CHROMOSOMAL MOSAICISM AND UNIPARENTAL DISOMY IN PRENATAL DIAGNOSIS: CLINICAL IMPLICATIONS FOR GENETIC COUNSELING

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Prenatally detected chromosomal mosaicism complicates genetic counseling as there is variability in phenotypic outcome and available information pertaining to phenotypic consequences is limited. The objective of this study was to identify the phenotypic effects of mosaicism that was diagnosed prenatally. A total of 4,599 CVS specimens and 15,688 amniocentesis specimens were collected between 1991 and 2005 and clinical information was reviewed for all mosaic cases.

Of those procedures, 76 CVS specimens (1.65%) and 66 amniocentesis specimens (0.42%) indicated a mosaic result. However, seven of the mosaic amniocentesis results were observed after a previous mosaic CVS result. When these specimens were removed from the calculation, the incidence of mosaic amniocenteses was 0.38%. Of the cases that had follow-up cytogenetic testing, CVS cases were found to have a true mosaicism rate of 23.6% while amniocentesis cases had a rate of 60.7%. The rates of prenatally detected mosaicism and true fetal mosaicism for Magee-Womens Hospital are comparable to the rates reported in literature. This study found mosaic results involving trisomy for chromosomes 2, 7, 8, 9, 10, 12, 13, 15, 16, 18, 20, 21, 22, X, and Y. In addition, there was monosomy for chromosomes 21, 22, and X, tetraploidy, structural aberrations, and supernumerary marker chromosomes. However, no cases

of UPD were identified. From this information, associations were made between the phenotypic outcomes observed in this study and those reported from previous studies.

Based on the information provided from this study, it is apparent that phenotype can vary, even when the same abnormality is involved and that more information is needed regarding long term consequences of prenatally diagnosed mosaicism. The results of this study are important to public health because it provides additional data regarding the phenotypic results after prenatal diagnosis of mosaicism for various chromosome abnormalities and increases the understanding of the role of mosaicism in prenatal diagnosis, enabling more effective patient counseling.

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1.0 INTRODUCTION

The presence of two or more karotypically different cell lines in an individual arising from a single zygote is called chromosomal mosaicism. (Grati, 2006). Many of the chromosomal abnormalities involving complete trisomies are lethal and do not survive to term unless a correction occurs early in embryonic life. The correction from the presence of three copies of a chromosome to two copies of that chromosome may result in one chromosome from each parent (biparental origin) or both chromosomes from the same parent (uniparental origin). This latter situation is termed uniparental disomy (UPD). (Shaffer et al., 2001; Robinson, 2000). Cases of UPD have been identified following the observation of prenatal mosaicism in chorionic villus sampling (CVS) and amniotic fluid. The observation of an aneuploidy in the placenta at CVS and then a normal fetal karyotype in the amniotic fluid (termed confined placental mosaicism) is also recognized as a risk factor for UPD (Shaffer et al. 2001).

This study reviewed the experience at the Pittsburgh Cytogenetics Laboratory to supplement our current understanding of the role of chromosomal mosaicism and uniparental disomy (UPD) in prenatal diagnosis and counseling. The objective of this study was to identify the phenotypic effects of mosaicism that was diagnosed prenatally. The following specific aims guided this study: 1. To review cases of mosaicism and uniparental disomy (UPD) detected by chorionic villus sampling (CVS) and amniocentesis performed during the time period 1991-2005 to determine if rates of mosaicism and true fetal mosaicism correlate with literature; 2. To

evaluate follow-up information obtained through Magee-Womens Hospital including pregnancy outcome, pregnancy complications, abnormal characteristics, and additional testing; 3. To conduct further follow-up in order to obtain more information pertaining to long-term phenotypic effects; 4. To analyze the findings to attempt karyotype-phenotype correlations.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 CHROMOSOMAL MOSAICISM

Chromosomal mosaicism occurs when an individual, who has developed from a single fertilized egg, has two or more genetically distinct cell lines of differing karyotypes. Usually, there will be some cells with a normal karyotype and other cells containing a numerical or structural chromosome abnormality (Gardner and Sutherland, 2004; Robinson, 2001). It has been previously reported that mosaicism is detected in 1-2% of CVS procedures and true mosaicism is detected in about 0.1-0.3% of amniocentesis procedures (Grati et al., 2006; Hsu et al, 1996).

Three different levels can be used to describe mosaicism detected prenatally. Level I mosaicism involves the observation of a single abnormal cell. This is usually a cultural artifact and considered pseudomosaicism. Level II mosaicism is present when two or more cells with the same chromosome abnormality are seen in a culture from a single flask or in a single abnormal colony from an in situ culture. The abnormality is not seen in colonies from other independent cultures. Additional studies may be performed but these cases are almost always pseudomosaicism. Lastly, Level III mosaicism is defined as the presence of two or more cells with the same chromosome abnormality that are distributed over two or more independent

cultures. These cases are likely to represent true mosaicism, which is mosaicism that is present in placental and/or fetal tissues (Gardner and Sutherland 2004).

The most common form of mosaicism found at prenatal diagnosis involves a trisomy, which is an additional chromosome, but mosaicism can occur with all types of chromosomal abnormalities (monosomy, polyploidy, structural changes, etc.). Trisomy mosaicism can occur in two ways: 1.) an abnormal fertilized egg containing 47 chromosomes may lose the extra chromosome during cell division (meiotic nondisjunction error) or 2.) a typical zygote containing 46 chromosomes may retain a duplicated chromosome during cell division (mitotic nondisjunction error). The first scenario is often referred to as "trisomic rescue," and if it occurs early in post-zygotic cell divisions and involves the cells destined to become the embryo, the originally abnormal chromosome content may result in a normal karyotype (Robinson, 2001; Shaffer et al., 2001). These cases are examples of confined placental mosaicism (CPM) because only the placenta is affected by chromosomal mosaicism.

CPM is usually diagnosed when an aneuploidy is observed in the placenta at CVS and then a normal fetal karyotype is present in amniotic fluid. There are three types of CPM, which are categorized by the placental cell lineage exhibiting the abnormal cell line. Mosaicism can be confined to the cytotrophoblast (type I), the chorionic stroma or mesenchyme (type II), or both (type III) (Kalousek & Vekemans, 1996). CPM resulting from trisomic rescue generally involves high proportions of abnormal cells, especially if the correction occurs after the first cell division. The majority of cells that are present during early development produce the cytotrophoblast so as a result, the cytotrophoblast will contain a significant number of trisomic cells with variable involvement of extra-embryonic mesenchyme. Therefore, trisomic rescue is anticipated to show type I or III distribution. Conversely, mitotic errors generally exhibit lower

percentages of abnormal cells, usually having type I or II distribution (Wolstenholme, 1996). Although the occurrence of CPM implies that the fetus is chromosomally normal, the possibility remains for a residual effect due to 1.) undetected or cryptic mosaic trisomy of the fetus; 2.) UPD of the fetus; and 3.) placental dysfunction as a consequence of a regional placental trisomy.

2.2 CRYPTIC FETAL MOSAICISM

Daniel et al. (2004) suggested that cryptic fetal mosaicism may be suspected if, in the absence of confirmatory karyotypic evidence, dysmorphic features characteristic of an aneuploidy that are unexplained by other means, such as CPM or UPD, are present. It has been estimated from published data that about 10% of apparent CPM cases for rare trisomy (trisomy not involving chromosomes 13, 18, 20, or 21) may actually be cryptic fetal mosaics not detected in amniocytes. In many cases, the cryptic mosaicism may be of limited clinical significance, but others may have obvious phenotypic effects (Daniel et al., 2004).

2.3 UNIPARENTAL DISOMY

Uniparental disomy is the abnormal situation in which both chromosomes in a pair are inherited from one parent, and the other parent's chromosome for that pair is missing (Shaffer et al. 2001; Robinson, 2000). UPD can result from chromosome loss in trisomy, gamete complementation, duplication in monsomy, and somatic recombination. The presence of two copies of one parental

chromosome is called isodisomy while the presence of a pair of homologous chromosomes from one parent is heterodisomy. Cases of UPD have been identified following the observation of prenatal or postnatal mosaicism, identification of a structurally abnormal chromosome, molecular investigation of recessive genetic disease, and a phenotype suggestive of a particular syndrome associated with imprinting (Shaffer, 2001). CPM is also recognized as a risk factor for UPD because, theoretically, CPM resulting from trisomic rescue could result in uniparental inheritance in one-third of cases (Hall, 1990; Engel and Delozier-Blanchet, 1991).

The first proven case of UPD was reported by Spence et al. (1988) and involved a 16-year-old girl with short stature and cystic fibrosis, who had inherited two identical copies of a maternal chromosome 7. A significant number of early reports of UPD in humans were ascertained due to the presence of autosomal recessive disease and in some cases, the identification of UPD resulted in the localization of a rare recessive disease (Ledbetter and Engel, 1995). Other examples of conditions that have been inherited from a single carrier parent include osteogenesis imperfecta, spinal muscular atrophy, congenital chloride diarrhea, and Bloom syndrome (Hall, 1997). However, recessive disease through UPD can occur for any recessive allele. In addition, UPD for X-chromosomes can result in the transmission of X-linked recessive conditions, such as hemophilia, from a father to a son (Engel and DeLozier-Blanchet, 1991).

There are no apparent phenotypic effects from UPD for most chromosomes, but there are a few chromosomes that involve parent-specific imprinting and have clinically recognizable phenotypic effects when involved in UPD. Genomic imprinting refers to the genetic marking of genes before fertilization so that one parental allele, depending on sex, is transcriptionally silenced (Hall, 1990). Currently, maternally derived chromosomes 7, 14, and 15 and paternally

derived chromosomes 6, 11, 14, and 15 are the only examples of definite phenotypic effect due to UPD and imprinting. Chromosomes 2, 16, and 20 are also being studied but it is unclear if their phenotypic effects are due to imprinting (Shaffer et al., 2001; Engel, 2003).

Paternal UPD for chromosome 6 and paternal duplications of 6q are associated with transient neonatal diabetes mellitus, which is a rare form of diabetes that usually resolves by 6 months of life. It is thought that about 20% of cases are due to UPD (Shaffer et al., 2001; Gardner et al., 1998). Russell-Silver syndrome is associated with prenatal and postnatal growth retardation with relative sparing of the head, triangular facies, and other dysmorphic features, limb and facial asymmetry, and clinodactyly. About 10% of cases are due to maternal UPD7 (Shaffer et al., 2001; Kotzot et al., 2000).

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome that is characterized by macroglossia, organomegaly, omphalocele, hemihypertrophy, genitourinary abnormalities, and a predisposition to embryonic tumors, including Wilms tumor. About 85% of cases are sporadic, but familial cases have been reported with or without associated chromosome rearrangements. Partial paternal UPD for the distal short arm of chromosome 11 occurs in approximately 20-25% of BWS. In addition, studies have indicated that UPD occurs as a somatic event rather than a meiotic nondisjunction event (Shaffer et al., 2001; Catchpoole et al., 1997).

Specific features characterize Maternal and paternal UPD for chromosome 14. Individuals with maternal disomy 14 have short stature, hypotonia, hyperextensible joints, scoliosis, minor facial dysmorphic features, mild developmental delay, and precocious puberty. However, individuals with paternal disomy 14 have a more severe phenotype than those with maternal disomy 14. Features include mental retardation, skeletal abnormalities that result in

short-limb dwarfism with narrow thorax, decreased survival due to respiratory difficulties, dysmorphic facies, and scoliosis. Both conditions have been associated with Robertsonian translocations and isochromosomes and maternal disomy 14 has also been associated with mosaicism (Shaffer et al., 2001; Sutton and Shaffer, 2000).

The best-studied examples of human genetic diseases due to imprinting are Prader-Willi syndrome (PWS) and Angelman syndrome (AS). Prader-Willi syndrome results from an abnormal methylation pattern of 15q11-q13 due to paternal deletion, maternal UPD for chromosome 15, or imprinting center mutation. About 25% of cases are due to maternal UPD and the majority of these cases represent heterodisomy as a result of maternal meiosis I nondisjunction. PWS is characterized by low birth weight, early feeding problems, and hypotonia followed by severe obesity associated with hyperphagia. Other features include developmental delay and/or mental retardation, short stature, behavior problems, and hypogonadism in males. Angelman syndrome also involves abnormal methylation of 15q11-15q13 but it can be caused by maternal deletion, paternal UPD, *UBE3A* gene mutation, or imprinting center defect. About 3-5% of cases are due to paternal UPD and the majority of these cases show complete isodisomy, suggesting a monosomy 15 conception followed by duplication of a single paternal chromosome or by long arm isochromosome formation. AS is characterized by severe mental retardation with absent speech, ataxic movements and gait, increased tone after infancy, seizures, and a happy disposition with paroxysmal laughter (Shaffer et al, 2001; EUCROMIC, 1999; L'Hermine et al., 2003).

2.4 PLACENTAL DYSFUNCTION

It has been estimated that approximately 16-22% of pregnancies with CPM exhibit prenatal or perinatal complications. These complications can include intrauterine growth retardation (IUGR), fetal loss, or poor perinatal outcome. The effects of CPM on development may vary with the timing of the mosaicism, the type of chromosome abnormality, the proportion of abnormal cell line to normal cell line, and the tissues affected (Kalousek and Vekemans, 1996). Studies indicate that an adverse outcome is more likely when there are high levels of trisomy in term placenta (Wolstenholme et al., 1994). Trisomy 16 is the most common trisomy observed in CPM. There have been reports of malformation in cases of maternal disomy 16, which raised the possibility of imprinting, but studies have thus far neither conclusively supported nor excluded imprinting effects. Studies have noted that the degree of trisomy 16 in the placenta seemed to correlate with IUGR of a chromosomally normal fetus independent of UPD status (Yong et al., 2002). Other chromosomes that have been implicated with pregnancy complications, such as prenatal and postnatal growth restriction, include 2, 7, and 22 (Wolstenholme, 1994).

2.5 PREVIOUS STUDIES

Cases of UPD are relatively rare; therefore, only a few cases have been identified. Many studies involve only a small number of cases and have limited follow-up (Kotzot 2002). The study that Thomas (1998) conducted analyzed pregnancy outcomes from CVS and amniocentesis procedures performed at Magee-Womens Hospital from 1991-1997 to determine the incidence of prenatally detected mosaicism and appropriate methods of pregnancy management. Thomas recommended that further research in mosaicism and UPD be pursued and that long-term follow-

up information on children with UPD was needed. This study reviewed all the cases of prenatally diagnosed mosaicism during 1991-2005 in order to improve our understanding of the mosaicism and UPD and to more effectively counsel patients.

3.0 METHDOLOGY

3.1 STUDY DESIGN

This was a retrospective study that included the analysis of patients who had previous prenatal diagnosis. The study included women who had a CVS or amniocentesis procedure performed at Magee-Womens Hospital between the years 1991 to 2005 with an outcome involving chromosomal mosaicism and/or UPD. All patients who had a cytogenetic report that listed the result of the CVS or amniocentesis as a mosaic were included. Clinical information was reviewed for all cases, but only pregnancies that resulted in a live birth were considered for further follow-up.

Reviewing outcomes from all CVS and amniocentesis procedures performed from 1991-2005 identified cases of mosaicism from CVS and amniocentesis results. Thomas (1998) had previously collected information pertaining to cases from 1991-1997. Therefore, information pertaining to cases from 1998-2005 were obtained. These outcomes, along with cytogenetic reports, were obtained from the Magee-Womens Hospital Genetics Information System (GIS). Medical records for these patients, obtained from patient files and the Magee-Womens Hospital Genetics Department's registry of follow-up performed on all prenatal specimens, were then reviewed in order to gain more information about the pregnancy following prenatal diagnosis,

including delivery and follow-up clinic visits. This information was collected for analysis and to determine who should be contacted for further follow-up.

IRB approval was required in order to contact patients for further follow-up. This process was quite time-consuming and approval was not obtained until the end of January of 2006. In addition, only a genetic counselor or physician who previously met with the patient could contact them and informed consent needed to be obtained before they could be interviewed. Due to time limitations, patients had not been contacted as of March 25, 2006. However, modifications are being submitted in order to allow this study to continue under the direction of Urvashi Surti, Ph.D.

Potential participants for follow-up were identified, and a genetic counselor or clinical geneticist with whom they had previously met will contact them to ask if they would participate in the study. They will explain why the potential participants are being contacted and the purpose of the study. If they do not wish to participate in the study, they were not contacted again. If they do wish to participate, they will be interviewed by phone. The questions asked during the interview will pertain to complications that occurred during pregnancy and/or childbirth and the postnatal clinical information about the participant's child. People who agreed to participate will also be asked if the study investigators could view their child's medical records as well as their records pertaining to the childbirth. Two consent forms and a self-addressed stamped envelope will be sent for the participant to review and sign. Medical record review for this study will not take place until the signed consent forms are obtained.

The data collected in this study was analyzed and correlations were made between specific chromosome abnormalities and their corresponding phenotypes. Broader conclusions about karyotype-phenotype correlations were also made, along with recommendations for

counseling. Information obtained after further follow-up will be added to current data and correlations will be adjusted accordingly.

3.2 CHORIONIC VILLUS SAMPLING (CVS)

Chorionic villus sampling procedures were performed either transcervically or transabdominally. Samples collected by catheter (transcervical) and by needle (transabdominal) were immediately placed in sterile media for transport to the laboratory. In order to minimize the possibility of maternal cell contamination, the villi were then cleaned by removing maternal decidua and blood clots with the guidance of a stereodissecting microscope. The samples were then dissociated. First, they were placed in 15 ml conical centrifuge tubes and then they were incubated at 37°C for 30 minutes in 5 ml of a 0.25% trypsin solution. Next, they were incubated for 30-45 minutes at 37°C in 4 ml of a collagenase solution. Two types of media were then added and then the cells were spread onto glass coverslips. Specimens were then incubated at 37°C with 5% CO2 levels and 5% O2 levels. The cells were then harvested when sufficient growth was achieved. This was either done by hand or by using TECAN or Genial, which are automated harvesting systems. The coverslips were then attached to glass slides, placed on a slide warmer at 60°C for approximately one hour, and then incubated overnight in a 60°C oven. Lastly, the specimens were prepared for analysis by Giemsa banding.

3.3 AMNIOCENTESIS

Amniotic fluid samples were collected by standard methods and transported to the laboratory. They were then spun in 15 ml conical centrifuge tubes at 1000 rpms for 10 minutes. Two types of media were then added to the pelleted cells and the cells were spread on glass coverslips. Specimens were then incubated at 37°C with 5% CO2 levels and 5% O2 levels. The cells were then harvested when sufficient growth was achieved. This was either done by hand or by using TECAN or Genial. The coverslips were then attached to glass slides, placed on a slide warmer at 60°C for approximately one hour, and then incubated overnight in a 60°C oven. Lastly, the specimens were prepared for analysis by Giemsa banding.

4.0 RESULTS

4.1 TOTAL MOSAIC CASES

A total of 4,599 CVS procedures were performed between 1991 and 2005. Of those procedures, 76 (1.65%) indicated a mosaic result. This incidence is comparable to other reported figures and is broken down by year in Table 1.

Table 1. Percentage of Mosaic CVS Results Per Year

Year	# of Mosaics	Total # of CVS Specimens	Percentage
1991	2	67	2.99%
1992	0	69	0.00%
1993	2	197	1.02%
1994	7	263	2.66%
1995	14	317	4.42%
1996	8	352	2.27%
1997	6	355	1.69%
1998	11	431	2.55%
1999	5	389	1.29%
2000	2	371	0.54%
2001	4	324	1.23%
2002	3	365	0.82%
2003	4	375	1.07%
2004	7	410	1.71%
2005	1	314	0.32%
Total	76	4599	1.65%

There were 8 mosaic CVS specimens between 1993 and 1996 that showed a deleted 10q cell line. It was hypothesized that these cases were most likely tissue culture artifacts due to growth factors and other chemicals added to the media to promote faster growth. Therefore, these cases were excluded from the mosaic CVS data.

The individual cytogenetic results for the mosaic CVS cases are listed in Table 2, in addition to the reason for referral and outcome for each case.

Table 2. Cytogenetic Results for Mosaic CVS Cases

Case	Reason for Referral	CVS Results	Outcome
1	AMA	47,XY,+2[6]/46,XY[42]$^{+}$	LB
2	AMA	47,XY,+2[2]/46,XY[21]$^{+}$	LB
3	AMA	47,XX,+2[4]/46,XX[21]$^{+}$	LB
4	AMA	47,XX,+2[15]/46,XX[5]	LB
5	AMA	47,XX,+2[3]/46,XX[47]	LB
6	AMA	47,XY,+2[6]/46,XY[14]	LB
7	AMA	47,XX,+2[12]/46,XX[18]	LB
8	AMA	48,XX,+2,+7[12]/46,XX[38]	LB
9	AMA	47,XX,+7[16]/46,XX[4]	LB
10	AMA	48,XXX,+7[7]/46,XX[13]	LB
11	BTC	47,XX,+7[6]/46,XX[24]	LB
12	AMA	47,XY,+8[8]/46,XY[4]$^{+}$	LB
13	AMA	47,XY,+8[2]/46,XY[48]	LB
14	AMA, PP-T18	47,XY,+8[7]/46,XY[17]	LB
15	AMA	47,XY,+9[4]/46,XY[16]$^{+}$	LB
16	AMA	47,XY,+9[18]/46,XY[32]	TA
17	AMA	47,XY,+9[3]/46,XY[32]	LB
18	AMA, increased NT	47,XY,+10[18]/46,XY[4]$^{+}$	LB
19	AMA	47,XY,+10[5]/46,XY[45]	LB
20	AMA, PP-T18	47,XY,+10[13]/46,XY[37]	SA
21	AMA	47,XX,+12[26]/46,XX[14]$^{+}$	LB
22	AMA	47,XY,+13[7]/46,XY[43]	LB
23	AMA	47,XY,+15[32]/46,XY[21]$^{+}$	LB
24	AMA	47,XY,+15[4]/46,XY[26]	N/A
25	N/A	47,XY,+16^{+}	LB
26	AMA	47,XX,+16[19]/46,XX[2]$^{+}$	TA
27	AMA	48,XX,+16,+20[16]/46,XX[74]	LB
28	AMA	47,XX,+18[9]/46,XX[11]	LB
29	AMA	47,XX,+18[10]/46,XX[10]	LB
30	AMA, PP-47,XXY	46,X,+21[17]/47,XX,+21[33]$^{+}$	TA
31	N/A	47,XX,+22[9]/46,XX[41]$^{+}$	N/A
32	AMA	45,XX,-22[4]/46,XX[18]	LB
33	AMA	45,X/46,XX^{+}	LB
34	AMA	45,X[7]/46,XX[23]	LB
35	AMA	45,X[15]/46,XX[5]	LB
36	AMA	45,X[2]/46,XX[48]$^{+}$	SA
37	AMA	45,X[2]/46,XX[48]$^{+}$	LB
38	AMA	45,X[2]/46,XX[48]$^{+}$	LB
39	AMA	45,X[10]/46,XX[10]	TA

Table 2. (continued)

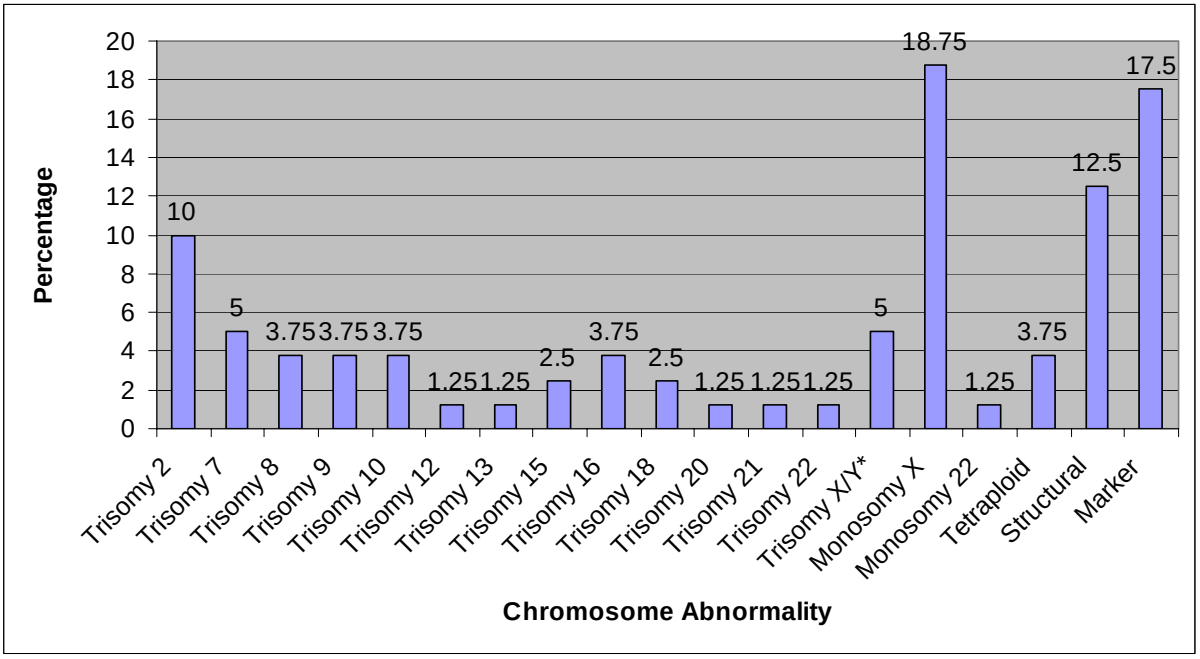
40	AMA	45,X[7]/46,XX[43]	SA
41	AMA	45,X[7]/46,XX[43]	LB
42	AMA	45,X[5]/46,XY[45]	LB
43	AMA	45,X[9]/46,XY[21]	LB
44	AMA	45,X[2]/46,XY[48]$^{+}$	LB
45	AMA	45,X[2]/46,XY[48]$^{+}$	LB
46	AMA	45,X[8]/46,XY[12]$^{+}$	LB
47	AMA	47,XXY[11]/46,XY[39]$^{+}$	LB
48	AMA	47,XXY[37]/46,XY[13]	LB
49	AMA, FHx DS	47,XXY[12]/46,XY[18]	LB
50	AMA	47,XX,+mar[3]/46,XX[47]$^{+}$	LB
51	AMA	47,XX,+mar[3]/46,XX[48]$^{+}$	LB
52	AMA	47,XX,+mar[4]/46,XX[46]$^{+}$	LB
53	AMA	47,XX,+mar[2]/46,XX[48]$^{+}$	LB
54	AMA	47,XX,+mar[4]/46,XX[25]$^{+}$	LB
55	AMA	47,XY,+mar[2]/46,XY[20]$^{+}$	LB
56	AMA	47,XX,+mar[2]/46,XX[18]$^{+}$	LB
57	AMA, increased NT	47,XX,+mar[3]/46,XX[18]$^{+}$	LB
58	AMA	47,XY,+mar[8]/46,X,+mar[2]/46,XY[20]$^{+}$ - marker identified as 17 in origin	LB
59	AMA	45,X[13]/46,X,+mar[6]/46,XY[4]$^{+}$ - marker identified as Y in origin	LB
60	AMA	47,XY,+mar(mat)[16]/46,XY[4]	N/A
61	AMA, PP-T16, T22 +mar	47,XY,+mar(mat)[15]/46,XY[5]	LB
62	AMA	46,XX/47,XX,+mar	TA
63	AMA	47,XY,+mar[8]/46,XY[12]	LB
64	AMA	92,XXXX[exact # not documented]/46,XX[20]$^{+}$	SA
65	AMA, BTC	92,XXXX[13]/46,XX[7]	LB
66	AMA	92,XXYY[41]/46,XY[11]	LB
67	AMA	46,XX,t(5;7)(p15.1;q34)[4]/46,XX[19]$^{+}$	LB
68	AMA	46,XX,der(5)t(5;?)(q35.1;?)[2]/46,XX[20]$^{+}$	LB
69	AMA	47,XX,+inv dup(8)(p23.1p12)[7]/46,XX[43]	LB
70	AMA, increased NT	46,XY,+9,der(13)t(9;13)(q10;q10)[3]/46,XY[18]	P
71	AMA	47,XX,+i(12p)[5]/46,XX[21]$^{+}$	LB
72	AMA	46,XX,del(13)(q22)[3]/46,XX[47]$^{+}$	LB
73	AMA, Abnormal u/s	46,XX,add(13)(p10).ish der(13)(wcp13+)[17]/ 46,XX,der(13;13)(q10;q10),+13[3]$^{+}$	TA
74	AMA	47,XX,r(15)[6]/46,XX[44]$^{+}$	LB
75	AMA	47,XY,+inv dup(15)(p10)[18]/46,XY	LB
76	AMA	45,X[2]/46,X,i(Xq)	TA

$^{+}$Previously reported in Thomas, 1998

AMA-Advanced Maternal Age, NT-nuchal translucency, u/s-ultrasound, BTC-balanced translocation carrier, FHx-family history, DS-Down syndrome, N/A-not available, LB-live birth, TA-therapeutic abortion, SA-spontaneous abortion, P-pregnant, PP-previous pregnancy, T22-Trisomy 22, T21-Trisomy 21, T18-Trisomy 18, T16-Trisomy 16

The majority of cases (96.1%) were referred because of advanced maternal age (35 years of age or older). Other reasons for referral included an abnormal ultrasound (5.3%), previous pregnancy with a chromosome abnormality (5.3%), and a family history of a chromosome abnormality or balanced translocation (3.9%). Some patients were referred for more than one reason, resulting in a total greater than 100%. The reason for referral was not available for two cases.

The frequency of each type of chromosome abnormality, including the chromosome involved with each trisomy and monosomy, is depicted in Figure 1.



*Includes 47,XXX and 47,XXY mosaics

Figure 1. Frequency of CVS Mosaics by Chromosome Abnormality

A total of 15,688 amniocentesis specimens were analyzed between 1991 and 2005. Of these, 66 (0.42%) indicated a mosaic result. However, 7 of these mosaic amniocentesis results were observed after a previous mosaic CVS result. When these specimens were removed from

the calculations, the incidence of mosaic amniocenteses became 0.38%. Both of these percentages are comparable to other studies and are broken down by year in Table 3.

Table 3. Percentage of Mosaic Amniocentesis Results Per Year

Year	# of Mosaics	Total # of Amnios	Percentage
1991	5	1012	0.49%
1992	3	1245	0.24%
1993	3	1318	0.23%
1994	2	1249	0.16%
1994 w/o CVS referrals*	1	1249	0.08%
1995	5	1433	0.35%
1995 w/o CVS referrals*	3	1433	0.21%
1996	9	1404	0.64%
1996 w/o CVS referrals*	7	1404	0.50%
1997	3	1286	0.23%
1997 w/o CVS referrals*	2	1286	0.16%
1998	4	1081	0.37%
1999	2	1009	0.20%
2000	7	1090	0.64%
2001	8	968	0.83%
2001 w/o CVS referrals*	7	968	0.72%
2002	8	779	1.03%
2003	3	703	0.43%
2004	2	599	0.33%
2005	2	512	0.39%
Total	66	15688	0.42%
Total w/o CVS referrals*	59	15688	0.38%

*Amnios performed due to a mosaic CVS were taken out of the mosaic amnio data

The individual cytogenetic results for each of the mosaic amniocentesis cases are listed in Table 4 and also includes the reason for referral and outcome for each case.

Table 4. Cytogenetic Results for Mosaic Amniocentesis Cases

Case	Reason for Referral	Amniocentesis Results	Outcome
77	AMA	47,XX,+2[8]/46,XX[42]$^{+}$	N/A
78	Abnormal u/s, Abnormal MMS-NTD	47,XX,+8[5]/46,XX[25]	LB
79	AMA, Abnormal MMS-T18, Abnormal u/s-Dandy Walker	47,XX,+9[9]/46,XX[13]	TA
80	N/A	47,XX,+12[2]/46,XX[48]$^{+}$	N/A
81	AMA	47,XX,+13[3]/46,XX[62]	LB
82	Abnormal CVS	47,XY,+15/46,XY*$^{+}$	LB
83	Abnormal CVS	47,XX,+16[19]/46,XX[7]*$^{+}$	TA
84	Abnormal u/s-choroid plexus cysts	47,XY,+18[46]/46,XY[4]$^{+}$	TA
85	Abnormal u/s-cystic hygroma	47,XX,+18[18]/46,XX[2]	N/A
86	AMA	47,XX,+20[5]/46,XX[45]$^{+}$	LB
87	AMA, Abnormal MMS-T21	47,XX,+20[6]/46,XX[11]$^{+}$	LB
88	Abnormal u/s-short limbs, duodenal atresia	47,XY,+20[7]/46,XX[41]$^{+}$	N/A
89	Abnormal MMS-T21	47,XX,+21[36]/46,XX[9]$^{+}$	LB
90	Abnormal MMS-T21	47,XX,+21[35]/46,XX[14]$^{+}$	TA
91	Abnormal MMS-T18	47,XX,+21[4]/46,XX[34]$^{+}$	LB
92	AMA, PPL	47,XX,+21[4]/46,XX[40]$^{+}$	LB
93	Abnormal MMS-T21	47,XX,+21[9]/46,XX[37]	TA
94	Abnormal u/s-increased NT	47,XY,+21[23]/46,XY[4]	LB
95	Abnormal MMS-T21	45,XY,-21[4]/46,XY[30]	N/A
96	N/A	45,X[9]/46,XX[36]$^{+}$	N/A
97	Abnormal u/s-cystic hygroma	45,X[48]/46,XX[2]$^{+}$	SA
98	AMA	45,X[15]/46,XX[35]$^{+}$	N/A
99	PC w/ CHIME	45,X[5]/46,XX[25]$^{+}$	N/A
100	AMA	45,X[7]/46,XX[8]$^{+}$	LB
101	AMA	45,X[5]/46,XX[10]	P
102	AMA	45,X[6]/46,XX[19]	P
103	AMA	45,X[3]/46,XX[17]$^{+}$	LB
104	Abnormal MMS-T21	45,X[33]/46,XX[17]$^{+}$	N/A
105	AMA	45,X[10]/46,XX[16]	LB
106	AMA	45,X[4]/46,XX[16]	LB
107	AMA	45,X[10]/46,XX[32]	LB
108	Abnormal MMS-T21	45,X[8]/46,XX[8]	LB
109	Abnormal FTS-T21	45,X[5]/46,XX[10]	TA
110	AMA	45,X[5]/46,XX[27]	LB
111	AMA	45,X[22]/46,XX[3]	N/A
112	Abnormal MMS-T18	45,X[39]/46,XX[7]	LB
113	AMA	45,X[10]/46,XX[5]	LB

Table 4. (continued)

114	Abnormal MMS-T21	45,X[5]/46,XY[25]	TA
115	AMA, Abnormal u/s-choroid plexus cysts	45,X[3]/46,XY[22]	LB
116	Abnormal MMS-T21	45,X[15]/46,XY[35]	LB
117	Abnormal MSAFP	45,X[2]/46,XY[18]$^{+}$	N/A
118	Abnormal MMS-T21	45,X[3]/46,XY[41]$^{+}$	LB
119	AMA	47,XXX[5]/45,X[3]/46,XX[22]	LB
120	AMA	47,XYY[13]/45,X[12]$^{+}$	LB
121	N/A	47,XXY/46,XY^{+}	LB
122	Abnormal CVS	47,XXY[5]/46,XY[40]*$^{+}$	LB
123	Abnormal CVS	47,XXY[2]/46,XY[48]*	LB
124	AMA	47,XXY[5]/46,XY[20]	LB
125	AMA	47,XXY[6]/46,XY[34]	N/A
126	AMA, Abnormal MMS-T21	47,XYY[8]/46,XY[8]	LB
127	AMA	47,XX,+mar[5]/46,XX[40].ish der(22)(D14Z1/D22Z1+,wcp22+)	N/A
128	Abnormal MMS-T21	47,XX,+mar[44]/46,XX[6] -identified as 6 in origin	LB
129	Abnormal u/s-cardiac anomalies	47,XX,+mar[6]/46,XX[9] -identified as 7 in origin	TA
130	AMA	47,XX,+mar[10]/46,XX[5].ish inv dup(13)(p10)	LB
131	AMA	47,XY,+mar[6]/46,XY[28].ish dup(21)(q11.2)	N/A
132	Abnormal MMS-T21	45,X[27]/47,X,inv(Y)(p11q12),+mar[5] /46,XY[13]$^{+}$	LB
133	Abnormal CVS	46,X,+mar[5]/46,XY[16].ish der(y)(wcp+)*$^{+}$	LB
134	AMA	46,XY,der(5)del(5)(p14.2)dup(5)(q14q22) t(5;14)(q13;q32)[9]/46,XY[31]	N/A
135	Abnormal CVS	47,XX,+i(12p)[1]/46,XX[62]*$^{+}$	LB
136	Abnormal u/s-diaphragmatic hernia	47,XY,+i(12)(p10)[10]/46,XY[5]	TA
137	AMA	46,XY,der(13)t(13;?)[5]/46,XY[44]$^{+}$	TA
138	Abnormal CVS	47,XY,+der(17)[6]/46,XY[68]*$^{+}$	LB
139	AMA	46,X,i(Xq)[6]/46,XX[90]$^{+}$	N/A
140	AMA	46,X,idic(Y)(q11.2)[9]/45,X[6]	LB
141	Abnormal MMS-T21	45,X[37]/46,X,psu idic (Y)(p11.32)[4]	LB
142	AMA, Abnormal u/s-increased NT	45,X[9]/46,X,i(Y)(p10)[6]	LB

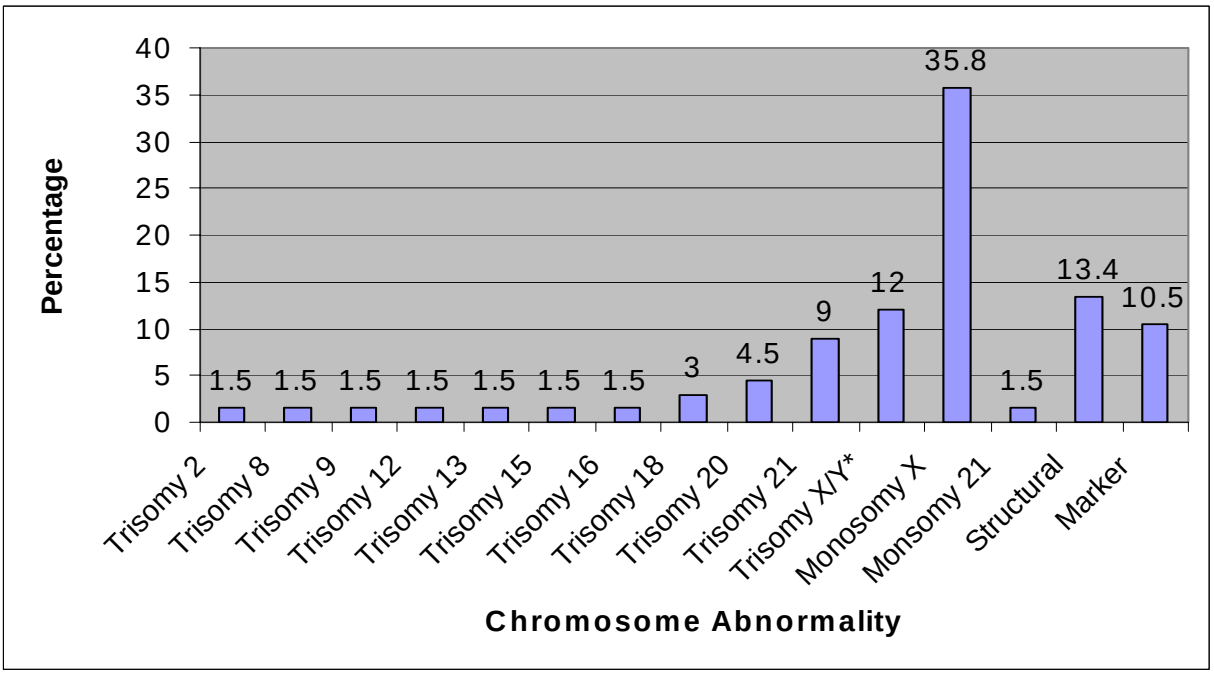
*Mosaicism was also seen on CVS specimen

$^{+}$Previously reported in Thomas, 1998

AMA-Advanced Maternal Age, NT-nuchal translucency, u/s-ultrasound, N/A-not available, LB-live birth, TA-therapeutic abortion, SA-spontaneous abortion, P-pregnant, PP-previous pregnancy, PPL-previous pregnancy loss, PC-previous child, T21-Trisomy 21, T18-Trisomy 18

The reason for referral for the majority of cases was also advanced maternal age (46.9%). However, there is a wider range of referral reasons for amniocentesis patients than CVS patients. Abnormal multiple marker and first trimester screens accounted for 30.3%, abnormal ultrasounds accounted for 16.7%, and abnormal CVS results accounted for 10.6%. In addition, one patient had previous pregnancy losses and one had a previous child with a genetic disorder. The reason for referral was not available for three cases and some of the patients were referred for more than one reason.

The frequency of each type of chromosome abnormality, including the chromosome involved with each trisomy and monosomy, is depicted in Figure 2. Amniocentesis specimens obtained from CVS referral are included.



*****Includes 47,XXX, 47,XXY, and 47,XYY mosaics

Figure 2. Frequency of Amniocentesis Mosaics by Chromosome Abnormality

4.2 MOSAIC CVS CASES

Pregnancy outcome data was collected for 73 of 76 CVS patients (96.1%) and are listed in Table 5. Of these 73 CVS patients, four had a spontaneous abortion (5.4%) and seven had therapeutic abortions (9.6%). The therapeutic abortions were performed because of the following results: 47,XY,+9/46,XY, 47,XX,+16/46,XX, 46,X,+21/47,XX,+21, 45,X/46,XX, 46,XX/47,XX,+mar, 45,X/46,X,i(Xq), and 46,XX,add(13)(p10)/46,XX,der(13;13)(q10;q10),+13. Three of these cases (26, 30, and 73) were confirmed to be true mosaics by either follow-up amniocentesis or tissue analysis while two (16 and 62) were found to be confined to the placenta. No further testing was performed for cases 39 and 76. Of the spontaneous abortions, tissue analysis was normal for cases 36 and 64 and mosaic for case 40 while case 20 had no further testing performed. Case 70 had not delivered as of March 25, 2006.

Table 5. Pregnancy Outcomes for Mosaic CVS Cases

Case	CVS Results	Outcome	Complications
1	47,XY,+2[6]/46,XY[42]$^{+}$	LB (8lb4oz)	None
2	47,XY,+2[2]/46,XY[21]$^{+}$	LB (8lb2oz)	None
3	47,XX,+2[4]/46,XX[21]$^{+}$	LB (8lb0oz)	None
4	47,XX,+2[15]/46,XX[5]	LB (7lb15oz)	None
5	47,XX,+2[3]/46,XX[47]	LB (6lb13oz)	None
6	47,XY,+2[6]/46,XY[14]	LB (4lb10oz)	preterm 36+ wks, early twin SA
7	47,XX,+2[12]/46,XX[18]	LB (7lb14oz)	None
8	48,XX,+2,+7[12]/46,XX[38]	LB	None
9	47,XX,+7[16]/46,XX[4]	LB (7lb10oz)	None
10	48,XXX,+7[7]/46,XX[13]	LB	None
11	47,XX,+7[6]/46,XX[24]	LB (9lb5oz)	None
12	47,XY,+8[8]/46,XY[4]$^{+}$	LB (8lb14oz)	pre-eclampsia
13	47,XY,+8[2]/46,XY[48]	LB	PROM 21wks, neonatal death
14	47,XY,+8[7]/46,XY[17]	LB (5lb8oz)	preterm 34+ wks
15	47,XY,+9[4]/46,XY[16]$^{+}$	LB	None
16	47,XY,+9[18]/46,XY[32]	TA	
17	47,XY,+9[3]/46,XY[32]	LB (7lb8oz)	None
18	47,XY,+10[18]/46,XY[4]$^{+}$	LB (5lb13oz)	None
19	47,XY,+10[5]/46,XY[45]	LB (7lb0oz)	None
20	47,XY,+10[13]/46,XY[37]	SA	IUFD 14+ wks
21	47,XX,+12[26]/46,XX[14]$^{+}$	LB (8lb4oz)	None
22	47,XY,+13[7]/46,XY[43]	LB (5lb2oz)	None
23	47,XY,+15[32]/46,XY[21]$^{+}$	LB (4lb7oz)	PROM, 34+ wks
24	47,XY,+15[4]/46,XY[26]	N/A	
25	47,XY,+16^{+}	LB	pre-eclampsia, IUGR, preterm 33+ wks
26	47,XX,+16[19]/46,XX[2]$^{+}$	TA	
27	48,XX,+16,+20[16]/46,XX[74]	LB (6lb15oz)	None
28	47,XX,+18[9]/46,XX[11]	LB (6lb6oz)	None
29	47,XX,+18[10]/46,XX[10]	LB	Preterm 27+ wks
30	46,X,+21[17]/47,XX,+21[33]$^{+}$	TA	
31	47,XX,+22[9]/46,XX[41]$^{+}$	N/A	
32	45,XX,-22[4]/46,XX[18]	LB (7lb3oz)	None
33	45,X/46,XX^{+}	LB (8lb3oz)	None
34	45,X[7]/46,XX[23]	LB (6lb11oz)	None
35	45,X[15]/46,XX[5]	LB (6lb3oz)	None
36	45,X[2]/46,XX[48]$^{+}$	SA	
37	45,X[2]/46,XX[48]$^{+}$	LB (9lb7oz)	None
38	45,X[2]/46,XX[48]$^{+}$	LB (8lb12oz)	None
39	45,X[10]/46,XX[10]	TA	
40	45,X[7]/46,XX[43]	SA	
41	45,X[7]/46,XX[43]	LB (7lb14oz)	None
42	45,X[5]/46,XY[45]	LB (8lb3oz)	None

Table 5. (continued)

43	45,X[9]/46,XY[21]	LB (6lb1oz)	None
44	45,X[2]/46,XY[48]+	LB (7lb5oz)	None
45	45,X[2]/46,XY[48]+	LB (7lb2oz)	None
46	45,X[8]/46,XY[12]+	LB (7lb4oz)	None
47	47,XXY[11]/46,XY[39]+	LB	
48	47,XXY[37]/46,XY[13]	LB (9lb6oz)	fetal cyst and tachycardia
49	47,XXY[12]/46,XY[18]	LB (7lb9oz)	None
50	47,XX,+mar[3]/46,XX[47]+	LB (8lb12oz)	None
51	47,XX,+mar[3]/46,XX[48]+	LB (5lb10oz)	None
52	47,XX,+mar[4]/46,XX[46]+	LB (4lb8oz)	None
53	47,XX,+mar[2]/46,XX[48]+	LB (3lb9oz)	chorioamnionitis, preterm 29 wks
54	47,XX,+mar[4]/46,XX[25]+	LB (7lb5oz)	None
55	47,XY,+mar[2]/46,XY[20]+	LB (8lb2oz)	None
56	47,XX,+mar[2]/46,XX[18]+	LB (6lb6oz)	None
57	47,XX,+mar[3]/46,XX[18]+	LB (7lb3oz)	None
58	47,XY,+mar[8]/46,X,+mar[2]/46,XY[20]+ - marker identified as 17 in origin	LB (7lb2oz)	None
59	45,X[13]/46,X,+mar[6]/46,XY[4]+ - marker identified as Y in origin	LB (7lb4oz)	None
60	47,XY,+mar(mat)[16]/46,XY[4]	N/A	
61	47,XY,+mar(mat)[15]/46,XY[5]	LB (8lb0oz)	None
62	46,XX/47,XX,+mar	TA	
63	47,XY,+mar[8]/46,XY[12]	LB (7lb14oz)	None
64	92,XXXX/46,XX[20]+	SA	
65	92,XXXX[13]/46,XX[7]	LB (5lb5oz)	preterm, 36+ wks
66	92,XXYY[41]/46,XY[11]	LB (7lb7oz)	None
67	46,XX,t(5;7)(p15.1;q34)[4]/46,XX[19]+	LB (8lb5oz)	None
68	46,XX,der(5)t(5;?)(q35.1;?)[2]/46,XX[20]+	LB	None
69	47,XX,+inv dup(8)(p23.1p12)[7] /46,XX[43]	LB (8lb6oz)	None
70	46,XY,+9,der(13)t(9;13)(q10;q10)[3] /46,XY[18]	P	
71	47,XX,+i(12p)[5]/46,XX[21]+	LB	preterm 22 wks, died at 47 min
72	46,XX,del(13)(q22)[3]/46,XX[47]+	LB (8lb2oz)	None
73	46,XX,add(13)(p10).ish der(13)(wcp13+) [17]/46,XX,der(13;13)(q10;q10),+13[3]+	TA	
74	47,XX,r(15)[6]/46,XX[44]+	LB (8lb4oz)	None
75	47,XY,+inv dup(15)(p10)[18]/46,XY	LB (8lb11oz)	None
76	45,X[2]/46,X,i(Xq)	TA	

+Previously reported in Thomas, 1998

N/A – not available; LB – live birth; SA – spontaneous abortion; TA – therapeutic abortion; P – currently pregnant; PROM – premature rupture of membranes

Pregnancy complications were seen in 11 of 62 (17.7%) CVS patients who did not have a spontaneous or therapeutic abortion. The patient who is currently pregnant was also excluded. All of these cases had a follow-up amniocentesis, with the exception of case 6. Five of the cases were previously reviewed in Thomas, 1998. Case 25 (47,XY,+16) had severe pre-eclampsia and IUGR and was delivered by C-section at 33+ weeks. Case 53 (46,XX/47,XX,+mar) had chorioamnionitis and was delivered by C-section at 29+ weeks. Case 12 (47,XY,+8/46,XY) had pre-eclampsia and was delivered vaginally at 39+ weeks. Case 71 (46,XX/47,XX,+i(12p)) was delivered at 22 weeks and the newborn died 47 minutes after birth. This patient had two amniocentesis procedures performed and Thomas (1998) suggested in her paper that the premature labor may have been due to multiple invasive procedures. Lastly, case 23 (46,XY/47,XY,+15) had PROM and was delivered by C-section at 34+ weeks.

Five additional cases resulted in preterm delivery. Case 13 (47,XY,+8/46,XY) had PROM and after delayed fetal development, was induced at 21 weeks. The newborn expired soon after birth. Case 6 (47,XY,+2/46,XY) was delivered by C-section at 36+ weeks. Of note, there was an early loss of a twin. Case 14 (47,XY,+8/46,XY) was delivered by C-section at 34+ weeks. Case 29 (47,XX,+18/46,XX) was delivered by C-section at 27+. Finally, case 69 (92,XXXX/46,XX) was delivered at 36+ weeks.

Other pregnancy complications occurred in one additional case. Case 48 (47,XXY/46,XY) was complicated by a persistent fetal intraabdominal cyst and fetal tachycardia.

Table 6 includes additional information, including unusual features and anomalies, which was recorded about the CVS cases at ultrasound, delivery, and/or follow-up genetic consultations.

Table 6. Reported Features for Mosaic CVS Cases

Case	CVS Results	Outcome	Reported Features
1	47,XY,+2[6]/46,XY[42]$^{+}$	LB	normal at delivery
2	47,XY,+2[2]/46,XY[21]$^{+}$	LB	
3	47,XX,+2[4]/46,XX[21]$^{+}$	LB	
4	47,XX,+2[15]/46,XX[5]	LB	normal at delivery
5	47,XX,+2[3]/46,XX[47]	LB	normal at delivery
6	47,XY,+2[6]/46,XY[14]	LB	normal at delivery
7	47,XX,+2[12]/46,XX[18]	LB	normal at delivery
8	48,XX,+2,+7[12]/46,XX[38]	LB	normal at delivery
9	47,XX,+7[16]/46,XX[4]	LB	normal at delivery
10	48,XXX,+7[7]/46,XX[13]	LB	normal at delivery
11	47,XX,+7[6]/46,XX[24]	LB	normal at delivery
12	47,XY,+8[8]/46,XY[4]$^{+}$	LB	
13	47,XY,+8[2]/46,XY[48]	LB	neonatal death
14	47,XY,+8[7]/46,XY[17]	LB	normal at delivery
15	47,XY,+9[4]/46,XY[16]$^{+}$	LB	
16	47,XY,+9[18]/46,XY[32]	TA	
17	47,XY,+9[3]/46,XY[32]	LB	normal at delivery
18	47,XY,+10[18]/46,XY[4]$^{+}$	LB	mild hypotelorism, epicanthal folds, single palmar crease- familial
19	47,XY,+10[5]/46,XY[45]	LB	normal at delivery
20	47,XY,+10[13]/46,XY[37]	SA	
21	47,XX,+12[26]/46,XX[14]$^{+}$	LB	
22	47,XY,+13[7]/46,XY[43]	LB	normal at 2 months
23	47,XY,+15[32]/46,XY[21]$^{+}$	LB	
24	47,XY,+15[4]/46,XY[26]	N/A	
25	47,XY,+16^{+}	LB	
26	47,XX,+16[19]/46,XX[2]$^{+}$	TA	
27	48,XX,+16,+20[16]/46,XX[74]	LB	normal at delivery
28	47,XX,+18[9]/46,XX[11]	LB	increased NT, resolved
29	47,XX,+18[10]/46,XX[10]	LB	normal at delivery
30	46,X,+21[17]/47,XX,+21[33]$^{+}$	TA	
31	47,XX,+22[9]/46,XX[41]$^{+}$	N/A	
32	45,XX,-22[4]/46,XX[18]	LB	normal at delivery
33	45,X/46,XX^{+}	LB	
34	45,X[7]/46,XX[23]	LB	normal at delivery
35	45,X[15]/46,XX[5]	LB	normal at delivery
36	45,X[2]/46,XX[48]$^{+}$	SA	
37	45,X[2]/46,XX[48]$^{+}$	LB	
38	45,X[2]/46,XX[48]$^{+}$	LB	
39	45,X[10]/46,XX[10]	TA	
40	45,X[7]/46,XX[43]	SA	
41	45,X[7]/46,XX[43]	LB	normal at delivery
42	45,X[5]/46,XY[45]	LB	normal at delivery

Table 6. (continued)

43	45,X[9]/46,XY[21]	LB	normal at delivery
44	45,X[2]/46,XY[48]+	LB	
45	45,X[2]/46,XY[48]+	LB	normal at delivery
46	45,X[8]/46,XY[12]+	LB	normal at delivery
47	47,XXY[11]/46,XY[39]+	LB	
48	47,XXY[37]/46,XY[13]	LB	normal at delivery
49	47,XXY[12]/46,XY[18]	LB	normal at delivery
50	47,XX,+mar[3]/46,XX[47]+	LB	
51	47,XX,+mar[3]/46,XX[48]+	LB	
52	47,XX,+mar[4]/46,XX[46]+	LB	
53	47,XX,+mar[2]/46,XX[48]+	LB	
54	47,XX,+mar[4]/46,XX[25]+	LB	
55	47,XY,+mar[2]/46,XY[20]+	LB	
56	47,XX,+mar[2]/46,XX[18]+	LB	
57	47,XX,+mar[3]/46,XX[18]+	LB	increased NT
58	47,XY,+mar[8]/46,X,+mar[2]/46,XY[20]+ - marker identified as 17 in origin	LB	
59	45,X[13]/46,X,+mar[6]/46,XY[4]+ - marker identified as Y in origin	LB	
60	47,XY,+mar(mat)[16]/46,XY[4]	N/A	
61	47,XY,+mar(mat)[15]/46,XY[5]	LB	normal at delivery
62	46,XX/47,XX,+mar	TA	
63	47,XY,+mar[8]/46,XY[12]	LB	normal at delivery
64	92,XXXX/46,XX[20]+	SA	
65	92,XXXX[13]/46,XX[7]	LB	normal at delivery
66	92,XXYY[41]/46,XY[11]	LB	normal at delivery
67	46,XX,t(5;7)(p15.1;q34)[4]/46,XX[19]+	LB	normal at delivery
68	46,XX,der(5)t(5;?)(q35.1;?)[2]/46,XX[20]+	LB	
69	47,XX,+inv dup(8)(p23.1p12)[7] /46,XX[43]	LB	normal at delivery
70	46,XY,+9,der(13)t(9;13)(q10;q10)[3] /46,XY[18]	P	increased NT
71	47,XX,+i(12p)[5]/46,XX[21]+	LB	dysmorphic features, Pallister Killian
72	46,XX,del(13)(q22)[3]/46,XX[47]+	LB	
73	46,XX,add(13)(p10).ish der(13)(wcp13+) [17]/46,XX,der(13;13)(q10;q10),+13[3]+	TA	
74	47,XX,r(15)[6]/46,XX[44]+	LB	
75	47,XY,+inv dup(15)(p10)[18]/46,XY	LB	normal at delivery
76	45,X[2]/46,X,i(Xq)	TA	

+ Previously reported in Thomas, 1998

NT – nuchal translucency

Unusual features were reported during the newborn period for 5 of the 73 CVS cases (6.8%). Three of these cases (28, 57, 70) showed increased nuchal translucency during pregnancy. One case (10) was reported to have mild hypotelorism, epicanthal folds, and a single palmar crease but these characteristics were felt to be familial. Finally, case 71 was documented to have dysmorphic features consistent with Pallister-Killian syndrome. More information about this case is available in Mowery-Rushton et al. (1997).

Additional cytogenetic testing was performed for the mosaic CVS cases and is included in Table 7. Follow-up amniocentesis was performed for 43 of the 76 cases (56.6%). Tissue analysis was performed for 21 of the 76 mosaic specimens (27.6%) and blood analysis, via cord or peripheral blood, was performed for 13 of 76 cases (17.1%). Overall, 55 of 76 cases (72.4%) had some type of follow-up cytogenetic testing.

Table 7. Follow-up Testing for Mosaic CVS Cases

Case	CVS Results	Amniocentesis Results	Tissue Results	Blood Results
2	47,XY,+2/46,XY^{+}		cord: 46,XY	
4	47,XX,+2/46,XX		amnion, cord, placenta: 46,XX	46,XX
7	47,XX,+2/46,XX	46,XX		
8	48,XX,+2,+7/46,XX	46,XX		
9	47,XX,+7/46,XX	46,XX		
10	48,XXX,+7/46,XX	46,XX		
11	47,XX,+7/46,XX	46,XX		
12	47,XY,+8/46,XY^{+}	46,XY.nuc ish 8cen(D8Z2 x2)		
13	47,XY,+8/46,XY	46,XY	skin, placenta: 46,XY	46,XY
14	47,XY,+8/46,XY	46,XY		
15	47,XY,+9/46,XY^{+}	46,XY		
16	47,XY,+9/46,XY	46,XY	villi 47,XY,+9[2]/46,XY[8], skin 46,XY[10], lung 46,XY[10], liver 46,XY[10]	
17	47,XY,+9/46,XY	46,XY		
18	47,XY,+10/46,XY^{+}	46,XY	villi: 46,XY[11]/47,XY,+10[19]	46,XY
21	47,XX,+12/46,XX^{+}	46,XX		
22	47,XY,+13/46,XY	46,XY		
23	47,XY,+15/46,XY^{+}	47,XY,+15/ 46,XY		
24	47,XY,+15/46,XY	46,XY		
25	47,XY,+16^{+}	46,XY	cord/mem 46,XY[50]/ plac II & IV 47,XY,+16[50]/plac I 46,XY[39]/47,XY,+16[11]/plac III 46,XY[2]/47,XY,+16[48]	46,XY
26	47,XX,+16/46,XX^{+}	47,XX,+16[9]/ 46,XX[7]	47,XX,+16[95]/46,XX[145] multiple tissues	
27	48,XX,+16,+20/46,XX		placenta: 46,XX	46,XX
28	47,XX,+18/46,XX	46,XX		
29	47,XX,+18/46,XX	46,XX		
30	46,X,+21/47,XX,+21^{+}		46,X,+21/47,XX,+21	
31	47,XX,+22/46,XX^{+}	46,XX		
32	45,XX,-22/46,XX		villi: 46,XX	46,XX
33	45,X/46,XX^{+}		45,X/46,XX	46,XX (one cell 45,X)
34	45,X/46,XX	46,XX		
35	45,X/46,XX	46,XX		
36	45,X/46,XX^{+}		46,XX	
40	45,X/46,XX		placenta: 45,X[2]/46,XX[18]	
41	45,X/46,XX		placenta: 45,X[5]/46,XX[25]	45,X[1]/ 46,X,+i(X)(q10)[1]/ 46,XX[28]
46	45,X/46,XY^{+}	46,XY		
47	47,XXY/46,XY^{+}	47,XXY[5]/ 46,XY[40]	placenta: 47,XXY[14]/46,XY[7]	47,XXY[5]/46,XY[45]

Table 7. (continued)

48	47,XXY/46,XY	47,XXY[2]/ 46,XY[48]	placenta: 47,XXY[3]/46,XY[47]	47,XXY[2]/46,XY[48]
49	47,XXY/46,XY			47,XXY[18]/46,XY[32]
53	47,XX,+mar/46,XX[+]	46,XX		
54	47,XX,+mar/46,XX[+]	46,XX		
55	47,XY,+mar/46,XY[+]	46,XY		
56	47,XX,+mar/46,XX[+]	46,XX		
57	47,XX,+mar/46,XX[+]	46,XX		
58	47,XY,+mar/46,X,+mar/46,XY[+] - identified as 17 in origin	47,XY, +der(17)[6] /46,XY[68]		
59	45,X/46,X,+mar/46,XY[+] - identified as Y in origin	46,X,+mar[5]/ 46,XY[16].ish der(y)(wcpy+)		
62	47,XX,+mar/46,XX		villi, lung: 46,XX	
63	47,XY,+mar/46,XY	46,XY		
64	92,XXXX/46,XX[+]		46,XX	
66	92,XXYY/46,XY	46,XY		
67	46,XX,t(5;7)(p15.1;q34) /46,XX[+]	46,XX		
68	46,XX,der(5)t(5;?)(q35.1;?) /46,XX[+]	46,XX		
69	47,XX,+inv dup(8)(p23.1p12)/ 46,XX			47,XX,+inv dup(8) (p23.1p12)[18]/46,XX[7]
70	46,XY,+9,der(13)t(9;13) (q10;q10)/46,XY	46,XY		
71	47,XX,+i(12p)/46,XX[+]	47,XX,+i(12p)/ 46,XX	47,XX,+i(12p)/46,XX	
72	46,XX,del(13)(q22)/46,XX[+]	46,XX	villi: 46,XX	46,XX
73	46,XX,add(13)(p10)/46,XX, der(13;13)(q10;q10),+13[+]		villi and amnion: 46,XX, der(13;13)(q10;q10),+13	
74	47,XX,r(15)/46,XX[+]	46,XX		

[+] Previously reported in Thomas, 1998

Mosaicism was confirmed for 13 of the 55 fetuses (23.6%) which had additional cytogenetic testing. Of these cases, 10 continued their pregnancies and three had complications. Case 40 resulted in a spontaneous abortion 15 days after the CVS procedure. As previously mentioned, one case (71) considered to have Pallister-Killian syndrome delivered at 22 weeks and resulted in a neonatal death. In addition, case 23 resulted in a preterm delivery at 34 weeks.

In some cases that involved a marker chromosome or structural aberration, the parents had blood analysis to determine if the chromosome abnormality was inherited or *de novo*. The results from this testing are listed in Table 8.

Table 8. Parental Blood Analysis for Mosaic CVS Cases

Case	CVS Results	Maternal Karyotype	Paternal Karyotype
51	47,XX,+mar[3]/46,XX[48]+	46,XX	47,XY,+mar/46,XY
52	47,XX,+mar[4]/46,XX[46]+	46,XX	46,XY
53	47,XX,+mar[2]/46,XX[48]+	46,XX	46,XY
54	47,XX,+mar[4]/46,XX[25]+	46,XX	47,XY
56	47,XX,+mar[2]/46,XX[18]+	46,XX	
58	47,XY,+mar[8]/46,X,+mar[2]/46,XY[20]+	46,XX	46,XY
60	47,XY,+mar(mat)[16]/46,XY	47,XX,+mar/46,XX	
61	47,XY,+mar(mat)[15]/46,XY	47,XX,+mar1[8] /47,XX,+mar2[2] /46,X,+mar1[2]/46,XX[8]	
62	46,XX/47,XX,+mar	46,XX	
63	47,XY,+mar[8]/46,XY[12]	46,XX	46,XY
67	46,XX,t(5;7)9p15.1;q34)[4]/46,XX[19]+	46,XX	46,XY
69	47,XX,+inv dup(8)(p23.1p12)[7]/46,XX[43]	46,XX	46,XY
70	46,XY,+9,der(13)t(9;13)(q10;q10)[3] /46,XY[18]	46,XX	46,XY
73	46,XX,add(13)(p10).ish der(13)(wcp13+)[17] /46,XX,der(13;13)9q10;q10),+13[3]+	46,XX	46,XY
75	47,XY,+inv dup(15)(p10)[18]/46,XY	46,XX	46,XY

+ Previously reported in Thomas, 1998

Of the 23 cases involving a marker chromosome or structural aberration, 15 (65.2%) had parental blood analysis. Three of these cases identified a marker in one of the parents' karyotypes. Parental karyotypes were normal in all of the structural aberration cases.

4.3 MOSAIC AMNIOCENTESIS CASES

Pregnancy outcome information was obtained for 43 of the 59 mosaic amniocentesis cases (72.9%). These outcomes are listed in Table 9. Although cases referred for mosaic CVS were not included in the above calculation, the amniocentesis outcomes are included in the table. Of the patients with available pregnancy outcomes, one had a spontaneous abortion (1.7%) and eight had a therapeutic abortion (13.6%). The therapeutic abortions were performed because of the following abnormal results: 47,XX,+9/46,XX; 47,XY,+18/46,XX; 47,XX,+21/46,XX; 45,X/46,XX; 45,X/46,XY; 46,XX,+mar/46,XX; 47,XY,+i(12)(p10)/46,XY; and 46,XY,der(13)t(13;?)/46,XY. Two cases (both 45,X/46,XX) had not delivered as of March 25, 2006.

Table 9. Pregnancy Complications for Mosaic Amniocentesis Results

Case	Amniocentesis Results	Outcome	Pregnancy complications
77	47,XX,+2[8]/46,XX[42]$^{+}$	N/A	
78	47,XX,+8[5]/46,XX[25]	LB (8lb0oz)	None
79	47,XX,+9[9]/46,XX[13]	TA	
80	47,XX,+12[2]/46,XX[48]$^{+}$	N/A	
81	47,XX,+13[3]/46,XX[62]	LB	
82	47,XY,+15/46,XY*$^{+}$	LB (4lb7oz)	PROM 34 wks
83	47,XX,+16[19]/46,XX[7]*$^{+}$	TA	
84	47,XY,+18[46]/46,XY[4]$^{+}$	TA	
85	47,XX,+18[18]/46,XX[2]	N/A	
86	47,XX,+20[5]/46,XX[45]$^{+}$	LB (7lb14oz)	None
87	47,XX,+20[6]/46,XX[11]$^{+}$	LB (4lb14oz)	? r/o IUGR
88	47,XY,+20[7]/46,XX[41]$^{+}$	N/A	
89	47,XX,+21[36]/46,XX[9]$^{+}$	LB (8lb3oz)	None
90	47,XX,+21[35]/46,XX[14]$^{+}$	TA	
91	47,XX,+21[4]/46,XX[34]$^{+}$	LB	None
92	47,XX,+21[4]/46,XX[40]$^{+}$	LB (7lb7oz)	None
93	47,XX,+21[9]/46,XX[37]	TA	
94	47,XY,+21[23]/46,XY[4]	LB (8lb1oz)	None
95	45,XY,-21[4]/46,XY[30]	N/A	
96	45,X[9]/46,XX[36]$^{+}$	N/A	
97	45,X[48]/46,XX[2]$^{+}$	SA	20 wk fetal demise
98	45,X[15]/46,XX[35]$^{+}$	N/A	
99	45,X[5]/46,XX[25]$^{+}$	N/A	
100	45,X[7]/46,XX[8]$^{+}$	LB (8lb5oz)	None
101	45,X[5]/46,XX[10]	P	
102	45,X[6]/46,XX[19]	P	
103	45,X[3]/46,XX[17]$^{+}$	LB (7lb6oz)	None
104	45,X[33]/46,XX[17]$^{+}$	N/A	
105	45,X[10]/46,XX[16]	LB (8lb10oz)	None
106	45,X[4]/46,XX[16]	LB (6lb4oz)	None
107	45,X[10]/46,XX[32]	LB (8lb0oz)	None
108	45,X[8]/46,XX[8]	LB (6lb0oz)	None
109	45,X[5]/46,XX[10]	TA	
110	45,X[5]/46,XX[27]	LB	
111	45,X[22]/46,XX[3]	N/A	
112	45,X[39]/46,XX[7]	LB	
113	45,X[10]/46,XX[5]	LB (6lb15oz)	induced - hypertension
114	45,X[5]/46,XY[25]	TA	
115	45,X[3]/46,XY[22]	LB (7lb11oz)	None
116	45,X[15]/46,XY[35]	LB (6lb14oz)	None
117	45,X[2]/46,XY[18]$^{+}$	N/A	
118	45,X[3]/46,XY[41]$^{+}$	LB	
119	47,XXX[5]/45,X[3]/46,XX[22]	LB (6lb4oz)	None

Table 9. (continued)

120	47,XXY[13]/45,X[12]+	LB (5lb2oz)	None
121	47,XXY/46,XY+	LB (7lb8oz)	None
122	47,XXY[5]/46,XY[40]*+	LB	
123	47,XXY[2]/46,XY[48]*	LB (9lb6oz)	fetal cyst, tachycardia
124	47,XXY[5]/46,XY[20]	LB (8lb5oz)	None
125	47,XXY[6]/46,XY[34]	N/A	
126	47,XYY[8]/46,XY[8]	LB (6lb10oz, 7lb0oz)	preterm 35+ wks
127	47,XX,+mar[5]/46,XX[40].ish der(22)(D14Z1/D22Z1+,wcp22+)	N/A	
128	47,XX,+mar[44]/46,XX[6] -identified as 6 in origin	LB (5lb8oz)	None
129	47,XX,+mar[6]/46,XX[9] -identified as 7 in origin	TA	ruptured membranes
130	47,XX,+mar[10]/46,XX[5].ish inv dup(13)(p10)	LB (7lb9oz)	None
131	47,XY,+mar[6]/46,XY[28].ish dup(21)(q11.2)	N/A	
132	45,X[27]/47,X,inv(Y)(p11q12),+mar[5] /46,XY[13]+	LB (6lb14oz)	None
133	46,X,+mar[5]/46,XY[16].ish der(y)(wcp+)*+	LB (7lb4oz)	None
134	46,XY,der(5)del(5)(p14.2)dup(5)(q14q22) t(5;14)(q13;q32)[9]/46,XY[31]	N/A	
135	47,XX,+i(12p)[1]/46,XX[62]*+	LB	preterm delivery 22 wks, died 47 mins
136	47,XY,+i(12)(p10)[10]/46,XY[5]	TA	
137	46,XY,der(13)t(13;?)[5]/46,XY[44]+	TA	
138	47,XY,+der(17)[6]/46,XY[68]*+	LB (7lb2oz)	None
139	46,X,i(Xq)[6]/46,XX[90]+	N/A	
140	46,X,idic(Y)(q11.2)[9]/45,X[6]	LB (6lb0oz)	None
141	45,X[37]/46,X,psu idic (Y)(p11.32)[4]	LB (3lb11oz)	preterm 32 wks
142	45,X[9]/46,X,i(Y)(p10)[6]	LB (8lb8oz)	None

*Mosaicism was also seen on CVS specimen

+Previously reported in Thomas, 1998

N/A – not available; LB – live birth; SA – spontaneous abortion; TA – therapeutic abortion; P – currently pregnant; PROM – premature rupture of membranes

Pregnancy complications were seen for 4 of 43 amniocentesis patients (9.3%). Cases that were excluded include patients who were referred because of a mosaic CVS result and those who had a spontaneous or therapeutic abortion. Two of these cases had preterm deliveries. Case 126 (47,XYY/46,XX) was delivered vaginally at 35+ weeks and case 141 (45,X/46,X,psu idic(Y)(p11.32)) was delivered vaginally at 32 weeks .

In addition, case 113 (45,X/46,XX) was induced due to hypertension, which may indicate that the beginnings of pre-eclampsia were present. Case 87 (47,XX,+21/46,XX) was 4 lbs. 14 oz. at birth, which might indicate that IUGR was present. It should also be mentioned that case 129 (47,XX,+mar/46,XX) was complicated by ruptured membranes but was electively terminated.

Table 10 includes additional information, including unusual features and anomalies, which was recorded about the amniocentesis cases at ultrasound, delivery, and/or follow-up genetic consultations.

Table 10. Reported Features for Mosaic Amniocentesis Cases

Case	Amniocentesis Results	Outcome	Reported Features
77	47,XX,+2[8]/46,XX[42]$^{+}$	N/A	
78	47,XX,+8[5]/46,XX[25]	LB	increased NT, mild ventriculomegaly, mild hydronephrosis (resolved), prominent pillars of philtrum, full lower lip, extra crease on both earlobes, tall stature, normal dev at 5 mos
79	47,XX,+9[9]/46,XX[13]	TA	Dandy Walker formation
80	47,XX,+12[2]/46,XX[48]$^{+}$	N/A	
81	47,XX,+13[3]/46,XX[62]	LB	
82	47,XY,+15/46,XY*$^{+}$	LB	
83	47,XX,+16[19]/46,XX[7]*$^{+}$	TA	
84	47,XY,+18[46]/46,XY[4]$^{+}$	TA	choroid plexus cysts
85	47,XX,+18[18]/46,XX[2]	N/A	cystic hygroma
86	47,XX,+20[5]/46,XX[45]$^{+}$	LB	
87	47,XX,+20[6]/46,XX[11]$^{+}$	LB	
88	47,XY,+20[7]/46,XX[41]$^{+}$	N/A	short limbs, duodenal atresia
89	47,XX,+21[36]/46,XX[9]$^{+}$	LB	Down syndrome
90	47,XX,+21[35]/46,XX[14]$^{+}$	TA	pathology report noted Simian crease
91	47,XX,+21[4]/46,XX[34]$^{+}$	LB	no clinical features of Down syndrome
92	47,XX,+21[4]/46,XX[40]$^{+}$	LB	distal axial triradii only feature of Down syndrome
93	47,XX,+21[9]/46,XX[37]	TA	
94	47,XY,+21[23]/46,XY[4]	LB	increased NT
95	45,XY,-21[4]/46,XY[30]	N/A	
96	45,X[9]/46,XX[36]$^{+}$	N/A	
97	45,X[48]/46,XX[2]$^{+}$	SA	cystic hygroma
98	45,X[15]/46,XX[35]$^{+}$	N/A	
99	45,X[5]/46,XX[25]$^{+}$	N/A	
100	45,X[7]/46,XX[8]$^{+}$	LB	coarctation of the aorta
101	45,X[5]/46,XX[10]	P	
102	45,X[6]/46,XX[19]	P	
103	45,X[3]/46,XX[17]$^{+}$	LB	
104	45,X[33]/46,XX[17]$^{+}$	N/A	
105	45,X[10]/46,XX[16]	LB	normal at delivery, no features of Turner at 5 months
106	45,X[4]/46,XX[16]	LB	normal at delivery, no features of Turner at 4.5 months
107	45,X[10]/46,XX[32]	LB	normal u/s and echo
108	45,X[8]/46,XX[8]	LB	diaphragmatic hernia, mild edema, hyperconvex nails, posteriorly rotated ears
109	45,X[5]/46,XX[10]	TA	
110	45,X[5]/46,XX[27]	LB	normal echo, no features of Turner
111	45,X[22]/46,XX[3]	N/A	
112	45,X[39]/46,XX[7]	LB	normal appearance and development at 9 mos

Table 10. (continued)

113	45,X[10]/46,XX[5]	LB	normal at delivery
114	45,X[5]/46,XY[25]	TA	
115	45,X[3]/46,XY[22]	LB	choroid plexus cysts, normal male genitalia on u/s
116	45,X[15]/46,XY[35]	LB	normal appearance and development 11.5 mos
117	45,X[2]/46,XY[18]$^{+}$	N/A	
118	45,X[3]/46,XY[41]$^{+}$	LB	
119	47,XXX[5]/45,X[3]/46,XX[22]	LB	
120	47,XXY[13]/45,X[12]$^{+}$	LB	
121	47,XXY/46,XY^{+}	LB	
122	47,XXY[5]/46,XY[40]*$^{+}$	LB	
123	47,XXY[2]/46,XY[48]*	LB	normal at delivery
124	47,XXY[5]/46,XY[20]	LB	normal at delivery
125	47,XXY[6]/46,XY[34]	N/A	
126	47,XYY[8]/46,XY[8]	LB	one twin mosaic, did not want to know which one, both appeared normal
127	47,XX,+mar[5]/46,XX[40].ish der(22)(D14Z1/D22Z1+,wcp22+)	N/A	
128	47,XX,+mar[44]/46,XX[6] -identified as 6 in origin	LB	normal appearance and development at 15 mos
129	47,XX,+mar[6]/46,XX[9] -identified as 7 in origin	TA	pump twin – hypoplastic left heart, left lung aplasia, acardiac twin - amorphous
130	47,XX,+mar[10]/46,XX[5] (inv dup(13)(p10))	LB	normal at delivery
131	47,XY,+mar[6]/46,XY[28].ish dup(21)(q11.2)	N/A	
132	45,X[27]/47,X,inv(Y)(p11q12),+mar[5]/46,XY[13]$^{+}$	LB	mild edema of hands and feet, hyperconvex nails
133	46,X,+mar[5]/46,XY[16].ish der(y)(wcp+)*$^{+}$	N/A	
134	46,XY,der(5)del(5)(p14.2)dup(5)(q14q22)t(5;14)(q13;q32)[9]/46,XY[31]	N/A	
135	47,XX,+i(12p)[1]/46,XX[62]*$^{+}$	LB	dysmorphic features - Pallister Killian
136	47,XY,+i(12)(p10)[10]/46,XY[5]	TA	diaphragmatic hernia, Pallister -Killian
137	46,XY,der(13)t(13;?)[5]/46,XY[44]$^{+}$	TA	
138	47,XY,+der(17)[6]/46,XY[68]*$^{+}$	LB	
139	46,X,i(Xq)[6]/46,XX[90]$^{+}$	N/A	
140	46,X,idic(Y)(q11.2)[9]/45,X[6]	LB	normal at delivery and at 4.5 years
141	45,X[37]/46,X,psu idic (Y)(p11.32)[4]	LB	umbilical hernia, hyperconvex nails, hypogonadism, last seen at 3 mos
142	45,X[9]/46,X,i(Y)(p10)[6]	LB	increased NT

*Mosaicism was also seen on CVS specimen

$^{+}$Previously reported in Thomas, 1998

NT – nuchal translucency; u/s - ultrasound

Of the 59 amniocentesis patients, 18 (30.5%) were reported to have some unusual features and anomalies. Five of these cases were electively terminated. Case 79 (47,XX,+9/46,XX) was found to have a Dandy Walker formation on ultrasound, and case 90 (46,XX/47,XX,+21) was noted to have a Simian crease by pathology report. Case 84 (47,XY,+18/46,XY) was found to have choroid plexus cysts on ultrasound. Case 129 (47,XX,+mar/46,XX) involved monochorionic twins and abnormalities were reported for both. Ultrasound showed that the "pump twin" had a hypoplastic left heart and left lung aplasia while the second, "acardiac twin," was amorphous. Finally, case 136 (47,XY,+i(12)(p10)/46,XY) was documented to have a diaphragmatic hernia on ultrasound and was considered to have Pallister-Killian syndrome.

Three cases with results that were mosaic for trisomy 21 had some features of Down syndrome. Case 89 was reported to have Down syndrome but no specific features were indicated. Case 92 was reported to have distal axial triradii, but that was the only feature of Down syndrome. Case 94 was reported to have increased nuchal translucency on ultrasound.

Four cases with results that were mosaic for monosomy X were reported to have anomalies. Case 97 (45,X/46,XX) was reported to have cystic hygroma by ultrasound. Case 100 (45,X/46,XX) was reported to have coarctation of the aorta. Case 108, (also 45,X/46,XX) was reported to have a diaphragmatic hernia, mild edema, and hyperconvex nails. The facial features were normal except for posteriorly rotated ears. Case 115 (45,X/46,XY) was documented to have choroid plexus cysts on ultrasound, but genitalia appeared normal.

Three other cases involving mosaic trisomies were reported to have anomalies. Case 78 (47,XX,+8/46,XX) was noted by ultrasound to have an increased nuchal translucency, mild ventriculomegaly, and mild hydronephrosis. The hydronephrosis resolved during pregnancy.

The infant was reported to have prominent pillars of philtrum, a full lower lip, an extra crease on both earlobes, and tall stature at five months of age, but she was found to be developing normally. Case 85 (47,XX,+18/46,XX) had cystic hygroma, which was identified by ultrasound and case 88 (47,XX,+21/46,XX) had short limbs and duodenal atresia, which were identified by ultrasound.

Lastly, three cases involving structural aberrations of the sex chromosomes were reported to have unusual features. Case 132 (45,X/47,X,inv(Y)(p11q12),+mar/46,XY) was reported to have mild edema of the hands and feet and hyperconvex nails. Case 141 (45,X/46,X,psu idic (Y)(p11.32)) was reported to have an umbilical hernia, hyperconvex nails, and hypogonadism. Finally, case 142 (45,X/46,X,i(Y)(p10)) was reported to have an increased nuchal translucency by ultrasound.

Follow-up cytogenetic testing was performed for 28 of 59 (47.5%) mosaic amniocentesis cases. These test results are listed in Table 11. A total of 17 of the 28 cases were confirmed as true mosaics (60.7%). Sixteen of the mosaic amniocentesis specimens (27.1%) had tissue follow-up performed. Of these, three did not grow, including a mosaic trisomy 18 case (84), a mosaic trisomy 21 case (91), and a mosaic monosomy X case (107). Seven of the tissues confirmed true fetal mosaicism (79, 90, 93, 118, 126,129, and 136) while three others indicated non-mosaic Turner syndrome. In addition, 18 mosaic amniocentesis cases (30.5%) had blood analysis. Of these, 13 confirmed true mosaicism, nine of which did not have tissue analysis. These cases include 78, 92, 107, 108, 110, 116, 124, 128, and 141. Case 132 (45,X/47,X,inv(Y)(p1.2q12),+mar/ 46,XY) was confirmed mosaicism by blood analysis while tissue analysis indicated non-mosaic Turner.

Table 11. Follow-up Testing for Mosaic Amniocentesis Results

Case	Amniocentesis Results	Tissue Results	Blood Results
77	47,XX,+2/46,XX[+]		46,XX
78	47,XX,+8/46,XX		47,XX,+8[11]/46,XX[19]
79	47,XX,+9/46,XX	lung, heart, brain, liver: 47,XX,+9[10]/46,XX[30]	
81	47,XX,+13/46,XX		46,XX
84	47,XY,+18/46,XY[+]	no growth	
90	47,XX,+21/46,XX[+]	47,XX,+21[32]/46,XX[18]	
91	47,XX,+21/46,XX[+]	no growth	46,XX
92	47,XX,+21/46,XX[+]		47,XX,+21[13]/46,XX[37]
93	47,XX,+21/46,XX	villi, kidney, lung: 47,XX,+21[11]/46,XX[29]	
96	45,X/46,XX[+]	46,XX	
97	45,X/46,XX[+]	45,X	
106	45,X/46,XX		46,XX
107	45,X/46,XX	villi: no growth	45,X[8]/46,XX[22]
108	45,X/46,XX		45,X[10]/46,XX[20]
110	45,X/46,XX		45,X[2]/46,XX[48]
112	45,X/46,XX	villi: 45,X	
114	45,X/46,XY	chorionic villi 45,X, lung 46,XY	
115	45,X/46,XY		46,XY
116	45,X/46,XY		45,X[3]/46,XY[56]
118	45,X/46,XY[+]	45,X[30]/46,XY[21]	45,X[1]/46,XY[49]
124	47,XXY/46,XY		47,XXY[6]/46,XY[15]
126	47,XYY/46,XY	villi: 47,XYY[7]/46,XY[3]	47,XYY[4]/46,XY[7]
128	47,XX,+mar/46,XX		47,XX,+mar[17]/46,XX[3].ish der(6)(D6Z1+,WCP6-)
129	47,XX,+mar/46,XX	twin A: 47,XX,+mar[20]/46,XX[20], twin B: no growth	47,XX,+mar[8]/46,XX[12].ish der(7)(wcp7+,7ptel-,D7Z1-, 7qtel-,ELN-,7p paint+)
132	45,X/47,X,inv(Y)(p11q12), +mar/46,XY[+]	45,X	45,X[9]/47,X,inv(Y)(p1.2q12),+ mar[7]/46,XY[4]
136	47,XY,+i(12)(p10)/46,XY	villi: 47,XY,+i(12p)(p10)[11] /46, XY[14], lung: 47,XY,+i(12p)(p10)[13] /46,XY[12]	
137	46,XY,der(13)t(13;?) /46,XY[+]	46,XY (one cell 45,X)	
141	45,X/46,X,psu idic (Y)(p11.32)		45,X[4]/46,X,psu idic(Y)(p11.32)[16]

[+]Previously reported in Thomas, 1998

In some cases that involved a marker chromosome or structural aberration, the parents had blood analysis to determine if the chromosome abnormality was inherited or *de novo*. The results from this testing are listed in Table 12.

Table 12. Parental Blood Analysis for Mosaic Amniocentesis Cases

Case	Amniocentesis Results	Maternal Karyotype	Paternal Karyotype
127	47,XX,+mar[5]/46,XX[40].ish der(22)	46,XX	46,XY
128	47,XX,+mar[44]/46,XX[6] -identified as 6 in origin	46,XX	46,XY
130	47,XX,+mar[10]/46,XX[5].ish inv dup(13)(p10)	46,XX	46,XY
131	47,XY,+mar[6]/46,XY[28].ish dup(21)(q11.2)	46,XX	46,XY
141	46,X,idic(Y)(q11.2)[9]/45,X[6]	46,XX	47,XYY

Of the 11 cases involving a marker chromosome or structural aberration, 5 (45.5%) had parental blood analysis. Four of these cases had normal results, but in case 141, the father had a 47,XYY karyotype.

4.4 UPD TESTING

UPD testing was also performed for 7 mosaic CVS patients (9.2%). These cases are listed in Table 13. All of the cases resulted in biparental inheritance.

Table 13. UPD Test Results

Case	CVS Result	Amnio Result	UPD Result
8	46,XX/48,XX,+2,+7	46,XX	biparental
9	46,XX/47,XX,+7	46,XX	biparental
11	46,XX/47,XX,+7	46,XX	biparental
22	46,XY/47,XY,+13	46,XY	biparental
23	46,XY/47,XY,+15	46,XY/47,XY,+15	biparental
24	46,XY/47,XY,+15	46,XY	biparental
25	47,XY,+16	46,XY	biparental

The frequency of each chromosome involved in UPD testing is indicated in Figure 3. Of note, a case with a 48,XX,+2,+7 CVS result was only tested for biparental inheritance of chromosome 7 (not chromosome 2).

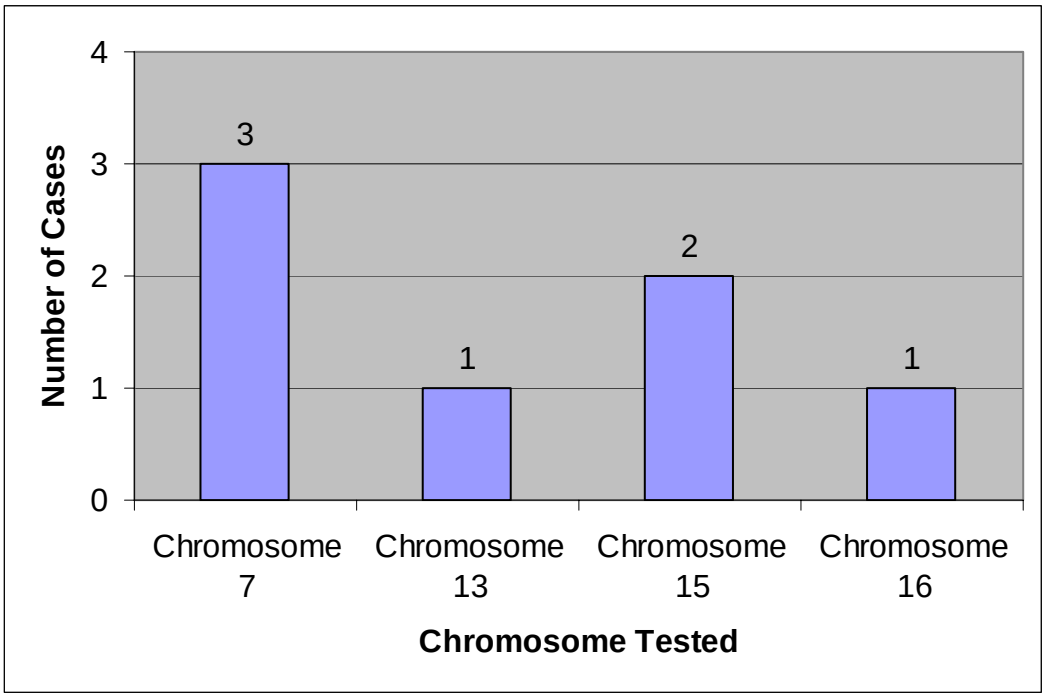


Figure 3. Frequency of UPD Testing by Chromosome

5.0 DISCUSSION

5.1 RATE OF MOSAICISM

To determine if the data from this study compared with literature, previous studies were reviewed. Thomas (1998) included many of these reports in her study, including information from Phillips et al. (1996), who reviewed thirteen studies on placental mosaicism detected by CVS. This information is contained in Table 14. Recent studies by Grati et al. (2006) and Stetten et al. (2004) were added to this information. Articles marked with the designation a, b, etc. indicate that the corresponding papers could contain some overlapping data. Of note, study 3 contains patients from studies 4a, 4b, 7a, 7b, 8, and 9.

Table 14. Review of Past Studies of CVS Mosaicism

#	Study-Author and Year	direct	cultured	# of cases	# of mosaics	% mosaicism
1a	Canadian Collaborative (1989)	yes	yes	947	19	2.00%
1b	*Teshima et al. (1992)	yes	yes	1,040	18	1.80%
2a	*Vejerslev and Mikkelsen (1989)	yes	yes	11,855	141	1.20%
2b	*Medical Research Party (1991)	yes	yes	1,102	18	1.63%
2c	Hahnemann and Vejerslev (1997)	yes	yes	92,246	1,415	1.50%
3	*Ledbetter et al. (1992)	yes	yes	11,436	108	0.94%
4a	Wapner, et al. (1992)	yes	yes	11,043	289	2.60%
4b	Johnson et al. (1990)	yes	yes	4,319	55	1.30%
5a	*ACC Collaborative (1994)	yes	yes	7,595	88	1.20%
5b	*Wolstenholme et al. (1994)	yes	yes	11,755	CPM 73	0.62%
6	*Wang et al. (1993)	yes	yes	2,612	56	2.10%
7a	Goldberg and Wohlferd (1997)	no	yes	11,200	140	1.30%
7b	*Hogge et al. (1986)	no	yes	1,000	12	1.70%
8	*Fryburg et al. (1993)	no	yes	1,724	20	1.16%
9	*Roland et al. (1994)	yes	yes	3,258	CPM 26	0.83%
10	*Smidt-Jensen et al. (1993)	yes	yes	2,928	30	1.02%
11	*Miny et al. (1991)	yes	yes	2,290	29	1.27%
12	*Callen et al. (1991)	yes	yes	1,312	20	1.52%
13	Breed et al. (1991)	yes	yes	2,103	26	1.20%
14	Phillips et al. (1996)	yes	yes	59,937	637	1.06%
15	Stetten et al. (2004)	yes	yes	4,000	38	0.95%
16	Grati et al. (2006)	yes	yes	15,109	273	1.81%
17	Magee-Womens Hospital (1991-2005)	no	yes	4,599	76	1.65%

*Studies reviewed by Phillips et al. (1996)

The percentage of mosaicism observed in the above CVS studies ranged from 0.62% (Wolstenholme et al., 1994) to 2.6% (Wapner et al., 1992). The mosaicism rate observed at Magee-Womens Hospital between the years of 1991 and 2005 was 1.65%. This number falls within the rate of mosaicism observed in literature.

Thomas (1998) also reviewed previous papers that observed mosaicism in amniocentesis samples. The data from these papers are listed in Table 15 along with the data from this study. As with Table 11, the a, b, and c designations refer to papers that could contain some overlapping data.

Table 15. Review of Past Studies of Amniocentesis Mosaicism

#	Study – Author and Year	# of amnios	# of level III mosaics	% mosaicism
1a	Worton and Stern (1984)	12,386	34	0.30%
1b	Canadian Collaborative (1989)	933	1	0.11%
1c	Teshima et al. (1992)	968	1	0.10%
2	Hsu et al. (1996)	179,663	555	0.30%
3	Smidt-Jensen et al. (1993)	1,075	1	0.10%
4	Magee-Womens Hospital (1991-2005)	15,688	59	0.38%

The percentage of mosaicism in the five articles reviewed ranged from 0.10% (Teshima et al., 1992; Smidt-Jensen et al., 1993) to 0.30% (Worton and Stern, 1984; Hsu et al., 1996). The rate of amniocentesis mosaicism observed in this study, excluding those referred for CVS mosaicism, was 0.38%. This rate is slightly higher than those observed in literature. However, it is closer to the rates associated with the larger studies (Worton and Stern, 1984; Hsu et al., 1996).

Fetal mosaicism in this study was seen in 23.6% of the CVS specimens that had follow-up cytogenetic testing and in 60.7% of amniocentesis specimens with follow-up. Previous studies have reported that fetal mosaicism is confirmed in approximately 10-20% of mosaic CVS cases and about 40% of amniocentesis cases (Smidt-Jensen, et al, 1993; Stetten et al., 2004; Hahnemann and Vejerslev, 1997; Smith et al., 1999). These studies looked at mosaicism detected by both direct and cultured CVS preparations. In addition, Ledbetter et al. (1992) studied mosaicism detected by only cultured CVS preparations and reported a 25% fetal mosaicism rate. Also, Hsu et al. (1997) reported that true mosaicism involving an autosome accounts for 44-47% of all mosaic cases detected in amiotic fluid. In our study, 55.6% of mosaic autosomal amniocentesis cases that had follow-up testing were found to be true mosaics. The

rates of fetal mosaicism in this study fall within the range of true fetal mosaicism detected by CVS reported in literature but are slightly higher than the reported rate detected by amniocentesis.

5.2 KARYOTYPE/PHENOTYPE CORRELATIONS

This study found mosaic results involving trisomy for chromosomes 2, 7, 8, 9, 10, 12, 13, 15, 16, 18, 20, 21, 22, X, and Y. In addition, there was monosomy for chromosomes 21, 22, and X, tetraploidy, structural aberrations, and supernumerary marker chromosomes. The percentage of each category of chromosome abnormality identified in CVS mosaic cases is listed in Table 16 and compared to the results reported by Phillips et al. (1996).

Table 16. Types of Chromosome Abnormalities Identified in Mosaic CVS Cases

Type of Mosaicism	Phillips et al. (1996)	Magee-Womens Hospital
Uncommon autosomal trisomies	40.1%	35.5%
Common autosomal trisomies (13, 18, 21)	16.8%	5.3%
Sex chromosome aneuploids	23.2%	22.4%
Marker chromosomes	6.4%	18.4%
Structural aberrations	7.5%	13.2%
Polyploidy	6.0%	3.9%
Monosomy		1.3%

When comparing our study to Phillips et a. (1996), there was a higher percentage of marker chromosomes and structural aberrations and a lower percentage of common trisomies. In studies by Grati et al. (2006) and Hahnemann and Vejerslev (1997), the most common of the autosomal trisomies included 2, 7, 13, 18, and 21. However, the most common autosomal trisomies in our study included 2, 7, 8, 9, 10, and 16.

Table 17 lists the percentage of each category of chromosome abnormality identified in amniocentesis mosaic cases and compares them to the results reported by Hsu et al. (1996).

Table 17. Types of Chromosome Abnormalities Identified in Mosaic Amniocentesis Cases

Type of Mosaicism	Hsu et al. (1996)	Magee-Womens Hospital
Autosomal numerical	26.5%	28.8%
Autosomal structural	10.3%	7.6%
Sex chromosome numerical	42.7%	47.0%
Sex chromosome structural	5.0%	6.1%
Marker	15.3%	10.6%

It has been estimated from previous studies that approximately 70% of mosaic autosomal trisomy cases detected in amniotic fluid involve chromosomes 13, 18, 20, and 21 (Wallerstein et al., 2000). The most common autosomal trisomies in our study were 18, 20, and 21, which is to be expected based on results from literature.

5.2.1 Trisomy 2

Complete trisomy 2 results in first trimester pregnancy loss and can only be compatible with life in a mosaic state that is predominantly confined to the placenta. Pregnancy outcome can range from normal to neonatal death and oligohydramnios and poor intrauterine growth are the most common features (Robinson, 2001). In most cases where trisomy is found by CVS but not by amniocentesis, the outcome is normal, but an abnormal outcome can occur. Shaffer et al. (1996) reported nine cases of confined placental mosaicism for trisomy 2. Of these cases, six had normal outcomes, two had intrauterine growth retardation (IUGR), and one was terminated and no outcome data was available. Although most of these cases had normal outcomes, Shaffer et al.

(1996) speculated that CPM for trisomy 2 may increase risk for IUGR. Trisomy 2 that is confined to the placenta is usually of mitotic origin, which explains the generally good outcome. Cases that have been associated with poor outcome were usually associated with maternal meiotic origin of trisomy (Wolstenholme, 1996).

Our study identified eight cases of trisomy 2 mosaicism by CVS. One of these cases (8) also showed trisomy 7 mosaicism. Of these cases, four (2, 4, 7, 8) were confirmed as confined to the placenta by follow-up testing while the other four (1, 3, 5, 6) had no further testing performed Case 6 was delivered by C-section at 36 weeks. This case also involved the spontaneous loss of a twin. Although one of the eight cases had pregnancy complications, none of the cases were noted to have IUGR or any other abnormalities. Also, it is possible that the presence of a second aneuploidy increased the risk for a pregnancy complication.

Abnormal outcome is more likely to occur when there are high levels of trisomy in the term placenta and there is a of low level trisomy in the fetus (Robinson, 2001). When trisomy 2 mosaicism is diagnosed by amniocentesis, the risk of poor outcome is much higher. A study by Hsu et al. (1997) suggested that an increased risk is associated with trisomy 2 mosaicism detected by amniocentesis. They identified 11 cases of trisomy 2 mosaicism detected in amniotic fluid. Of these cases, one resulted in a normal live birth, one resulted in a live birth with IUGR, four resulted in a live birth with IUGR and multiple anomalies, three resulted in stillbirths or intrauterine deaths, and two resulted in elective terminations due to abnormal findings. The one normal outcome had only four percent trisomy 2 cells in the amniocytes.

Our study identified one case of trisomy 2 mosaicism detected by amniocentesis. Blood analysis indicated a normal karyotype, but no pregnancy outcome information was available.

Information pertaining to the pregnancy would have been useful but accurate conclusions could not have been drawn based on one case.

To date, six cases of maternal UPD2 have been reported. Four of these cases have been associated with IUGR and varying abnormalities associated with oligohydramnios, but these outcomes are most likely explained by cryptic fetal mosaicism. The other two cases were found in healthy females. Based on these cases, it is unlikely that there is an imprinting effect associated with maternal UPD2. No cases of paternal UPD2 have been reported (Robinson, 2001). UPD2 testing was not performed for any of the cases identified in this study.

5.2.2 Trisomy 7

Complete trisomy 7 is not compatible with life, but it is one of the most common aneuploidies detected on CVS. As an example, Sachs et al. (1990) reported five cases of trisomy 7 mosaicism detected by CVS, and all five of these cases resulted in normal outcomes. Trisomy 7 that is confined to the placenta usually results from the somatic duplication of chromosome 7. The mitotic origin indicates a generally good outcome and a low risk for fetal UPD (Wolstenholme, 1996). Kalousek et al., (1996) reported 14 pregnancies with trisomy 7 mosaicism, which were identified by CVS. All of these cases were confirmed as CPM, and UPD7 was only present in one case, illustrating the relatively low occurrence of UPD7 associated with CPM.

Our study identified four cases of trisomy 7 mosaicism by CVS. One of these cases also involved trisomy 2 mosaicism, and another case also involved mosaicism for trisomy X. All four of these cases were confirmed as CPM by amniocentesis. None of these cases had significant pregnancy complications, which is to be expected based on reports from literature.

Studies have shown that CPM for trisomy 7 with biparental inheritance is not associated with adverse effects on fetal growth (Kalousek et al., 1996). However, maternal UPD7 is associated with severe growth restriction and is found in approximately 10% of cases with Russell-Silver syndrome. Several studies have also confirmed that postnatal growth restriction leading to short stature is also a finding of maternal UPD7 (Ledbetter and Engel, 1995; Kalousek et al., 1996). Three of the four cases involved in the study were tested for UPD7 and all three showed biparental inheritance.

Trisomy 7 detected by amniocentesis is generally associated with a good outcome. For example, Hsu et al. (1997) reported eight cases of trisomy 7 mosaicism detected in amniotic fluid. One case was found to have facial asymmetry, mild developmental delay and hypomelanosis of Ito at 7 years of age while the other seven cases resulted in normal live births. However, no cases of trisomy 7 mosaicism were identified in our study by amniocentesis so no correlations to previous data could be made.

5.2.3 Trisomy 8

Complete trisomy 8 results in early spontaneous pregnancy loss, but mosaic trisomy 8 is a well-described syndrome. The associated features are variable but may include mental retardation, dysmorphic facies, skeletal anomalies, congenital heart defects, and kidney malformations. Trisomy 8 that is confined to the placenta is relatively common and is generally of mitotic origin (Webb et al., 1998). In addition, cases involving CPM do not appear to present long-term consequences to the fetus (Saks et al, 1998). Saks et al., (1998) reported a case of what appeared to be confined placental mosaicism for trisomy 8 mosaicism. The pregnancy resulted in IUGR with catch-up growth during the neonatal period and the infant did not exhibit features of trisomy

8 mosaicism. Based on these findings and previous studies, they suggest that IUGR occurs commonly when type II CPM for trisomy 8 is present but postnatal growth and developmental are generally normal. In addition, a normal amniocentesis result after the identification of trisomy 8 mosaicism by CVS does not exclude the possibility of phenotypic and neoplastic consequences due to cryptic mosaicism. Chromosome 8 carries two oncogenes, c-myc and c-mos, which may account for the development of cancer among some patients with trisomy 8 mosaicism (Saks et al., 1998).

Our study identified three cases of trisomy 8 mosaicism by CVS. All three of these cases were confirmed as CPM by amniocentesis. None of these cases were reported to have features of trisomy 8 mosaicism, but they all had pregnancy complications. One case (13) had PROM and was induced at 21 weeks due to delayed fetal growth. This case resulted in neonatal death. Another case (14) was delivered prematurely by C-section at 34 weeks, and the last case (12) exhibited pre-eclampsia. PROM, prematurity, and pre-eclampsia were not commonly reported in reviewed literature and suggests that trisomy 8 CPM may increase risk for other pregnancy complications other than IUGR.

When trisomy 8 mosaicism is identified by amniocentesis, the resulting infant often appears normal. This is in part due to the fact that the clinical diagnosis of mosaic or non-mosaic trisomy is difficult in a newborn (and even more difficult in an aborted fetus) because abnormalities are usually subtle (Hsu et al., 1997). Hsu et al. (1997) reported 14 cases of trisomy 8 mosaicism detected in amniotic fluid. One case with 77% trisomy 8 cells was reported to be abnormal while the other 13 cases resulted in apparently normal terminations or live births. Ten of the 13 normal-appearing cases had follow-up cytogenetic testing which confirmed the

presence of trisomy 8 mosaicism. This study illustrates the importance of follow-up testing in cases of trisomy 8 so that a diagnosis will not be missed.

Our study identified one case (78) of mosaic trisomy 8 by amniocentesis, which contained 16.7% trisomic cells. No pregnancy complications were indicated but several abnormal features were reported. Ultrasound indicated increased nuchal translucency, mild ventriculomegaly, and mild hydronephrosis, which resolved. Features documented at five months of age included prominent pillars of philtrum, full lower lip, extra crease on both earlobes, and tall stature, but development was reported to be normal. Follow-up blood analysis confirmed the presence of mosaicism, which explains the mild features that are associated with trisomy 8 mosaicism. The fact that this child was examined a few months after birth most likely aided in the identification of subtle features.

There have been no reports of imprinted genes on chromosome 8 (Ledbetter and Engel, 1995). A case of paternal UPD8 and a case of maternal UPD8 have been reported, but they both had normal growth and development, making it unlikely that there are imprinted genes of major effect on chromosome 8 (Robinson, 2001). No cases of trisomy 8 in this study had UPD8 testing.

5.2.4 Trisomy 9

Trisomy 9 can occur in a mosaic or non-mosaic state and is characterized by growth retardation, mental retardation, congenital heart defects, kidney abnormalities, skeletal abnormalities, and distinct facial features (Arnold et al, 1995). In most cases where trisomy 9 is detected by CVS but not by amniocentesis, the outcome is normal, but an abnormal outcome can occur (Robinson,

2001). Confined placental mosaicism for trisomy 9 is generally of mitotic origin, which is more commonly associated with a good outcome (Wolstenholme, 1996).

Our study identified three cases (15, 16, 17) of trisomy 9 mosaicism by CVS. All of these cases were found to be CPM through follow-up cytogenetic testing. One case was electively terminated while the other two cases resulted in apparently normal live births. Although there were few cases, the generally good outcome supports findings in previous studies.

When trisomy 9 is detected by amniocentesis, the risk for an abnormal outcome is much higher. This statement is supported by Hsu et al (1997). In their study, they observed 25 cases of trisomy 9 mosaicism detected in amniotic fluid. Of those cases, 14 resulted in abnormal offspring (eight had multiple congenital anomalies, seven had facial dysmorphism, four had congenital heart disease, three had urogenital abnormalities, three had skeletal problems, and three had IUGR).

In our study, one case (79) was reported to have trisomy 9 mosaicism identified in amniotic fluid. This case was electively terminated. However, ultrasound indicated a Dandy Walker formation, and tissue analysis confirmed fetal mosaicism. Even though there was only one case, the observation of an anomaly on ultrasound further supports the increased risk for abnormalities when trisomy 9 mosaicism is present in amniotic fluid.

Based on cases reported to date, it is unlikely that chromosome 9 is associated with imprinting effects (Ledbetter and Engel, 1995). None of the cases in this study with trisomy 9 mosaicism had follow-up UPD testing.

5.2.5 Trisomy 10

Complete trisomy 10 is rare and lethal. There have been five cases reported of liveborn children with trisomy 10 mosaicism, and in all cases, the outcome was abnormal (Robinson, 2001). Knoblauch et al (1999) suggested that common clinical features include growth retardation, feeding problems, failure to thrive, distinct facial features, high arched palate, a long slender trunk, cardiac defects, renal, skeletal and central nervous system (CNS) abnormalities, and early death.

Three cases (18, 19, 20) of trisomy 10 mosaicism were observed in our study. One of these cases (20) resulted in IUFD at 14+ weeks. The other two cases resulted in apparently normal live births. One case (18) was confirmed as confined to the placenta by further testing and features noted at birth included mild hypotelorism, epicanthal folds, and a single palmar crease. However, these features were felt to be familial. The second case did not have further testing.

Trisomy 10 mosaicism is not often found in amniotic fluid. For instance, Hsu et al. (1997) did not identify any cases of trisomy 10 mosaicism in a large case report of chromosomal mosaicism detected by amniocentesis. In our study, no cases of trisomy 10 mosaicism were detected in amniotic fluid.

One case of maternal UPD10 has been reported with no apparent imprinting effect (Ledbetter and Engel, 1995). UPD testing was not performed for any of the trisomy 10 mosaic cases in this study.

5.2.6 Trisomy 12

The majority of cases of trisomy 12 detected prenatally have had normal outcomes (Robinson, 2001). Data suggests that trisomy 12 is often of mitotic origin, which, again, may explain the good outcome (DeLozier-Blanchet et al., 2000). However, the possibility of neoplastic consequences may exist since trisomy 12 is the most frequent chromosomal abnormality in chronic lymphocytic leukemia, which is also of mitotic origin (DeLozier-Blanchet et al., 2000). Our study identified one case (21) of trisomy 12 mosaicism by CVS. This case was found to be confined to the placenta, and the pregnancy resulted in an apparently normal live birth, which is expected based on previous case reports.

Abnormal outcomes were observed in 6 of 23 (26.1%) cases of trisomy 12 detected in amniotic fluid in a large study by Hsu et al (1997). Of these cases, 10 resulted in live births (three had abnormal findings including congenital heart defects and digit anomalies), two ended in fetal demise (one was associated with IUGR) and 11 pregnancies were terminated (one was reported to have facial dysmorphism and multiple anomalies on autopsy). Based on this information, they suggest that a diagnosis of trisomy 12 mosaicism in amniotic fluid should not be taken lightly because the risk of abnormality is significant. Our study identified one case (80) of trisomy 12 mosaicism by amniocentesis. However, no pregnancy outcome information was available and no follow-up testing was performed. Therefore, no correlation to previous studies could be made.

There have been no reports of imprinted genes on chromosome 12 (Ledbetter and Engel, 1995). UPD12 testing was not performed for any of the trisomy 12 mosaicism cases observed in this study.

5.2.7 Trisomy 13

Trisomy 13 occurs in approximately 1 in 10,000 live births with mosaic trisomy 13 accounting for approximately 5% of these cases (Eubanks et al., 1998). Individuals with mosaic trisomy 13 may present with clinical findings ranging from severe mental retardation and multiple congenital anomalies to milder mental retardation and physical features. Prenatal detection of mosaic trisomy 13 most often represents confined placental mosaicism but true mosaicism is possible (Delatycki et al., 1998). As an example, Hahnermann and Vejerslev (1997) reported 15 cases of trisomy 13 mosaicism detected on CVS. Of these cases, 13 were confined to the placenta and resulted in normal outcomes and two were confirmed in the fetus.

Our study identified one case (22) of trisomy 13 mosaicism by CVS. Follow-up amniocentesis indicated that it was confined to the placenta, and the pregnancy resulted in a normal live birth. The infant was reported to appear normal at two months of age. This outcome further confirms previous studies.

When trisomy 13 cells are detected in amniotic fluid, it is difficult to predict the severity of outcome. Wallerstein et al (2000) reported 25 cases of trisomy 13 mosaicism diagnosed by amniocentesis with 10 cases resulting in an abnormal outcome. Of these cases, five had multiple congenital anomalies, two had IUGR, and three died in utero. In addition, Delatycki et al (1998) reported six cases of trisomy 13 mosaicism detected by amniocentesis with two cases confirmed in the fetus. Both cases presented with low-level fetal mosaicism with no major phenotypic effects. The range of clinical severity most likely depends on the proportion of trisomy 13 cells and the way they are distributed throughout the body. However, based on previous reports, there appears to be a poor correlation between the level of abnormal cells in peripheral blood analysis and the severity of clinical outcome.

In our study, one case (81) of trisomy 13 mosaicism was identified by amniocentesis. The result was an apparently normal live birth, and blood analysis indicated a normal karyotype. Because outcome can vary and there was only one case, it is difficult to correlate this result to previous studies.

Neither maternal nor paternal UPD13 is associated with an abnormal phenotype so it is unlikely that chromosome 13 is associated with imprinting effects (Ledbetter and Engel, 1995). UPD testing was performed for one case of trisomy 13 mosaicism that was originally detected by CVS. The results indicated biparental inheritance.

5.2.8 Trisomy 15

Complete trisomy 15 is a lethal abnormality. Trisomy 15 mosaicism detected by CVS is most likely confined to the placenta and associated with a normal outcome (Robinson, 2001). Our study identified two cases (23 and 24) of trisomy 15 mosaicism by CVS. For one case (24), amniocentesis indicated that the mosaic cells were confined to the placenta, but pregnancy outcome information was not available. The other case (23) had follow-up amniocentesis, which further confirmed mosaicism. This case resulted in PROM and preterm delivery at 34 weeks. It is possible that the pregnancy complications seen in this case were due to the trisomy 15 mosaicism.

True fetal mosaicism for trisomy 15 is rare, but it is associated with a high risk for developmental abnormalities when present (Robinson 2001). Hsu et al. (1997) reported 11 cases of trisomy 15 mosaicism detected by amniocentesis. Of these cases, four resulted in normal live births, one was born at term with IUGR and multiple heart defects and died at 13 days, and six were terminated (five of these cases had abnormalities). A higher percentage of abnormal cells

in amniotic fluid appeared to correlate with a worse outcome. No cases in this study were identified by amniocentesis, but as previously mentioned, one case was identified by CVS and further confirmed by amniocentesis. No other testing was performed and no abnormalities were reported.

Imprinting defects are known for both maternal and paternal UPD15. Therefore, UPD studies are always suggested when trisomy 15 mosaicism is detected prenatally. Maternal UPD15 is associated with Prader Willi syndrome, and paternal UPD15 is associated with Angelman syndrome. Trisomy 15 mosaicism is usually due to a maternal meiosis error so maternal UPD15 is of greater concern. Both cases of trisomy 15 mosaicism observed in this study had UPD testing and both showed biparental inheritance.

5.2.9 Trisomy 16

Trisomy 16 is the most commonly occurring trisomy in humans and is thought to occur in more than 1% of clinically recognized pregnancies. Complete trisomy 16 usually results in spontaneous abortion during the first trimester. Therefore, when trisomy 16 is diagnosed prenatally in a normally developing fetus, it is almost always mosaic (Robinson, 2001). In most cases of trisomy 16 diagnosed by CVS, the outcome will be good even if the placenta indicates complete trisomy. Adverse outcome is more common when trisomic cells are seen in amniotic fluid. The most common complication when trisomy 16 is diagnosed prenatally is IUGR. Other risks include fetal malformations, maternal hypertension, and fetal or neonatal death. Malformations that have been associated with trisomy 16 include heart defects, hypospadias, two vessel cord, clinodactyly, and pulmonary hypoplasia. There is also an increased risk for preterm delivery (Yong et al., 2003).

Langlois et al. (submitted 2005) compiled follow-up information for 36 cases of trisomy 16 mosaicism detected on CVS or amniocentesis. Of these cases, 20 were diagnosed by CVS (with normal or unknown amniocentesis result) and showed normal development. In addition, catch-up growth was noted in most cases with IUGR. Of sixteen cases diagnosed by amniocentesis, four cases showed global developmental delay and more than one major malformation.

In our study, three cases (25, 26, 27) of trisomy 16 mosaicism were identified by CVS. For one of these cases (26), amniocentesis further confirmed the mosaic karyotype. The patient electively terminated, and tissue analysis confirmed the presence of mosaicism in the fetus. The other two cases had follow-up cytogenetic testing, which confirmed that the mosaicism was confined to the placenta. One case (25) was complicated by pre-eclampsia, IUGR, and preterm delivery at 33+ weeks. No other cases of trisomy 16 mosaicism were identified in amniotic fluid. The fact that both cases of trisomy 16 CPM resulted in pregnancy complications supports the findings of previous studies.

Almost all cases of trisomy 16 mosaicism result from an error in maternal meiosis. Fetuses with UPD16 tend to be smaller at birth than fetuses with biparental inheritance, but trisomy 16 in the placenta seems to have an adverse effect on growth even in the absence of UPD. Therefore, the consequences of UPD16 are not yet clear (Yong et al, 2003). One case (25) of trisomy 16 mosaicism identified in this study had follow-up UPD16 testing. Thomas (1998) reported that this case indicated biparental inheritance and resulted from an error of maternal meiosis.

5.2.10 Trisomy 18

Trisomy 18 is one of the few trisomies that can survive to term in a non-mosaic state. As a result, when trisomy 18 is diagnosed prenatally, the risk for true mosaicism is greater than for other trisomies. However, trisomy 18 can be confined to the placenta and result in a normal birth (Robinson, 2001). For example, Smith et al. (1999) reported 19 cases of mosaic trisomy 18 detected on CVS of which five were confirmed in the fetus. In 11 cases of presumed confined placental mosaicism, one pregnancy was terminated, one outcome was unknown, and nine resulted in normal live births.

Two cases (28 and 29) of trisomy 18 mosaicism were identified by CVS in our study. Both had normal karyotypes in amniotic fluid and resulted in live births. One case (29) was noted to have increased nuchal translucency on ultrasound, which resolved, and was delivered prematurely by C-section at 27+ weeks. It is possible that the increased nuchal translucency could have been due to low level mosaicism that was not detected by amniocentesis.

In a study by Wallerstein et al. (2000), it was found that 54% of cases, involving trisomy 18 mosaicism detected in amniotic fluid, resulted in an abnormal outcome, including phenotypic abnormalities, IUGR, or fetal demise. They reported 31 cases of trisomy 18 mosaicism detected by amniocentesis. Of these cases, three resulted in normal live births, 11 resulted in normal abortions, and 17 resulted in abnormal abortions. Of the abnormal cases, 10 were reported to have multiple congenital anomalies, two had dysmorphic facies, three resulted in unexplained intrauterine fetal death (IUFD), and two had IUGR. The risk of abnormal outcome increased with detection in fetal blood.

In our study, two cases (84 and 85) of trisomy 18 mosaicism were detected in amniotic fluid. One case (84) was terminated, and although there was follow-up tissue analysis, the cells

did not grow. This case was reported to have choroids plexus cysts on ultrasound. The other case (85) was reported to have cystic hygroma on ultrasound, but pregnancy outcome could not be obtained. In addition, no further cytogenetic testing was performed. These cases do not provide much information. However, cystic hygroma is associated with trisomy 18 and may indicate some level of trisomy 18 mosaicism in the fetus.

To date, there have been no reports of imprinted genes on chromosome 18 (Ledbetter and Engel, 1995). None of the trisomy 18 mosaicism cases in this study had follow-up UPD18 testing.

5.2.11 Trisomy 20

Complete trisomy 20 is not viable, and trisomy 20 mosaicism detected by CVS is rare. Trisomy 20 mosaicism is more often detected in direct CVS analysis than in CVS cultures, and the amniocentesis result and pregnancy outcome is generally normal in these cases (Robinson, 2001).

One case (27) of trisomy 20 mosaicism was observed in our study, and trisomy 16 mosaicism was also present. This pregnancy resulted in an apparently normal live birth. Blood and tissue analysis indicated normal karyotypes.

Trisomy 20 is one of the more common mosaic trisomies detected by amniocentesis. When trisomy 20 mosaicism is detected in amniotic fluid, the outcome is normal in 90-95% of cases. Abnormal outcomes that have been reported include unexplained fetal demise, IUGR, and multiple congenital anomalies (Robinson, 2001). Wallerstein et al. (2000) reported 152 cases of trisomy 20 mosaicism detected in amniotic fluid. Of these cases, 10 (6.5%) had abnormal outcomes, including IUGR, IUFD, hypotonia, multiple congenital anomalies, CNS

abnormalities, facial dysmorphism, failure to thrive, and developmental delay. Robinson et al. (2005) reported six additional cases of trisomy 20 mosaicism. Four cases with low levels of trisomy in amniotic fluid were associated with a normal outcome while the other two cases had high levels of trisomy in amniotic fluid and had abnormal outcomes (one had developmental delay and the other was a stillbirth with IUGR and severe oligohydramnios). The study also further confirmed an association between the level of trisomy and outcome, citing only 4% abnormal outcomes when less than 40% trisomic cells were observed.

Our study identified three cases (86, 87, 88) of trisomy 20 mosaicism in amniotic fluid. None of these cases had follow-up cytogenetic testing. Two of these cases (86 and 87) resulted in apparently normal live births while pregnancy outcome was not available for the third case (88). However, case 87 had a low birth weight so the possibility of IUGR is present and case 88 was reported to have short limbs and duodenal atresia on ultrasound. The fact that pregnancy complications and abnormalities were found for two of the three cases indicates that there is a possible risk for adverse outcome.

UPD20 appears to be rare in trisomy 20 mosaicism. Due to the limited number of reported cases, a conclusion has not been made concerning the possible imprinting effects (Robinson et al., 2005). However, it is thought that maternal imprinting may be associated with parathyroid hormone resistance and paternal imprinting may be necessary for embryofetal neurological development (Engel, 2003). None of the trisomy 20 mosaicism cases in this study had follow-up UPD testing.

5.2.12 Trisomy 21

Trisomy 21 (Down syndrome) is the most common chromosome abnormality among live births with an incidence of 1 in 800. In general, the features of mosaic Down syndrome are similar to those of full Down syndrome. Features tend to be milder, but the effects can vary depending on the level and distribution of trisomic cells. Therefore, individuals may range from normal to having a full expression of Down syndrome. Associated characteristics include mental retardation, distinctive dysmorphic facial features, cardiac anomalies, and duodenal atresia. In addition, generalized edema may be identified prenatally (Robinson, 2001). It has been difficult for studies to predict the outcome of prenatally diagnosed trisomy 21 mosaicism since most pregnancies are terminated. For instance, Sachs et al. (1990) reported four cases of trisomy 21 mosaicism detected by CVS. All four pregnancies were terminated and mosaic trisomy 21 was confirmed in fetal tissue.

In our study, one case (30) of complete trisomy 21 that was mosaic for monosomy X was identified by CVS. This case was terminated and the karyotype was confirmed in fetal tissues. No other information was available.

Wallerstein et al. (2000) identified 97 cases of trisomy 21 mosaicism detected by amniocentesis and 49 (51%) had abnormal outcomes. Of these cases, two resulted in normal live births, 41 resulted in therapeutic abortions that appeared normal, six resulted in abnormal live births, and 43 resulted in abortions that appeared abnormal. Of the six abnormal live births, five cases had Down syndrome facies and associated findings and one had an isolated congenital heart defect. Of the 43 abnormal abortions, 18 cases had Down syndrome facies, 15 had multiple congenital anomalies, five resulted in IUFD, four had IUGR, and one had an isolated congenital heart defect. This study further illustrates the high proportion of pregnancy

terminations associated with a trisomy 21 result and also indicates that the majority of cases detected by amniocentesis are associated with some features of Down syndrome.

Six cases (89-94) of trisomy 21 mosaicism detected by amniocentesis were observed in our study. Three of these cases (90, 92, 93) had results that were confirmed in the fetus by follow-up cytogenetic testing while one (91) was not found in the fetus and two (89, 94) did not have further testing. Two cases (90 and 93) were terminated, and one (90) was reported to have a Simian crease on pathology report. The other four cases resulted in live births. One (89) was reported to have Down syndrome but no specific features were documented. One (92) had distal axial triradii, and another (94) had increase nuchal translucency on ultrasound. One case (91) had no documented features of Down syndrome. These results illustrate the range of clinical outcomes that can be seen with mosaic trisomy 21.

Uniparental disomy for chromosome 21 is not thought to have any phenotypic effect (Robinson, 2001). None of the cases in this study involving trisomy 21 had follow-up UPD21 testing.

5.2.13 Trisomy 22

Trisomy 22 is the second most common autosomal trisomy found among spontaneous abortions, accounting for 3-5%. Complete trisomy 22 may survive to birth, but it is very rare (Robinson, 2001). Clinical findings that are associated with complete trisomy 22 include IUGR, microcephaly, hypertelorism, epicanthal folds, hypoplastic or low-set ears, midface hypoplasia, hypoplastic distal phalanges, and genitalia anomalies in males (Bacino et al., 1995). Other reported findings include cleft palate, cardiac and/or renal anomalies and anal atresia/stenosis. When prenatally diagnosed mosaic trisomy 22 is confined to the placenta, the outcome can be

normal, but there is a risk for low birth weight. The outcome is variable when confirmed in the fetus. The behavior of trisomy 22 CPM appears to be similar to trisomy 16 CPM (Robinson, 2001).

Seven cases of trisomy 22 mosaicism detected by CVS with low or absent levels of trisomy in follow-up amniocentesis have been reported to date. Of these, three cases had a normal outcome, three had IUGR, and one had IUGR and some anomalies. All of the cases were of maternal meiotic origin (Robinson, 2001). One case (31) of trisomy 22 mosaicism was detected by CVS in our study. Follow-up amniocentesis indicated a normal karyotype, but pregnancy outcome information could not be obtained.

Six cases of mosaic trisomy 22 detected in amniotic fluid have been reported in literature. IUGR was common but four of the six cases were not reported to have any obvious anomalies at birth (Robinson, 2001). No cases of trisomy 22 mosaicism detected by amniocentesis were identified in our study.

UPD22 is not known to be associated with imprinting effects, and maternal UPD22 has been found in normal individuals. It should be noted, however, that all five cases of maternal UPD22 associated with trisomy detected prenatally or at birth did have low birth weight (Robinson, 2001). UPD testing was not performed for the trisomy 22 mosaic case in our study.

5.2.14 Trisomy X/Y

A small number of 47,XXX, 47,XXY, and 47,XYY cases have been detected by CVS and confirmed in fetal tissues, and follow-up information is limited. Information pertaining to the outcome of mosaic CVS cases is also limited, especially for 47,XYY mosaicism (Smith et al., 1999). Smith et al. (1999) confirmed 47,XXX mosaicism for 2 of 4 cases and 47,XXY

mosaicism for 1 of 3 cases. Sex chromosome abnormalities that are confined to the placenta have not been closely associated with adverse pregnancy outcome (Wolstenhome et al., 1994).

Our study included three cases (47-49) with a 47,XXY/46,XY result by CVS. All three cases were confirmed in the fetus by follow-up cytogenetic testing and resulted in normal live births. However, one case (48) was complicated by a persistent fetal intraabdominal cyst and fetal tachycardia. One case with a 48,XXX,+7/46,XX CVS result was also observed. As previously mentioned, amniocentesis indicated a normal karyotype, and the pregnancy resulted in a live birth.

In addition, four (120, 121, 124, and 125) cases with a 47,XXY/46,XY result were identified by amniocentesis. One of these cases (124) was confirmed in the fetus by blood analysis while the other three did not have follow-up testing. Three (120, 121, and 124) cases resulted in apparently normal live births while pregnancy outcome information was not available for the third case. One case of 47,XYY/46,XY (126) was also detected in amniotic fluid. This case was one of twins, and the mother did not want to know which twin was affected. Follow-up blood analysis confirmed the presence of mosaicism in the fetus. The pregnancy resulted in preterm delivery at 35+ weeks, but both twins were reported to appear normal. The preterm delivery could have been the result of a twin pregnancy (twin pregnancies have a tendency to deliver prematurely). These results indicate that trisomies involving choromosomes X and Y tend to have good outcomes. However, complications could still present at puberty so follow-up testing would be helpful.

5.2.15 Monosomy 21

Nine cases of monosomy 21 have been described to date. Of these cases, six resulted in live births and three were spontaneously aborted. However, many of these cases were reported in the late 1970's and early 1980's when banding techniques were not as high quality. It is possible that some of these cases were chromosome 21 translocations instead of true monosomy 21 (Robinson, 2001). One case (95) of monosomy 21 was detected by amniocentesis in this study. No follow-up testing was performed and no pregnancy outcome information was available.

5.2.16 Monosomy X

45,X (Turner syndrome) is a common cause of early pregnancy loss, accounting for about 7%, and is present in 1-2 per 10,000 live births. Approximately 30% of Turner syndrome patients are mosaic with a 45,X cell line and either a normal cell line or one containing a rearranged X chromosome (Hook and Warburton, 1983). Individuals with mosaic monosomy X will generally have a milder phenotype than those with complete monosomy X. It has been determined that the monosomy X is maternally derived in 80% of cases (Robinson, 2001).

Sachs et al. (1990) reported seven cases of monosomy X mosaicism detected by CVS. Six cases involved a normal female cell line and one involved a normal male cell line. Of these cases, six resulted in normal outcomes and one was terminated due to lack of growth. This study indicates that the detection of monosomy X mosaicism by CVS is generally associated with a good outcome.

Nine cases (33-41) with a 45,X/46,XX CVS result were observed in our study. Six of these cases (33, 34, 35, 37, 38, and 41) resulted in apparently normal live births, two (36 and 40)

resulted in spontaneous abortions, and one (39) pregnancy was terminated. Six of the nine cases had follow-up cytogenetic testing. Four (33, 34, 35, 36) were found to have normal karyotypes while two cases (40 and 41) showed confirmed mosaicism in the fetus. No features of Turner syndrome were reported for either of these cases. One case (76) of 45,X/46,X,+i(X)(q10) was also observed. This case was terminated and no follow-up testing was performed. Five cases (42-46) with a 45,X/46,XY CVS result were also observed in this study. One case (46) had a follow-up amniocentesis, which indicated a normal karyotype. The other cases did not have follow-up testing. All five cases resulted in apparently normal live births. These results also indicate that mosaicism involving monosomy X that is detected by CVS will most likely have a normal result.

Eighteen cases (96-113) with a 45,X/46,XX result, detected by amniocentesis, were also observed in this study. Of these cases, nine resulted in live births, one (97) resulted in a 20 week fetal demise, one (109) was terminated, two (101 and 102) were still in utero as of March 25, 2006, and pregnancy information was not available in five cases (96, 98, 99, 104, and 111). Of the nine liveborn cases, three had pregnancy complications and/or abnormalities. One case (100) reportedly had coarctation of the aorta, and another case (107) was reported to have a diaphragmatic hernia, mild edema, hyperconvex nails, and posteriorly rotated ears. Also, case 113 was induced because of hypertension, indicating the possibility of the beginnings of pre-eclampsia. In addition, case 97, which resulted in fetal demise, was reported to have cystic hygroma on ultrasound. Seven of the eighteen cases had follow-up testing. Two (96 and 106) indicated a normal karyotype, two (97 and 112) indicated a 45,X karyotype, and three (107, 108, 110) confirmed a mosaic karyotype. Although information was unavailable for several patients, these results show that a 45,X/46,XX karyotype detected in amniotic fluid can often result in

pregnancy complications and features of Turner syndrome. Complications could also occur at puberty so follow-up evaluations would provide more information for these outcomes.

Five cases (114-118) with a 45,X/46,XY amniocentesis result were also observed. Of these cases, three (115, 116, and 118) resulted in apparently normal live births, one (114) was terminated, and one (117) had no available pregnancy outcome information. One (115) of the liveborn cases was reported to have choroid plexus cysts and normal genitalia on ultrasound. Four cases had follow-up cytogenetic testing. Testing indicated a normal karyotype for two cases (114 and 115) and a mosaic karyotype for the other two cases (116 and 118). A case (142) with a 45,X/46,X,i(Y)(p10) result was also observed. Increased nuchal translucency was documented on ultrasound, and it resulted in an apparently normal live birth. These results indicate a generally good outcome for 45,X/46,XY mosaic cases. However, problems may develop at puberty so a follow-up would be helpful for further information.

5.2.17 Structural Aberrations

True mosaicism involving autosomal structural aberrations other than small supernumerary chromosomes is rare but does occur. These cases account for approximately 10% of all prenatally diagnosed cases of chromosome mosaicism (Hsu et al., 1996). Clinical implications vary depending on the type of structural abnormality. Hsu et al. (1996) studied various types of autosomal structural aberrations detected in amniotic fluid. From their data, they made several karyotype – phenotype correlations. Their data indicated that mosaic cases for a balanced structural rearrangement, including reciprocal translocations, Robertsonian translocations, and inversions, were usually associated with a normal phenotype. This was not true for cases of mosaicism involving an unbalanced structural abnormality. The overall risk for an abnormal

outcome in an case with an unbalanced structural abnormality (excluding those involving i(20q) and +i(12p)) was estimated to be 40.4%. All cases involving i(20q) resulted in a normal outcome, and almost all cases involving +i(12p), which is associated with Pallister-Killian syndrome, were associated with an abnormal outcome.

In our study, nine cases involving autosomal structural abnormalities were observed by CVS. One of these cases (67) was a balanced reciprocal translocation. This case had a normal karyotype in amniotic fluid and resulted in a normal live birth. The other eight cases had unbalanced structural aberrations and of these cases, seven had follow-up cytogenetic testing. Four cases (68, 70, 72 and 74) had normal karyotypes, two (69 and 71) had confirmed mosaicism, and one case (73) indicated complete structural aberration. Four cases resulted in normal live births, one (73) was electively terminated, and two had pregnancy complications and/or reported anomalies. One case (71) resulted in preterm delivery at 22 weeks and neonatal death shortly after birth. The mosaic karyotype was confirmed by amniocentesis and tissue analysis, and the fetus was reported to have dysmorphic features consistent with Pallister-Killian syndrome. Another case (70) was reported to have increased nuchal translucency on ultrasound. This patient is still pregnant so it is not known if there will be pregnancy complications.

Of the amniocentesis cases in this study, three had autosomal structural aberrations and all were unbalanced. Two of the cases were terminated (136 and 137) and one case (134) did not have available pregnancy outcome information. For case 136, ultrasound indicated a diaphragmatic hernia and tissue analysis confirmed the mosaic karyotype in the fetus. This case was considered to be consistent with Pallister-Killian syndrome. For case 137, no abnormalities were reported and tissue analysis indicated a normal karyotype. These results support the finding that unbalanced structural rearrangements are more likely to cause complications than

balanced rearrangements when mosaicism is diagnosed prenatally. However, an unbalanced rearrangement can result in a normal outcome, particularly if the aberration is confined to the placenta.

5.2.18 Supernumerary Markers

A marker chromosome is a structurally abnormal chromosome that cannot be identified by routine cytogenetics, and examples include unidentified rings, derivatives, dicentrics, and minute chromosomes. The risk for phenotypic abnormalities due to a marker chromosome depends on inheritance, mode of ascertainment, chromosomal origin, and the morphology, content, and structure of the marker. When markers are inherited directly from a phenotypically normal parent, there are usually no phenotypic consequences, but there can be exceptions, such as imprinting effects from UPD or low-level, tissue-specific mosaicism for the marker in a parent without phenotypic manifestations (Graf et al., 2005).

The first major study to offer general risk figures for marker chromosomes was conducted by Warburton (1991). This study suggested, based on 133 prenatal cases involving marker chromosomes, an overall risk of 13% for phenotypic abnormalities in prenatally obtained *de novo* cases of supernumerary marker chromosomes. However, fluorescence in situ hybridization (FISH) technology was not available at the time, which limited their ability to fully characterize the markers. A later study by Crolla (1998) confirmed that most marker chromosomes originate from acrocentric chromosomes (13, 12, 15, 21, and 22), and that these cases were much less likely to be associated with a phenotypic abnormality.

In a recent study by Graf et al. (2005), the risk for a phenotypic abnormality was estimated to be 26% for a *de novo* supernumerary marker diagnosed prenatally with no other

defining information. This risk was reduced to 18% if high resolution ultrasound studies were normal. In addition, the study revealed that there is a 4% risk for phenotypic affects in pregnancy if one of the parents was found to have the marker chromosome (in a non-mosaic state).

In our study, 14 cases involving supernumerary marker chromosomes were detected by CVS. Ten of these cases were apparently *de novo* with no identified origin. Eight of these cases resulted in apparently normal live births (although one had increased nuchal translucency on ultrasound), one resulted in a live birth that delivered prematurely at 29 weeks and was complicated by chorioamnionitis, and one was electively terminated. Five of these cases had follow-up cytogenetic testing which revealed a normal karyotype while the other five cases had no additional testing. Two additional cases, which were also detected by CVS, were later confirmed in amniotic fluid and the chromosome origin was determined (derivatives of 17 and Y). Both cases resulted in apparently normal live births. Lastly, two cases identified by CVS were determined to be of maternally inherited. One resulted in an apparently normal live birth while pregnancy information was not available for the second. Neither had additional testing.

In addition, this study observed six cases involving supernumerary markers, which were diagnosed by amniocentesis. One case (132) also involved mosaicism for monosomy X. This case resulted in a live birth that was noted to have mild edema of the hands and feet. Blood analysis confirmed the mosaic karyotype while tissue indicated a 45,X karyotype. Two cases involved markers that were identified (inv dup(13)(p10) and dup(21q11.2)). One resulted in a live birth with no documented anomalies (inv dup(13)(p10)) and there was no pregnancy outcome information available for the second. Neither case had follow-up cytogenetic testing. The chromosomal origins were determined for the three remaining cases. One case was derived

from chromosome 22. No pregnancy outcome information was available and no follow-up cytogenetic testing was performed. A second case was derived from chromosome 6. This case resulted in a live birth with normal appearance and development reported at 15 months of age. The third case was derived from chromosome 7 and was terminated. Before termination, the placenta was documented to have ruptured membranes and both twins, who were monochorionic, had abnormalities. One twin (the "pump twin") had a hypoplastic left heart and left lung aplasia while the second twin (the "acardiac twin") was noted to be amorphous. Fetal mosaicism for these last two cases was confirmed in follow-up testing.

The results from our study seem to show an overall good outcome for prenatally diagnosed marker chromosomes, especially when they are confined to the placenta. However, abnormal outcome associated with a chromosome 7 marker shows that the effects from marker chromosomes can be quite severe.

5.2.19 Tetraploidy

It is not uncommon to detect tetraploid cells in prenatal diagnosis. These cases are generally considered to be at no increased risk for adverse outcomes and are not reported. Therefore, there are very few clinical reports of individuals with tetraploidy mosaicism, and they were most likely reported when abnormalities were present (probably by coincidence) (Robinson, 2001). Two cases (64 and 65) with a 92,XXXX/46,XX result were detected by CVS in this study. One of these cases resulted in spontaneous abortion, and tissue analysis indicated a normal karyotype. The other case resulted in an apparently normal live birth that delivered prematurely at 36+ weeks. One case (66) with a 92,XXYY/46,XY result was also detected by CVS. This case had a follow-up amniocentesis with a normal karyotype and resulted in an apparently normal live birth.

No tetraploid cases were observed by amniocentesis. These results further support that tetraploidy that is confined to the placenta generally has a normal outcome. However, one of our cases was delivered prematurely, may or may not be due to tetraploidy mosaicism.

5.3 SUMMARY

One specific aim of this study was to review cases of mosaicism and uniparental disomy (UPD) detected by chorionic villus sampling (CVS) and amniocentesis performed during the time period 1991-2005 to determine if rates of mosaicism and true fetal mosaicism correlate with literature. The CVS cases had a mosaicism rate of 1.65%, and the amniocentesis results had a mosaicism rate of 0.38%. Both rates were comparable to those reported in previous studies. The rate of true fetal mosaicism for CVS cases was 23.6% and was 60.7% for amniocentesis cases. Both of these rates are also comparable to literature.

Another specific aim was to evaluate follow-up information obtained through Magee-Womens Hospital, including pregnancy outcome, pregnancy complications, abnormal characteristics, and additional testing. This information was obtained through the GIS database and by calling the offices of patients' gynecologists/obstetricians. Pregnancy outcome information was obtained for 73 of 76 (96.1%) CVS cases and 43 of 59 (72.9%) amniocentesis cases. The three CVS cases with unavailable information were considered lost to follow-up. The 16 amniocentesis cases with unavailable information were either lost to follow-up or were samples that were obtained from outside practices. The samples from outside practices did not

receive counseling at Magee-Womens Hospital, and therefore, information was not available for further contact.

A third specific aim was to conduct further follow-up in order to obtain more information pertaining to long-term phenotypic effects. This part of the study required IRB approval, and while approval was obtained, patients were not contacted as of March 25, 2006. However, the opportunity to gain further information through contacting patients is available and will be performed in the near future.

The last specific aim was to analyze the findings to attempt karyotype-phenotype correlations. This study found mosaic results involving trisomy for chromosomes 2, 7, 8, 9, 10, 12, 13, 15, 16, 18, 20, 21, 22, X, and Y. In addition, there was monosomy for chromosomes 21, 22, and X, tetraploidy, structural aberrations, and supernumerary marker chromosomes. Pregnancy complications and documented features and anomalies were reported for each type of chromosomal mosaicism and compared to other cases reported in literature. However, further information regarding development and features that manifest as a child gets older would provide more information and allow for better karyotype-phenotype correlations.

6.0 CONCLUSIONS

Chromosomal mosaicism, when detected prenatally, complicates genetic counseling as phenotypic outcome can vary depending on the chromosome involved and the level of mosaicism that is present in the fetus. In addition, UPD and/or cryptic mosaicism, which can be missed by routine cytogenetic testing, could cause an abnormal outcome. Although several large studies have provided some information pertaining to mosaicism for different types of abnormalities, much is still unknown and long-term follow-up information is limited.

Based on the information provided from this study, it is apparent that most cases of prenatally diagnosed mosaicism result in a normal outcome but more information is needed regarding long term consequences. This study will be continued in order to gain more information about our cases. In addition, all cases of mosaicism detected by CVS or amniocentesis should have follow-up cytogenetic testing, including amniocentesis for CVS cases and tissue and blood analysis for all cases, in order to determine if the result represents true mosaicism. One suggestion is that samples of foreskin from males after circumcision could be used because these samples may provide a more information in addition to the term placenta and cord blood that is currently being used for analysis. Obtaining information pertaining to pregnancy and delivery complications through routine follow-up should also be continued and maintained. Also, any cases involving chromosomes that are known to have imprinting affects should have testing for UPD.

Future studies could include a prospective study that would obtain consent for the ascertainment of medical records and contact for future follow-up at the time of prenatal diagnosis. This would eliminate the complications associated with obtaining consent years after the procedure was performed. In addition, several of the cases in our study with a trisomy 8 mosaic result had pregnancy complications, including PROM, preterm delivery, and pre-eclampsia. Trisomy 8 mosaicism has not been associated with an increased risk for pregnancy

complications in literature but our findings may indicate the need for future studies to investigate this possible association. Also, a match control study could be performed to examine the frequency of preterm labor and IUGR to determine if the rate is higher among patients with a mosaic result.

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