# Chapter 2. Natural history of trisomy 18

## 2.1 The medical disorder: trisomy 18 and its variants

In the late 1950s and 1960s, karyotyping was limited, due to its difficulty and expense. It was likely that most perinatal deaths, for example, would not be routinely karyotyped. Thus, data from this earlier time period may underestimate the prevalence of the disorder, as well as the type and frequency of clinical manifestations (more severe cases that died early would often not be karyotyped or counted). On the other hand, widespread prenatal screening for Down syndrome (and trisomy 18) may also bias the more recent data, as the more severely affected that might not survive to term may be prenatally diagnosed and terminated. Table 2.1-1 provides summary information from four large representative studies regarding the natural history of trisomy 18, spanning the time period from 1964 through 2006. Three types of information are presented: clinically apparent findings from a physical examination, characteristics at birth and after, and findings at autopsy (earlier studies) or high resolution ultrasound (later studies). The last column contains the same data, but for mosaic trisomy 18 (to be discussed later).

The most common clinical findings for trisomy 18 infants are malformed ears, a small jaw (micrognathia), clenched/overlapping fingers, prominent calcaneus (heel bone leading to the term 'rocker bottom' feet), and a prominent occiput (back of the head). Other findings that are more variable or less common include ocular hypertelorism (wide set eyes), short sternum, limited hip abduction, extra skin at nape of neck (nuchal folds), hypertonia and a high palate. Infants with trisomy 18 are small for gestational age, with an average birthweight of about 2000 grams. They often fail to suckle and thus suffer from failure to thrive. All are developmentally delayed. The most common heart defects are ventricular septal defects (VSD), atrial septal defects (ASD), and persistent ductus arteriosus. Also common are renal and diaphragmatic defects. Companion papers (Ramirez-Castro and Bersu, 1978; Bersu and Ramirez-Castro, 1977) provide extensive autopsy data regarding the head and neck (Bersu and Ramirez-Castro, 1977) as well as the upper and lower limbs (Ramirez-Castro and Bersu, 1978).

All of the originally reported cases of trisomy 18 (Edwards *et al.*, 1960; Smith, 1960) were complete, or full, trisomy 18, as they involved 47 chromosomes. By 1963, it was clear that several clinically defined cases of trisomy 18 had only 46 chromosomes, but with an additional translocated $18^{th}$ chromosome (or part of an $18^{th}$ chromosome) (Hecht

*et al.*, 1963). These are also called partial trisomy 18. Among 36 cases collected by Hecht (Hecht *et al.*, 1963), four (11%) were due to a translocation. As might be expected, among those cases of trisomy 18 that were clinically identified, there was no apparent difference between those with, or without, a translocation. However, further study suggested a variable phenotype, depending on how much, and which, material from the extra chromosome is duplicated (Carey, 2005). Trisomy 18 can also be mosaic, where an individual has two (or more) cell lines; one normal, and the other trisomy 18. In a 2005 summary of the literature (Carey, 2005), 165 of 176 affected newborns had a full trisomy 18 karyotype (94%, 95% CI 89% to 97%), eight were mosaic trisomy 18 (4.6%, 95% CI 2.0% to 8.8%) and the remaining three had a translocation or partial trisomy 18 (1.7%, 95% CI 0.4% to 4.9%).

A mosaic trisomy 18 can have all the features of full trisomy 18, or have no dysmorphic features, including normal intelligence. In one study summarizing 33 patients reported in the literature (Tucker *et al.*, 2007), nine (27%) were karyotyped only because of infertility, recurrent miscarriages, birth of an affected child, or an attempt to donate bone marrow. It is possible that some proportion of mosaic trisomy 18 cases will not be identified, unless routine diagnostic testing is undertaken in a wider setting. The proportion of trisomic cells varies by tissue tested, and it cannot be used to predict phenotype.

The last column of Table 2.1-1 summarizes the phenotypes of mosaic trisomy 18 reported in the literature as summarized by Tucker and colleagues (Tucker *et al.*, 2007). On average, the mosaicism was higher for cytogenetic studies of blood (average 53% of cells, range 8% to 100%) than for study of skin cells (average 29%, range 0% to 100%). Individual case reports may, however, not be representative of the totality of mosaic trisomy 18 individuals, because a diagnosis is more likely to have been made (and be more publishable) if found at a more advanced age. For example, one report in the literature refers to the loss of three individuals with mosaic trisomy 18 in early pregnancy, but there is no information about their phenotype (Carter *et al.*, 1985).

**Table 2.1-1. Characteristics of infants with trisomy 18**

| | **Canada** (Lewis, 1964) | **England** (Taylor, 1968) | **Taiwan** (Lin *et al.*, 2006) | **Indiana** (Tucker *et al.*, 2007) |
|---|---|---|---|---|
| **Year published** | 1964 | 1968 | 2006 | 2007 |
| **Number of samples** | 48 | 27 | 39 / 31 | 33 mosaic[a] |
| Clinically apparent features (>50%) | | | | |
| Heart defect | >90% | 85% | >90% | 77% |
| Micrognathia (small jaw) | 92% | 92% | 64% | 22% |
| Malformed ears | 90% | 88% | 90% | 26% |
| Flexion of fingers | 75% | 89% | - | - |
| Overlapping fingers | 58% | 89% | 95% | 4% |
| Prominent calcaneus | - | 77% | 90% | 7% |
| Prominent occiput | 54% | 93% | 72% | 22% |
| Ocular hypertelorism | - | 81% | 33% | 5% |
| Short sternum | 63% | 68% | 23% | 33% |
| Limited hip abduction | 48% | 68% | 59% | - |
| Extra skin at nape of neck | - | 56% | - | - |
| Hypertonia | - | 50% | - | 27% |
| High palate | 54% | | 38% | 71% |
| Characteristics after birth (>50%) | | | | |
| Feeding difficulty | - | 96% | - | 67% |
| Failure to thrive | - | 96% | - | - |
| Developmental delay | - | 96% | - | 59% |
| Mental retardation (mod to severe) | - | 96% | - | 36% |
| Birthweight (gm) | - | 2242 | 1977 | - |
| Features identified at autopsy/US (>25%) | | | | |
| Ventricular Septal Defect (VSD) | 93% | 43% | 94% | 46% |
| Atrial Septal Defect (ASD) | 24% | 31% | 68% | 8% |
| Persistent ductus arteriosus | 68% | 53% | 77% | 7% |
| Renal anomaly | 71% | 62% | - | 25% |
| Diaphragmatic defects | 34% | 40% | - | - |

[a] many features not evaluated in all 33 cases

## 2.2 Birth prevalence of trisomy 18

Cytogenetic typing of products of conception shows that nearly every autosome can be associated with trisomy (Byrne *et al.*, 1985). Among very early losses, trisomy 16 is most common, but usually not associated with an organized embryo. Many of the other trisomies are nearly always associated with miscarriage of fetal tissue membranes. These include chromosomes 2, 5, 7, 8, 15, 20 and 22. That study (Byrne *et al.*, 1985) found that the widest phenotypic expression was among miscarriages affected with trisomies that can be associated with live birth (*i.e.*, 13, 18 and 21). Among the 17 fetuses >30 mm in length that were karyotyped, there were seven trisomy 21, six trisomy 18 and one trisomy 13 (the three remaining fetuses were trisomy 7, 15 and 20).

As early as 1963 (Hecht *et al.*, 1963), evidence was convincing that trisomy 18 occurred more often with advancing maternal age, similar to the relationship already reported for Down syndrome. Table and Figure 2.2-1 summarize the 12 published datasets identified via a structured literature search, in which the birth prevalence of trisomy 18 (per 10,000 births) can be directly computed or estimated. None of these studies provided results stratified by maternal age, except for those above and below 35 years of age. One additional study was identified after the initial searching took place (Savva *et al.*, 2010). This large study from the UK is also included in the table. The studies include over 6 million births and 674 live-born trisomy 18 pregnancies. Only the most recent study (Savva *et al.*, 2010) was sufficiently large to report maternal age-specific birth prevalences. In five of the earlier studies (Hecht *et al.*, 1963; Smith, 1964; Taylor, 1967; Taylor, 1968; Root, 1994), the birth prevalence could be directly computed as prenatal diagnosis and selective termination were either not available or not widely available. In the remaining studies (Parker *et al.*, 2003; Forrester and Merz, 1999; Nielsen, 1991; Maeda *et al.*, 1991; Forrester and Merz, 2002; Crider *et al.*, 2008) prenatal diagnoses and terminations of trisomy 18 fetuses were separately recorded. In some instances, there were more terminations than live births (Parker *et al.*, 2003) where there were nine observed live births but 66 terminations. Of course, not all of the terminations would have been live-born. An estimated 65% would be spontaneously lost between the time of amniocentesis (15 to 20 weeks' gestation) and term (Morris and Savva, 2008). To account for this, the number of terminations was multiplied by 0.35, the proportion likely to survive. For each rate, the 95% confidence interval is provided, using the binomial distribution. The overall rate of 1.9 per 10,000 was derived using a random effects model (95% CI 1.5 to 2.4 per 10,000) that also showed significant and important

heterogeneity (Q=44, $I^2$=77%, p=0.004). Figure 2.2-1 presents these data in graphic form. Much of the heterogeneity is likely due to the underlying maternal age distribution. One study (Savva *et al.*, 2010) stratified their results into two time periods (1989-1996, and 1997-2004). Using the age-associated model developed in their data, the observed rates for these two periods both showed 25% increases in birth prevalence for trisomy 18 (e.g., 1.81 / 10,000 to 2.27 / 10,000). The best estimate for England and Wales for 1997 through 2004 is the modeled rate of 2.37 / 10,000 (Savva *et al.*, 2010).

**Table 2.2-1. Estimated birth prevalence of trisomy 18 in population-based cohorts**

| Study | Years | Births | Trisomy 18 | | Rate per 10,000 | 95% CI |
|---|---|---|---|---|---|---|
| | | | Live / Termination[a] | Adjusted[b] | | |
| (Hecht *et al.*, 1963) | 1962-1963 | 999 | 2 / 0 | 2 + 0 = 2 | 20 | 2.0 - 72 |
| (Smith, 1964) | 1960-1964 | 10,345 | 3 / 0 | 3 + 0 = 3 | 2.9 | 0.6 - 8.5 |
| (Taylor, 1967) | 1962-1963 | 9,688 | 1 / 0 | 1 + 0 = 1 | 1.0 | 0.1 - 5.7 |
| (Taylor, 1968) | NR | 94,000 | 11 / 0 | 11 + 0 = 11 | 1.2 | 0.6 - 2.1 |
| (Nielsen, 1991) | 1969-1988 | 34,910 | 7 / 3 | 7 + 1 = 8 | 2.3 | 1.0 - 4.5 |
| (Maeda *et al.*, 1991) | 1975-1986 | 14,835 | 6 / 0 | 6 + 0 = 6 | 4.0 | 1.4 - 8.8 |
| (Root, 1994) | 1979-1988 | 388,563 | 64 / 0 | 64 + 0 = 64 | 1.6 | 1.3 - 2.1 |
| (Embleton *et al.*, 1996) | 1986-1992 | 282,583 | 34 / 23 | 34 + 8 = 42 | 1.5 | 1.1 - 2.0 |
| (Forrester and Merz, 2002) | 1986-1999 | 282,900 | 38 / 64 | 35 + 22 = 57 | 2.0 | 1.6 - 2.6 |
| (Parker *et al.*, 2003) | 1997-2001 | 259,009 | 9 / 66 | 9 + 23 = 32 | 1.2 | 0.9 - 1.8 |
| (Crider *et al.*, 2008) | 1994-2003 | 457,000 | 53 / 89 | 53 + 31 = 84 | 1.8 | 1.5 - 2.3 |
| (Savva *et al.*, 2010) | 1980-2004 | 4,500,000 | 447 / 1,334[c] | | 2.3 | 2.1 - 2.5 |
| **All[c]** | | **6,334,832** | **675/ 1,585** | | **1.9** | **1.5 - 2.4** |

[a] Number of live-born trisomy 18/number of trisomy 18 fetuses selectively terminated within the cohort

[b] Adjusted for selective terminations by counting each as a 0.35 live birth (expressed as an integer).

[C] Also included in the study were 313 cases with known fetal losses and 160 cases with unknown time of diagnosis (adjustments for fetal loss performed by the author)

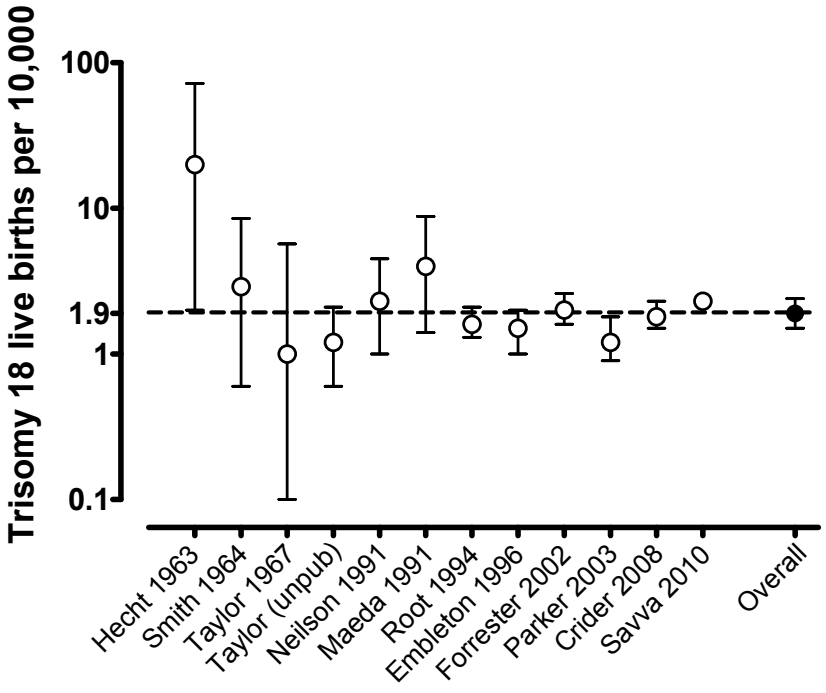


**Figure 2.2-1. The birth prevalence of trisomy 18.** Table 2.2-1 provides the data for this graph. In five of the earlier studies, no selective terminations of trisomy 18 pregnancies were observed. In the remaining six studies, the live births were estimated by adding the observed births to the number of selective terminations * 0.35, to account for fetal loss between the time of diagnosis and delivery. The overall rate was computed using a random effects model. Important heterogeneity was observed ($I^2$ = 77%), most likely due to differences in the underlying maternal age distributions.

## 2.3 Recurrence risk for trisomy 18

Fewer data are available on the recurrence risk for trisomy 18 among women who have already delivered an affected infant. It is generally thought that the risk of non-disjunction is not chromosome-specific (*i.e.*, equal recurrence risks for trisomies 13, 18 and 21). The recurrence risk (for any trisomy) among women diagnosed with a trisomy 21 offspring has been reported to be about 1% higher than the age associated risk (Stene *et al.*, 1984), and this rate is often used for counseling (Gardener, 1996). Seven studies provide information about recurrence risks after an initial trisomy 18 birth, and these are summarized in Table 2.3-1. A European collaborative study on prenatal diagnoses examined 171 karyotypes collected after an initial diagnosis of trisomy 18; two chromosomal abnormalities (both trisomy 18) were found (Stene *et al.*, 1984). A Yugoslavian group diagnosed 107 fetuses and newborns with trisomy 18 as part of clinical practice and found only one with an affected sibling (Ristic *et al.*, 1991). Another study reported recurrence risks among 98 women who had delivered a child with trisomy 18 (Baty *et al.*, 1994a). No trisomies occurred among 168 subsequent sibs or among 98 previously born sibs. However, one woman subsequently had a fetal loss that was karyotyped as trisomy 13 (among 42 pregnancy losses; some of which were selective terminations). Among a Japanese cohort of 170 women with a trisomy 18 birth (Uehara *et al.*, 1999), none delivered another infant with a trisomy. In another cohort of 107 trisomy 18 fetuses, the authors found only one woman with a recurrence (Ristic *et al.*, 1991). A report from Finland (Ryynanen *et al.*, 1997) found one recurrence of trisomy 18 in 28 pregnancies in 23 women with a trisomy 18 fetus. The largest study of 495 women have five trisomy 18 pregnancies diagnosed (among 676 subsequent pregnancies) is based on Australian data (De Souza *et al.*, 2009).

Together, these studies are consistent with an estimated risk of recurrence of 0.8%. This can be compared with the corresponding risk for Down syndrome. For example, the large study from Japan (Uehara *et al.*, 1999) provided recurrence risks for Down syndrome as well, and found 10 recurrences among 842 women, for a rate of 1.1% (95% CI 0.6% to 2.2%). One explanation for a higher than expected recurrence risk for autosomal trisomies is that the age-related risk is non-chromosome specific predisposition to non-disjunction (FitzPatrick and Boyd, 1989). This was demonstrated in a case report involving a 40 year old woman who received a diagnosis of trisomy 21 and chose to terminate the pregnancy at 16 weeks' gestation. In her next pregnancy, trisomy 13 was diagnosed at 16 weeks' gestation and again termination was chosen. No

family history of chromosomal abnormalities was reported. At age 43, her third pregnancy was diagnosed with trisomy 18.

**Table 2.3-1. Trisomy 18 recurrence risk for women diagnosed with a trisomy 18 fetus**

| Study | Number of women | Number of fetuses | Recurrences | Recurrence rate (%) |
|---|---|---|---|---|
| (Stene *et al.*, 1984) | NR | 171 | 47,XX+18<br>46,XY,inv(18) | 1.1 |
| (Ristic *et al.*, 1991) | NR | 107 | 47,XX+18 | 0.9 |
| (Baty *et al.*, 1994a) | 98 | 308[a] | None[b] | 0.0 |
| (Ryynanen *et al.*, 1997) | 23 | 28 | 1 | 3.6 |
| (Uehara *et al.*, 1999) | 170 | 200 | None | <0.1 |
| (Warburton *et al.*, 2004) | 235 | 391 | 1[c] | 0.2 |
| (De Souza *et al.*, 2009) | 495 | 676 | 5 | 0.7 |
| **All** | | **1,205** | **10** | **0.8**<br>95% CI (0.4 to 1.5) |

[a] includes previous children and spontaneous losses (the one affected fetus was from a previous therapeutic termination)

[b] reported a trisomy 13 in a subsequent pregnancy

[c] also reported two other viable trisomies that were not trisomy 18

NR=not reported

## 2.4 Fetal loss during pregnancy

A literature search identified seven studies that provided data on the proportion of trisomy 18 fetuses spontaneously aborted during pregnancy. The most commonly reported loss rates are from the time of CVS (around 12 weeks' gestation) and from the time of amniocentesis (around 18 weeks' gestation), to term. Table 2.4-1 summarizes the results by gestational age at the onset of monitoring, from earliest to latest. By far the most comprehensive study to date is by Morris and Savva (Morris and Savva, 2008) who examined five congenital anomaly registers in England. Rather than limiting the study to those women choosing to continue their pregnancy, they utilized all data via a survival analysis. Thus, their report provides a week-by-week proportion surviving that can be compared with all previously published results. Their data are provided as a reference for the other six studies in Table 2.4-1.

- At the time of CVS (12 weeks' gestation): Snijders and her colleagues (Snijders *et al.*, 1994) reported a fetal loss rate of 45% for trisomy in association with a first trimester Down syndrome screening program, but this was based on a limited number of observations. Morris and Savva found the loss rate to be much higher, at 72% (95% CI 61% to 81%) (Morris and Savva, 2008). One possible explanation for the discrepancy is the small number of observations in the Snijders study (Snijders *et al.*, 1994). Alternatively, that group is composed of skilled sonographers, who may have provided prognostic information that was used by some women in their decision-making process, resulting in a tendency for the less severely affected cases to be continued.
- At the time of amniocentesis (18 weeks' gestation): The first three of these reports (Hook, 1978; Hook *et al.*, 1989; Embleton *et al.*, 1996) focused on women having a prenatal diagnosis of trisomy 18 via amniocentesis performed due to advanced maternal age. The data from the two reports from Hook are combined in the latter publication (Embleton *et al.*, 1996). They are based on small numbers, as only women who chose not to terminate after prenatal diagnosis were eligible for study. Taken together, between 60% and 75% of the trisomy 18 fetuses viable at the time of amniocentesis were lost prior to delivery (Anandakumar *et al.*, 1999). A small study from England (Parker *et al.*, 2003) found a lower rate, but again with a small sample set. A larger study from California found a much lower loss rate of 32%, after second trimester serum screening (Won *et al.*, 2005). Morris and Savva found the loss rate to be consistent with the earlier studies, at 65% (95% CI 47% to

79%). One possible explanation for the lower rate found in the California study is that all those women also received an ultrasound examination as part of the diagnostic process. That prognostic information may have factored into the decision-making process, resulting in a tendency for the less severely affected cases to be continued.

- One study looked at sonographically identified viable trisomy 18 pregnancies at 28 weeks' gestation and found a 45% loss rate to term (Yamanaka *et al.*, 2006). The corresponding rate from Morris and Savva is 52% (95% CI 41% to 65%). These two rates agree reasonably well, even though the cases were identified via an abnormal ultrasound. This may be due to the late time in gestation in which the cases have been identified, and the lack of access to termination.

Overall, the studies provide a reasonably consistent picture of fetal loss for trisomy 18 pregnancies from 12 weeks' gestation to term. Figure 2.4-1 is the survival curve (with 95% confidence interval) from Morris and Savva (Morris and Savva, 2008). Included on the figure are the seven additional estimates derived from the remaining studies (solid straight lines). There is some indication that when ultrasound-based prognosis is available early in pregnancies (when termination is readily available), the fetal loss rate appears lower. This may be due to a systematic use of the prognostic information in the women's' decision-making process.

By comparing the rate of chromosome abnormalities at the time of CVS with that found at amniocentesis (some 6 weeks later), Kratzer and his colleagues (Kratzer *et al.*, 1992) found evidence for a higher rate of loss as maternal age increases from age 34 to 50 for Down syndrome. Fewer data were available to study this age-enhanced spontaneous miscarriage for trisomy 18. The trend was in the same direction, but the results were not statistically significant. A plausible basis for this might include a lessening in the ability of the maternal compartment to compensate for the imbalances in biochemistry brought on by the trisomic fetuses.

Overall, the fetal loss during pregnancy for trisomy 18 fetuses is consistent. In future analyses, the loss rates of 72% and 65% (Morris and Savva, 2008) will be used, as estimates from the late first trimester (11 to 13 weeks' gestation) and the early second trimester (15 to 20 weeks' gestation), respectively.

**Table 2.4-1. Spontaneous loss rates for trisomy 18 pregnancies, from specified gestational age to term**

| Study | Source | Number | | From (wks)[a] | Loss (%) |
|---|---|---|---|---|---|
| | | Total | Lost | | |
| (Snijders *et al.*, 1999) | After 1st trimester screening | 7 | | 12 | 86 |
| (Morris and Savva, 2008) | Congenital anomaly registries | 475 | | 12 | 72 |
| (Hook *et al.*, 1989) | Advanced maternal age | 36 | 24 | 18 | 68 |
| (Embleton *et al.*, 1996) | Advanced maternal age | 5 | 3 | 18 | 60 |
| (Snijders *et al.*, 1999) | After amniocentesis | 7 | | 18 | 70 |
| (Parker *et al.*, 2003) | After abnormal US | 8 | | 18 | 38 |
| (Won *et al.*, 2005) | After 2nd trimester serum | 106 | | 18 | 32 |
| (Morris and Savva, 2008) | Congenital anomaly registries | 475 | | 18 | 65 |
| (Yamanaka *et al.*, 2006) | After 2nd trimester ultrasound | 63 | | 28 | 45 |
| (Morris and Savva, 2008) | Congenital anomaly registries | 475 | | 28 | 52 |

[a] From the provided gestational week to term (amniocentesis set to 18 weeks, CVS set to 12 weeks)

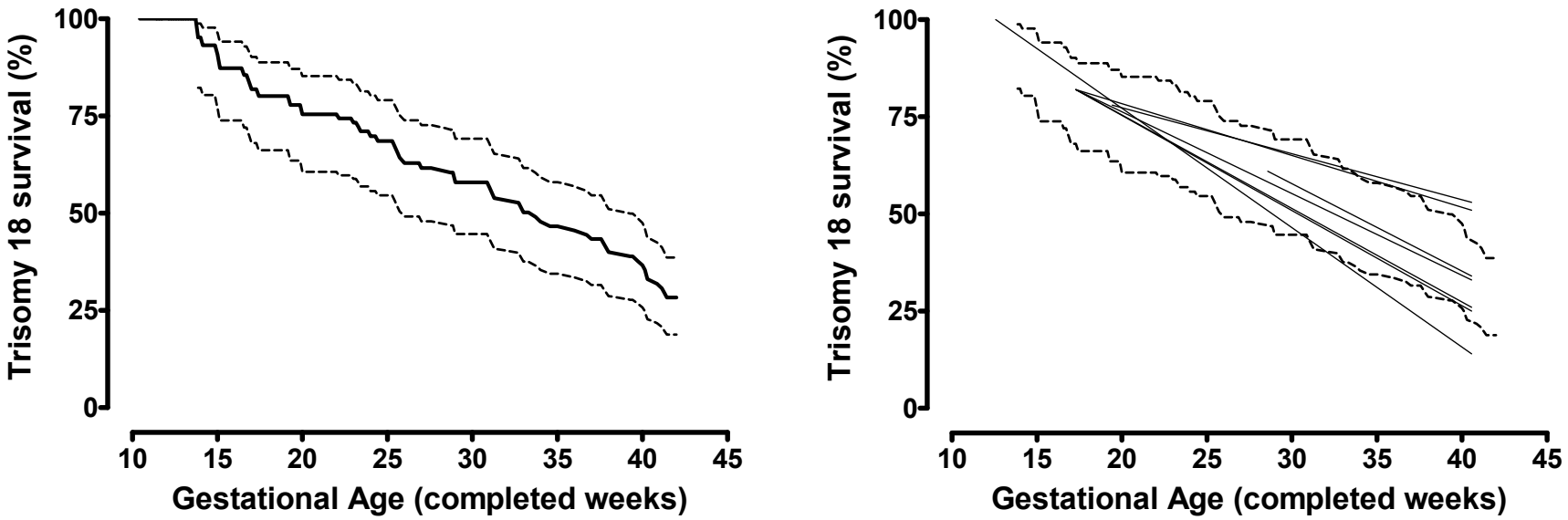


**Figure 2.4-1. Survival of trisomy 18 fetuses during pregnancies.** The horizontal axis provides the gestational age in completed weeks. The vertical axis shows the proportion of trisomy 18 fetuses surviving. In the left graphic, the solid line indicates the Kaplan-Meier estimate for the survival of trisomy 18 fetuses from 12 weeks' to term from the largest available study.(Morris and Savva, 2008). The upper and lower dashed lines indicate the 95% confidence interval of that estimate. In the right graphic, the solid line is removed, and seven loss rates from six other studies are superimposed on the 95% confidence intervals. The seven estimates begin at 12 weeks', 18 weeks', or 28 weeks' gestation (data for the graphic can be found in Table 2.4-1).

## 2.5 Complications of a trisomy 18 pregnancy

As shown earlier (Section 2.1), most fetuses with trisomy 18 will be small for gestational age. Late in pregnancy, fetuses with trisomy 18 are also often associated with hydramnios and fetal distress. If undiagnosed, these findings can lead to a cesarean section, with associated maternal morbidity. A study from the US (Schneider *et al.*, 1981) found a higher cesarean section rate in trisomy 18 pregnancies. Between 1969 and mid-1975, the rate was 20% (4 of 20 cases) compared to 6% in the general population. Between late 1974 and 1979, the rate was 56% (15 of 28 cases) compared to 10% in the general population. A similar study from England reported 11 of 21 affected pregnancies (all undiagnosed) required a cesarean section (Young *et al.*, 1986). Four were planned, due to a small for gestational age fetus, while the other seven were emergency procedures due to fetal distress. Avoidance of an emergency cesarean section is one important reason to identify trisomy 18 early in pregnancy.

## 2.6 Survival after birth

Trisomy 18 is often said to be a lethal condition, and this is generally true. Survival is usually very short (measured in days and weeks). Several studies have identified a cohort of newborns with trisomy 18 for a more exact documentation. Table 2.6-1 summarizes 13 studies reporting survival among newborns diagnosed with trisomy 18. One study (Weber, 1967) was a summary analysis of the existing literature prior to 1967. The studies varied in their methods for identifying affected newborns, and this is likely to have led to important biases that will be discussed later. The studies also varied in the time points chosen to report the proportion of surviving individuals, making summary analysis difficult. The 13 studies are arranged chronologically (by date of publication) from left to right, with the exception of two excluded studies that are listed first. Rows are defined by selected time points used in the various studies, ranging from one day to six years. All of the data refer to live-born infants; the one exception being the Australian study (Carter *et al.*, 1985) that included three stillborn males. These have been removed and the proportion alive at each interval adjusted. In many of the studies, only a figure was present and the data had to be estimated. In some instances, later authors obtained additional information from the original authors, and this has been used instead of the original data. Eight of the studies reported fewer than 100 cases, while the remaining five included between 114 and 680 cases. The last row of Table 2.6-1

provides the median survival in days. In 11 of the studies, the median survival is between 2.5 and 14.5 days. In another two, the median survival is 70 and 201 days. In one study it was not possible to definitively determine the median survival, but fewer than 50% survived to 14 days (Naguib *et al.*, 1999). The cause of this heterogeneity may be due to specific study design issues. The following studies were removed from the summary analysis for the following reasons.

- The earliest study providing a summary of existing literature (Weber, 1967) found a median survival of 70 days. That study collected data published prior to 1967, a time when karyotyping was difficult and expensive. It is likely that early losses (at one or two days) might not have been routinely karyotyped, even if key abnormalities had been present. This was acknowledged by the author (Weber, 1967).
- One of the studies from Utah (Baty *et al.*, 1994a) found a median survival of 201 days. To collect these data, the authors queried members of the Support Organization for Trisomy 18, 13 and Related Disorders (SOFT) for information about their affected child. It is plausible that the longer an affected child lives, the more likely the parents are to find and to join a support organization and register their child's information. This would bias that dataset towards longer survival.

**Table 2.6-1. Summary of studies reporting survival of live-born trisomy 18 infants**

| | **New York** (Weber, 1967) | **Utah** (Baty *et al.*, 1994a) | **Denmark** (Goldstein and Nielsen, 1988) | **Australia** (Carter *et al.*, 1985) | **England** (Young *et al.*, 1986) | **Utah** (Root, 1994) | **England** (Embleton *et al.*, 1996) | **Kuwait** (Naguib *et al.*, 1999) | **Texas** (Nembhard *et al.*, 2001) | **Scotland** (Brewer, 2002) | **Georgia** (Rasmussen *et al.*, 2003) | **Taiwan** (Lin *et al.*, 2006) | **Switzerland** (Niedrist *et al.*, 2006) | **Total Cases (All)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number** | 192[a] | 98 | 76 | 36[b] | 21 | 64 | 34 | 118 | 680 | 84 | 114 | 39 | 352 | **1,584** |
| **Alive at** | **NOT USED** | | | **Proportion of live-born trisomy 18 infants surviving (%)** | | | | | | | | | | |
| 1 day | 98[a] | | 60 | 65 | 67 | 86 | 71 | | 83 | 88 | 86 | 95 | 68 | **78** |
| 1 week | 89 | 88 | 44 | | 32 | 45 | 29 | | 56 | 43 | 63 | 47 | 40 | **47** |
| 2 weeks | 81 | | 32 | 39 | 27 | 41 | | 47 | | | 50 | 27 | 31 | **37** |
| 1 month | 72 | 79 | 21 | | 18 | 34 | 15 | 18 | 40 | 28 | 38 | 16 | 22 | **36** |
| 2 months | 52 | | | | 13 | 22 | | 6 | | | 30 | 11 | 17 | **17** |
| 3 months | 38 | 64 | | 6 | 10 | 20 | 6 | | | | 21 | 5 | 13 | **13** |
| 4 months | 30 | | | | 5 | 14 | | | | | 19 | 5 | 12 | **11** |
| 5 months | 23 | | 3 | | 0 | 9 | | | | | 12 | 3 | 9 | **7** |
| 6 months | 13 | 56 | | | | 9 | | | | | 11 | 3 | 9 | **7** |
| 1 year | 8 | 41 | 1 | | | 5 | 0 | 1 | 10 | 3 | 6 | 3 | 6 | **5** |
| 2 years | 5 | | 1 | 0 | | 5 | | | | | | 3 | 4 | **4** |
| 3 years | 3 | | | | | 5 | | | | | | 3 | 3 | **2** |
| 4 years | 2 | | | | | 5 | | | | | 5 | 3 | 2 | **2** |
| 5 years | 1 | 10 | | | | 3 | | | | | | 3 | 2 | **2** |
| 6 years | 0.3 | | | | | 3 | | | | | | 3 | 1 | **2** |
| Median (days) | 70 | 201 | 6 | 5 | 2.5 | 4 | 3 | NR[e] | ~14 | 6 | 14.5 | 6 | 4 | **6** |

[a] numbers as extrapolated in Root and Carey, 1994.
[b] three stillbirths removed from the original data

All of the remaining studies were in Caucasians or Asians, and relied on karyotype reports to confirm the diagnosis of trisomy 18. The summary analysis is based on 10 studies, after excluding two (Weber, 1967; Baty *et al.*, 1994a).

The last column of Table 2.6-1 shows the summary proportion of trisomy 18 newborns alive at each time interval, weighted by the number of observations in the seven included studies. Based on these data, the median survival is about five days. Another important finding, however, is that about 1 in 20 newborns with trisomy 18 are expected to be alive at one year. Figure 2.6-1 provides a graphic representation of the data in Table 2.6-1. The horizontal logarithmic axis shows the survival time, from one day to 1,000 days (about 2.7 years). The vertical axis shows the proportion of live-born trisomy 18 infants still alive for each of the 11 included studies (thin solid lines). The summary estimate is shown by the thick solid line. This type of comprehensive analysis of these data has not previously been reported.

Long-term survival with trisomy 18 is defined as being greater than one year. Assuming four million live births and a birth prevalence of 1.9 per 10,000 (Table 2.2-1), approximately 760 trisomy 18 infants may be born each year in the US (in the absence of prenatal detection and selective termination). Of these 780 newborns, 38 (5%) might be expected to survive for more than one year. A more reasonable estimate might be fewer than half that number, given current access to prenatal screening, diagnosis and selective termination. An invited commentary (Carey, 2006) included an analysis of the SOFT (Support Organization For Trisomy 18 and 13, and related disorders) database. It contains five times the number of children with full trisomy 18 (N=51) over the age of 10 than are contained in the entire medical literature (Kelly *et al.*, 2002; Petek *et al.*, 2003; Shanske, 2006). The database also contains 15 females over the age of 20. These data clearly indicate that a small proportion of full trisomy 18 newborns, especially females, can survive for years.

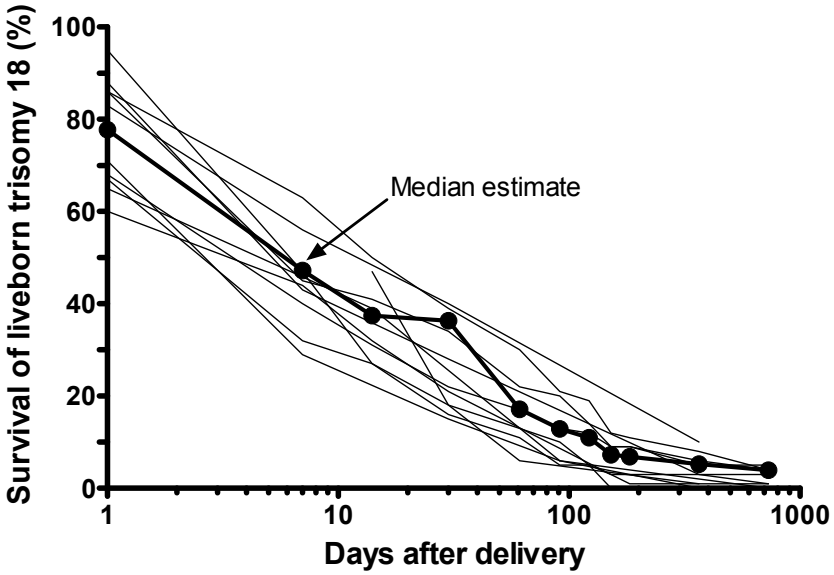


**Figure 2.6-1. Survival of live-born infants with trisomy 18.** From 11 studies suitable for analysis (thin solid lines), along with the median of those estimates (solid thick line). Corresponding data in Table 2.6-1.

A difference in survival based on gender was reported as early as 1963 (Hecht *et al.*, 1963) (1 male:2.7 female). The authors found this to be perplexing, as they did not find that girls survived longer. Using a much larger series in 1967 (Weber, 1967), Weber found that males do have poorer survival after birth than females. The ratio of males to females was 1:1.8 at 14 days, then 1:2.9 after three months or more. Given the bias already described in this study, however, other sources were sought to confirm differences in survival by gender. Of the seven acceptable studies used in Table 2.6.1, four provided results stratified by gender, and these are shown in Table 2.6-2. In all of these, there is an important survival advantage for females, especially over the first few weeks. None of the males were alive at one year, while about 5% of females survived.

This higher rate of loss after live birth in males compared to females with trisomy 18 is the continuation of a pattern reported by others studying fetal loss. Using a very large dataset (Morris and Savva, 2008), UK researchers found that the male:female ratio at the time of diagnosis (1:1.2) and at birth (1:1.6) both favor females. An earlier large dataset from California (Huether *et al.*, 1996) reported similar ratios at the time of prenatal diagnosis (1:1.1) and term (1:1.4). These findings support the hypothesis that males are subject to preferential spontaneous loss as pregnancy nears term.

**Table 2.6-2. Survival of live-born trisomy 18 infants stratified by gender**

| | Australia (Carter *et al.*, 1985)[a] | | Utah (Root, 1994) | | Taiwan (Lin *et al.*, 2006) | | Switzerland (Niedrist *et al.*, 2006) | | All[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gender** | **Males** | **Females** | **Males[b]** | **Females[b]** | **Males** | **Females** | **Males** | **Females** | **Males** | **Females** |
| **Number** | 13 | 23 | | | 17 | 22 | 26 | 37 | **82** | **120** |
| **Alive at** | **Percent of trisomy live-born infants** | | | | | | | | | |
| 1 day | 46 | 76 | 79 | 87 | 88 | 100 | 46 | 100 | **65** | **92** |
| 1 wk | | | 22 | 46 | 23 | 68 | 26 | 48 | **23** | **52** |
| 2 wk | 38 | 40 | 12 | 41 | 6 | 50 | 15 | 40 | **16** | **43** |
| 1 mo | | | 12 | 35 | 6 | 32 | 7 | 32 | **9** | **33** |
| 2 mo | | | 8 | 22 | 0 | 22 | 7 | 23 | **6** | **23** |
| 3 mo | 0 | 10 | 8 | 20 | | 9 | 5 | 18 | **4** | **15** |
| 4 mo | | | 4 | 14 | | 9 | 5 | 16 | **2** | **13** |
| 5 mo | | | 4 | 9 | | 5 | 2 | 13 | **2** | **9** |
| 6 mo | | | 4 | 9 | | 5 | 2 | 13 | **2** | **9** |
| 1 yr | | | 0 | 5 | | 5 | 0 | 10 | **0** | **7** |
| 2 yr | | 0 | | 5 | | 5 | | 6 | | **4** |

[a] three male stillbirths removed from the original data

[b] Only total of 138 reported, but male:female ratio assumed to be the same as for the other three studies (56:82)

NR = not reported

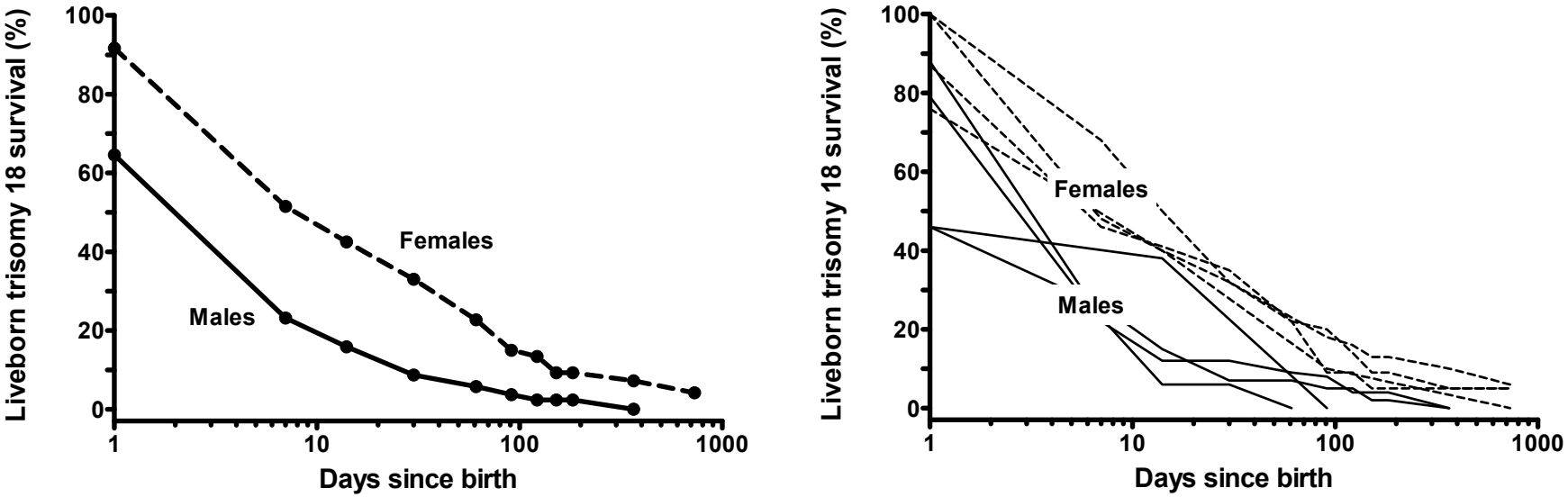


**Figure 2.6-2. Survival of live-born infants with trisomy 18, stratified by gender.** The left graphic shows the summary survival curve for the females (dashed line) and males (solid line). The right graphic shows the survival curves for the four individual studies. Corresponding data in Table 2.6-2.

Some of the survival studies already noted also stratified results by other factors. Carter found only a small advantage (among live-born infants) for infants with no defects requiring surgery, with or without cardiac defects (Carter *et al.*, 1985). Root and Carey suggest that gestational age at delivery and clinical care are likely to play a major role in survival (Root, 1994). Care of newborns/infants with trisomy 18 is addressed in Section 2.8. Rasmussen and colleagues had access to 115 trisomy 18 births, in a racially diverse population (Rasmussen *et al.*, 2003). Although there is some evidence that the data may be biased through the use of birth records, stratified analyses might still be instructive. The median survival among Caucasian infants was 4 days (N=59), versus 24 days (N=51) among African American newborns. Both the one month and one year survival rates were significantly higher among African Americans (p=0.02, p=0.01, respectively). If a heart defect was present, median survival was 14 days (N=67) compared to 20 days for those without a heart defect. There was a clear temporal trend towards increasing median survival with 10, 14 and 19 days for the periods of 1968 to 1979, 1980 to 1989, and 1990 to 1999, respectively. A Swiss group (Niedrist *et al.*, 2006) showed that gestational age at delivery was a strong predictor. The median survival was <1 day, 2 days, and 7 days for <32, 32-36 and 37 weeks' gestation and later at delivery.

## 2.7 Diagnostic testing for trisomy 18

In the 1950s and early 1960s, determining the karyotype required fresh cells, usually from the bone marrow. Thus, it was not possible to karyotype an individual after death. As described earlier, it was also not possible to determine the specific chromosome, only the group (Table 1.1-1). With chromosome banding and the ability to store sample specimens, karyotyping became more widely available, and it was possible to not only identify the chromosome, but parts of chromosome involved in balanced and unbalanced translocations. With prenatal procedures such as amniocentesis and chorionic villus sampling (CVS), it became possible in the 1980s to karyotype the fetus and offer prenatal diagnosis and selective termination. However, because of the procedure-related risk and costs, diagnostic testing could not be made available to all pregnant women.

Currently, prenatal diagnosis relies on the collection of fetal cells by either amniocentesis or CVS. Amniocentesis is usually performed no earlier than 15 weeks' gestation. Earlier than 14 weeks can result in an excess risk of talipes (club foot) (Johnson *et al.*, 1999). In amniocentesis, an ultrasound-guided needle is inserted into the amniotic sac, and 10 to 20 mL of amniotic fluid is removed. Fetal (and maternal) cells are present in the fluid. Various methods are used to culture the fetal cells, while inhibiting the growth of maternal cells. It is important to avoid maternal cell contamination, so that the final karyotype is fetal-specific.

The CVS procedure collects placental tissue either trans-abdominally or trans-vaginally under ultrasound guidance. The placenta and fetus are nearly always karyotypically identical (in some instances confined placental mosaicism exists and a subsequent amniocentesis must be performed). CVS is performed at 10 or 11 weeks' gestation or later, due to the risk of limb reduction abnormalities, if done earlier (Golden *et al.*, 2003; Burton *et al.*, 1992). In the U.S, CVS is rarely performed after 13 weeks' gestation while in Europe it may also be performed in the second trimester. One advantage to CVS sampling is that a direct karyotype may be performed, reducing the time to diagnosis. However, culturing of cells is more reliable due to the possibility of the direct karyotype being performed on maternal cells (maternal cell contamination). The main advantage of CVS is that it can be performed earlier than amniocentesis. The main advantages for amniocentesis are that it is more widely available and is likely to be associated with a lower procedure-related fetal loss rate (www.cochrane.org/reviews/en/ab003252.html).

Less commonly performed is percutaneous umbilical blood sampling (PUBS), in which fetal blood is taken directly from the umbilical artery. This has the advantage of rapid karyotyping, but is associated with a higher risk of fetal loss. This procedure might be appropriate if an ultrasound identified clinical signs of trisomy 18 (*e.g.,* heart defect and clenched fists) and the pregnancy is relatively late (*e.g*., 19 weeks' gestation). A rapid karyotype would allow more time for the couple's decision-making process.

Although a karyotype is still considered the gold standard for identifying chromosome abnormalities, it requires a specialized high-complexity laboratory, is expensive, and usually takes seven to 10 days (or more) for a final result. Recent advances in genetic testing have provided alternatives to karyotyping, and they will be reviewed in a later Section.

## 2.8 The child with trisomy 18

Case histories of two infants (Van Dyke and Allen, 1990) are paraphrased in the next sections as an introduction to the range of experiences possible with a trisomy 18 child who survives for more than one year.

Case 1: An infant girl delivered at 2166 g with respiratory difficulties necessitating transfer to pediatric intensive care. During the first four weeks, life was complicated by multiple infections, poor feeding, heart murmur and respiratory difficulties. A genetic consult resulted in a peripheral blood karyotype of 47,XX +18. By one year of age, the child weighed 3.3 kg. She continued to have severe hypotonia and severe developmental delay. She was diagnosed with a ventricular septal defect. Pulmonary hypertension and central cyanosis developed. As congestive heart failure became more difficult to control, apneic episodes and upper respiratory-type infection developed, resulting in a gradual deterioration and death at 19 months.

Case 2: An infant girl delivered at 1845 g and was karyotyped as 47 XX +18 using peripheral blood. She was diagnosed with a ventricular septal defect and a patent ductus arteriosus that were surgically repaired at two years. At five years of age she showed many of the phenotypic features of trisomy 18, including significant developmental delay. She could not sit or stand until she was three. At six years of age she was crawling on hands and knees and using a walker. She attended a special school program for children with severe developmental disabilities. Teachers reported that she stood with support, made vowel sounds, did not have speech, but was able to feed herself finger foods.

A widely quoted study regarding the cause of death in live-born trisomy 18 is from Northern England (Embleton *et al.*, 1996). A cohort of 66 trisomy 18 pregnancies was followed, with 34 live births. Twenty-one of these were delivered by caesarean section, with only one of these (a twin pregnancy) diagnosed prior to delivery. Average gestational age at delivery was 37 weeks with a mean birthweight of 1.8 kg. The median survival was three days, and only one lived longer than a week. The most common cause of death was central apnea (32%), followed by “never stabilized” (29%) and “episodic cyanosis” (13%). The remaining cases of death were sepsis (10%), “extubated” (10%) and unknown (6%). There was no relationship between cardiac malformations and the mode of death, except for two newborns with double outlet right ventricle. These died at ages two and three days without any signs of cardiac failure. Given this information, few thought that aggressive cardiac interventions would be warranted.

Until recently, there were no studies of systematic aggressive treatment protocols for infants born with trisomy 18. A 2008 study from Japan (Kaneko *et al.*, 2008) reported the impact of routine intensive cardiac management on a consecutive series of trisomy 18 and trisomy 13 newborns between 2000 and 2005. During the first time period, all cardiac treatment was withheld (10 trisomy 18 and three trisomy 13), during the second time period pharmacological interventions were allowed, but surgery was not (five trisomy 18, four trisomy 13), and during the third time period, aggressive treatment was allowed (seven, two) that was equivalent to that available for other neonates without an identified trisomy. All patients in the first group died within 79 days (median survival seven days). Patients in the second group all died by 367 days (median survival 23 days). Four of the nine patients in the last group were still surviving at 834 days (median survival 243 days). The survival advantage was statistically significant for the third group compared to the other two groups, but there was no clear advantage between the first two groups.

Data collected from the Support Organization for Trisomy 18, 13 and Related Disorders (SOFT), can be used to summarize psychomotor development as reported by parents of affected children (Baty *et al.*, 1994b). The developmental quotient (assessed developmental age divided by the chronological age) was always below 0.8, and in all but a few, below 0.3 by two years of age. Rather than a loss in skill, the reduction is due to an increase in skills for the comparative group of normal children. When skill areas are examined separately, trisomy 18 children are better at using language and daily living skills (mean developmental age of about 8 to 9 months) but are less adept at communication and motor skills (mean developmental age of 4 to 5 months). This source of these data must be viewed carefully because of likely selection bias, but can provide insight into the capabilities of a subset of children with trisomy 18.

Two reports provide specific guidance on caring for children with trisomy 18 and other life-limiting diagnoses. A group from the Children's Hospital of Philadelphia addresses palliative care for the family with a lethal condition (Munson and Leuthner, 2007). They stress communications between the care givers and the family, as well as examining the role of spirituality and the roles that family members might wish to play in creating memories. Many of their suggestions can be implemented, regardless of the family choice. Based on the WHO definition of palliative care, they suggest seven tenets of palliative care (Munson and Leuthner, 2007) that are summarized below:

- Affirm life while accepting death
- Intend to neither hasten nor postpone death
- Offer a support system to help family cope
- Aim interventions at comfort and quality of life
- Consider values beyond the physical needs of a dying individual
- Apply palliative care early in the course of illness in conjunction with other therapies
- Begin pediatric palliative care at diagnosis and continue regardless when treatment is directed at the disease

A formal method of classifying sick newborns/children in Japan was reviewed recently (Kosho, 2008). Class A includes all possible treatments. Class B restricts care by withholding aggressive treatments, such as surgeries and hemodialysis. Class C continues only routine care, such as nutrition and temperature control. Class D discontinues all treatment. In Japan, trisomy 18 infants fall under the C classification. He also reported the results of an informal survey from 107 health care institutions in Japan reporting that the most common condition in which "withholding or withdrawal of treatment had been considered was trisomy 18". Sample palliative care plans are available (Leuthner, 2004).

## 2.9 Do we 'screen' for trisomy 18?

Screening can be defined as (Wald, 2008):

> the systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder

Would the use of maternal age, ultrasound markers, serum markers or other markers of increased risk of trisomy 18 satisfy this definition of screening? Certainly, trisomy 18 is an important disorder, prenatal identification is medically useful, and systematic methods of identifying those at high risk have been developed and will be examined in more detail in subsequent sections. Applying the test in the general pregnancy population satisfies the last condition. The key condition that may, or may not, be satisfied is whether the risk of trisomy 18 is sufficient to "benefit from", further investigation. To "benefit from" implies "Something that promotes or enhances well-being; an advantage". Both the justification and benefits from screening can be examined from the medical, social/ethical, and economic perspective, as there is the potential for harms to be associated with these actions, including unnecessary anxiety and options that include procedure-related fetal losses of unaffected pregnancies.

From the medical perspective, one can ask whether testing will result in actions that will improve the health of the mother and fetus? One could ask whether the benefits of identifying (and terminating) some proportion of trisomy 18 fetuses is considered an acceptable action by the local population in general as well as individual women and their partners? Would there be an impact on the care of newborns with trisomy 18 associated with a prenatal testing program? Lastly, the question can be viewed from the economic perspective. A formal cost effectiveness analysis would be difficult to conduct as it requires a monetary value to be placed on human life. Rather, it would be important to consider the additional monetary costs associated with the prenatal testing process for trisomy 18 and balance this with the additional family and societal costs associated with the birth and care of a newborn with trisomy 18.