**6**	**10**
Joint Deformities	1	1	**2**	0	0	0	**0**	2	0	0	**2**	**4**
Toes - Sandal Gap	0	0	**0**	0	0	0	**0**	3	1	0	**4**	**4**
Toes - Syndactyly	1	1	**2**	1	1	1	**3**	9	6	0	**15**	**20**
Trunk/Other General Malformations												
Abdominal/ventral wall defects	0	0	**0**	0	0	0	**0**	4	7	0	**11**	**11**
Asymmetry - Body	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**

	Digynic			Diandric				Unknown			Total	
	69,XXX	69,XXY	Total	69,XXX	69,XXY	69,XYY	Total	69,XXX	69,XXY	Unknown	Total	
Asymmetry - Face	1	0	**1**	0	0	0	**0**	0	0	0	**0**	**1**
Asymmetry - Limbs	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Dermatoglyphics - Abnormal	0	0	**0**	0	0	0	**0**	1	0	0	**1**	**1**
Hematopoietic abnormalities	0	0	**0**	0	0	0	**0**	3	3	0	**6**	**6**
Hypotonia/Dyskinesia	2	1	**3**	1	0	0	**1**	3	3	0	**6**	**10**
Kyphosis/Lordosis/Scoliosis	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Nipples - Abnormal/Supernumerary	0	1	**1**	0	0	0	**0**	2	0	0	**2**	**3**
Pigmentary anomalies	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Truncal obesity	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Developmental/Neurological												
Feeding difficulty/Dysphagia	0	1	**1**	0	0	0	**0**	0	0	0	**0**	**1**
Hearing Loss	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Mental/Psychomotor Retardation	0	1	**1**	0	0	0	**0**	1	0	0	**1**	**2**
Neonatal Areflexia/Dysreflexia	1	0	**1**	1	0	0	**1**	1	3	0	**4**	**6**
Neonatal Respiratory Distress	2	1	**3**	2	0	0	**2**	5	2	0	**7**	**12**
Postnatal growth deficiency	0	0	**0**	0	0	0	**0**	1	0	0	**1**	**1**
Seizures/Abnormal EEG	0	1	**1**	0	0	0	**0**	1	0	0	**1**	**2**
Central Nervous System												
Cerebellum - Abnormalities	0	0	**0**	0	0	0	**0**	0	2	0	**2**	**2**
Cerebrum - General/Gyral Anomalies	1	0	**1**	2	0	0	**2**	3	5	0	**8**	**11**
Corpus Callosum - Agenesis	1	0	**1**	0	0	0	**0**	2	4	0	**6**	**7**
Holoprosen/telencephaly	3	2	**5**	0	0	1	**1**	1	3	2	**6**	**12**
Hydrocephaly/Ventriculomegaly	2	0	**2**	0	0	0	**0**	3	5	1	**9**	**11**
Myelomeningocele/Spina bifida	0	0	**0**	0	1	0	**1**	0	5	1	**6**	**7**
Cardiovascular/Pulmonary Anomalies												
Atrial/Ventricular septal defect	0	2	**2**	0	0	0	**0**	6	2	0	**8**	**10**
PDA/PFO	0	0	**0**	0	0	0	**0**	1	2	0	**3**	**3**
Complex heart disease	1	0	**1**	2	0	0	**2**	2	3	2	**7**	**10**
Valvular defects	0	0	**0**	0	0	0	**0**	1	1	0	**2**	**2**
Lungs - Abnormal lobation	1	0	**1**	1	0	0	**1**	4	0	0	**4**	**6**
Lungs - Hypoplastic/Atelectatic	3	0	**3**	1	0	0	**1**	7	5	0	**12**	**16**
Gastrointestinal Abnormalities												
Esophagus - Atresia/TE fistula	1	0	**1**	0	1	0	**1**	1	0	0	**1**	**3**
Gallbladder - A/Dysgenesis	1	0	**1**	2	0	1	**3**	4	3	0	**7**	**11**
Hepatomegaly	0	0	**0**	2	1	0	**3**	1	2	0	**3**	**6**
Intestinal Malrotation	0	0	**0**	0	1	0	**1**	0	0	0	**0**	**1**
Splenomegaly	0	0	**0**	0	0	0	**0**	2	0	0	**2**	**2**
Genito-Urinary Abnormalities												
Cryptorchidism	0	1	**1**	0	0	1	**1**	0	8	0	**8**	**10**
Genitalia - Ambiguous	0	0	**0**	0	1	0	**1**	0	9	0	**9**	**10**
Genitalia - Hypoplastic/Small	1	0	**1**	1	1	1	**3**	1	5	0	**6**	**10**
Leydig Cell Hyperplasia	0	0	**0**	0	0	0	**0**	0	4	0	**4**	**4**
Ovarian abnormalities	1	0	**1**	1	0	0	**1**	5	0	0	**5**	**7**
Ovotestes	0	0	**0**	0	0	0	**0**	0	1	0	**1**	**1**

	Digynic			Diandric				Unknown			Total	
	69,XXX	69,XXY	Total	69,XXX	69,XXY	69,XYY	Total	69,XXX	69,XXY	Unknown	Total	
Renal abnormalities	2	0	**2**	2	2	0	**4**	8	6	0	**14**	**20**
Endocrine/Metabolic Disorders												
Adrenal hypoplasia	2	0	**2**	2	2	1	**5**	7	6	0	**13**	**20**
Thymus - A/Dysgenesis	1	0	**1**	0	1	0	**1**	1	3	0	**4**	**6**
Thyroid - A/Dysgenesis	0	0	**0**	0	0	1	**1**	1	1	0	**2**	**3**
Hypobilirubinemia/Jaundice	0	0	**0**	2	0	0	**2**	2	1	3	**3**	**5**
Placental Abnormalities												
PHM with Abnormal Fetus	0	0	**0**	1	3	1	**5**	7	4	2	**13**	**18**
PHM with Normal Fetus	0	0	**0**	0	0	0	**0**	0	0	0	**0**	**0**
Other/Non-molar	0	0	**0**	0	1	0	**1**	2	5	0	**7**	**8**
Small/Hypoplastic	3	1	**4**	0	0	0	**0**	6	0	0	**6**	**10**

Table 16. Phenotype comparison between 2n/3n mixoploidy and complete triploidy

	2n/3n	3n
Totals	62	**67**
Prenatal		
Polyhydramnios	**1**	**4**
Oligohydramnios	**5**	**10**
IUGR	**21**	**35**
Premature birth (< 37 weeks)	**8**	**17**
Craniofacial		
Cranium - Asymmetric/Dysplastic	**8**	**6**
Ears - Low set/Dysplastic	**17**	**29**
Epicanthal folds ?	**2**	**3**
Facies - Peculiar/Other	**9**	**12**
Fontanelles - Abnormal size	**2**	**6**
Forehead - Bossed/Prominent	**13**	**3**
Hypertelorism/Telecanthus	**10**	**10**
Hypotelorism	**1**	**1**
Macrocephaly	**3**	**16**
Macroglossia	**4**	**2**
Microcephaly	**4**	**5**
Micro(retro)gnathia	**19**	**17**
Microstomia	**8**	**10**
Nose - Unusual shape	**18**	**17**
Ocular anomalies	**10**	**11**
Palate/Lip - Cleft	**5**	**10**
Palate - High Arched	**3**	**2**
Palpebral Fissures - Abnormal	**8**	**8**
Upper Limbs		
Thin/Hypoplastic	**7**	**1**
Fingers - Arachnodactyly	**3**	**3**
Fingers - Clino/Camptodactyly	**15**	**5**
Fingers - Syndactyly	**27**	**23**
Hands/Digits - Aberrant placement	**2**	**9**
Joint Deformities	**8**	**4**
Palmar crease - Single transverse	**16**	**12**
Lower Limbs		
Thin/Hypoplastic	**8**	**1**
Feet - Rocker bottom/Talipes	**12**	**10**
Joint Deformities	**6**	**4**
Toes - Sandal Gap	**5**	**4**
Toes - Syndactyly	**22**	**20**
Trunk/Other General Malformations		
Abdominal wall defects	**1**	**11**
Asymmetry - Body	**11**	**0**
Asymmetry - Face	**11**	**1**
Asymmetry - Limbs	**7**	**0**

	2n/3n	3n
Dermatoglyphics - Abnormal	**2**	**1**
Hematopoietic abnormalities	**3**	**6**
Hypotonia/Dyskinesia	**17**	**10**
Kyphosis/Lordosis/Scoliosis	**12**	**0**
Nipples - Abnormal/Supernumerary	**4**	**3**
Pigmentary anomalies	**16**	**0**
Truncal obesity	**12**	**0**
Developmental/Neurological		
Feeding difficulty/Dysphagia	**6**	**1**
Hearing Loss	**3**	**0**
Mental/Psychomotor Retardation	**29**	**2**
Neonatal Areflexia/Dysreflexia	**4**	**6**
Neonatal Respiratory Distress	**6**	**12**
Postnatal growth deficiency	**8**	**1**
Seizures/Abnormal EEG	**13**	**2**
Central Nervous System		
Cerebellum - Abnormalities	**2**	**2**
Cerebrum - General/Gyral Anomalies	**3**	**11**
Corpus Callosum - Agenesis	**2**	**7**
Holoprosen/telencephaly	**1**	**12**
Hydrocephaly/Ventriculomegaly	**7**	**11**
Myelomeningocele/Spina bifida	**1**	**7**
Cardiovascular & Pulmonary Abnormalities		
Atrial/Ventricular septal defect	**8**	**10**
PDA/PFO	**4**	**3**
Complex heart disease	**3**	**10**
Valvular defects	**2**	**2**
Lungs - Abnormal lobation	**1**	**6**
Lungs - Hypoplastic/Atelectatic	**2**	**16**
Gastrointestinal Abnormalities		
Esophagus - Atresia/TE fistula	**0**	**3**
Gallbladder - A/Dysgenesis	**1**	**11**
Hepatomegaly	**1**	**6**
Intestinal Malrotation	**2**	**1**
Splenomegaly	**0**	**2**
Genito-Urinary Abnormalities		
Cryptorchidism	**6**	**10**
Genitalia - Ambiguous	**6**	**10**
Genitalia - Hypoplastic/Small	**12**	**10**
Genitalia - Normal female - XX/XXY	**2**	
Leydig Cell Hyperplasia	**1**	**4**
Ovarian abnormalities	**1**	**7**
Ovotestes	**3**	**1**
Precocious puberty	**4**	
Renal abnormalities	**4**	**20**
Endocrine/Metabolic Disorders		

	2n/3n	3n
Adrenal hypoplasia	**6**	**20**
Thymus - A/Dysgenesis	**0**	**6**
Thyroid - A/Dysgenesis	**0**	**3**
Hypobilirubinemia/Jaundice	**0**	**5**
Placental Abnormalities		
PHM with Abnormal Fetus	**1**	**18**
PHM with Normal Fetus	**4**	**0**
Other/Non-molar	**1**	**8**
Small/Hypoplastic	**1**	**10**
Apparent CPM	**1**	0

APPENDIX D

DATA USED IN THE CONTSTRUCTION OF FIGURE 1

Table 17 shows the raw data used in the construction of Figure 1. For each study where the gestational ages of individual cases were listed, the gestational ages (given in weeks) are divided between diandric and digynic cases. The numbers in bold next to the words "diandric" and "digynic" represent the mean gestational ages of that group of cases in that particular study. The two earliest studies initially reported their data in menstrual age and this was converted to gestational age by subtracting two weeks. Additionally, most studies listed the gestational age in the format (weeks)+(days). For the purpose of constructing this figure, gestational ages listed as (weeks)+(4-6 days) were rounded up to the next whole week and those listed as (weeks)+(0-3 days) were rounded down to the whole week. Table 18 shows the total number of diandric and digynic triploids listed by gestational age in one week intervals from six weeks or less to 22 weeks or more. Because the distribution for individual weeks was uneven, and particularly due to a large discrepancy in the number of diandric versus digynic cases at 18 weeks gestation, it was necessary to use two week intervals to produce a neater graph. Additionally, since there were 34 more cases of diandric triploidy than digynic triploidy, the totals for digynic triploidy on each two week interval were multiplied by a factor of approximately 1.45 in order to adjust the population so it appeared the data included equal numbers of diandric and digynic triploids. These adjusted values are shown in Table 19. The numbers in table 19 represent the final form of the data used to construct Figure 1.

Table 17. Gestational ages of individual cases

Jacobs et al., 1982 - Gestational ages (Menstrual age - 2 weeks)							
Diandric		**15.54**		**Digynic**		**8.50**	
7	17	18	22	7	9	10	7
17	18	18	11	7	22	6	9
13	19	9	22	7	10	13	7
5	18	13	16	8	9	7	5
17	29	10	26	7	8	7	8
16	15	22	13	7	7		
16	14	11	12				
17	15	15	25				
10	15	17	12				
11	13	10	20				
20	18	17	14				
12	16	27	14				
18	9	13	16				
16	10	16	11				
15							
Proctor et al., 1994 - Gestational ages (Menstrual age - 2 weeks)							
Diandric		**11.17**		**Digynic**			
10	19	7	6				
13	12						
Miny et al., 1995							
Diandric		**16.20**		**Digynic**		**19.82**	
18	10	17	18	16	8	33	19
18				17	19	28	21
				19	16	22	
Baumer et al., 2000 - Gestational ages							
Diandric		**22.80**		**Digynic**		**20.50**	
28	37	22	19	19	29	34	17
8				25	21	17	17
				17	22	24	22
				14	19	18	17
				30	20	20	8
Zaragoza et al., 2000 - Gestational ages							
Diandric		**12.02**		**Digynic**		**9.89**	
14	10	6	18	6	7	12	11
13	18	18	5	10	15	8	13
12	8	12	12	10	10	5	8
14	13	10	13	11	11	12	12

6	13	9	7	8	10	9	7
7	12	12	12	9	5	7	13
11	10	13	16	19	7	12	
14	11	16	13				
16	10	11	10				
15	13	5	14				
15	14	13	15				
11	11	7	12				
13	10	15	13				
19	11	10	13				
13	12	13	9				
McFadden & Robinson, 2006 - Gestational ages							
Diandric		**13.38**		**Digynic**		**9.88**	
18	9	8	10	8	10	8	9
17	15	15	15	12	10	14	5
				10	6	17	10
				10	8	10	11

Table 18. Breakdown of diandric and digynic triploids by gestational age

	Diandric	Digynic
≤ 6 weeks	6	7
7 weeks	5	14
8 weeks	3	11
9 weeks	5	6
10 weeks	14	12
11 weeks	10	4
12 weeks	12	5
13 weeks	19	4
14 weeks	8	2
15 weeks	12	1
16 weeks	10	2
17 weeks	8	7
18 weeks	13	1
19 weeks	4	6
20 weeks	2	1
21 weeks	1	2
≥ 22 weeks	9	12
Totals	**141**	**97**

Table 19. Final form of the data used to construct Figure 1

Gestational age (weeks)	Diandric	Digynic	Digynic (Adjusted)*
≤ 7	11	21	30.52577
8-9	8	17	24.71134
10-11	24	16	23.25773
12-13	31	9	13.08247
14-15	20	3	4.360825
16-17	18	9	13.08247
18-19	17	7	10.17526
20-21	3	3	4.360825
≥ 22	9	12	17.4433
Totals	**141**	**97**	**141**
* Adjustment value for digynic triploids: 1.453608			

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