

The Risk of Fetal Loss Following a Prenatal Diagnosis of Trisomy 13 or Trisomy 18

Joan K. Morris^{1*} and George M. Savva²

¹Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, St. Bartholomew's and the London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London, UK

²Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

Received 12 July 2007; Accepted 23 November 2007

The objective of this study is to determine the risk of fetal loss (spontaneous abortion or stillbirth) following a prenatal diagnosis of trisomy 13 (T13; Patau syndrome) or trisomy 18 (T18; Edwards syndrome). Five regional congenital anomaly registers in England and Wales provided details on the outcomes of 198 pregnancies prenatally diagnosed with T13 and 538 prenatally diagnosed with T18. For each pregnancy the time from prenatal diagnosis until birth, miscarriage or termination occurred was calculated and these times were analyzed using Kaplan–Meier survival functions. Our results showed that between 12 weeks gestation and term an estimated 49% (95% CI: 29–73%) of pregnancies diagnosed with T13 and 72% (61–81%) of pregnancies diagnosed with T18 ended in a miscarriage or stillbirth. Between 18 weeks

and term the proportions were 42% (18–72%) for T13 and 65% (57–79%) for T18 and between 24 weeks and term the proportions were 35% (5–70%) for T13 and 59% (49–77%) for T18. Male fetuses with T18 appeared to be more likely to be lost than female fetuses. These are the most precise estimates currently available for the risk of loss in a general population. These estimates should be useful in counseling women who are carrying an affected fetus and knowing the risk of fetal loss is essential to compare the performance of prenatal screening programs occurring in the first and second trimester. © 2008 Wiley-Liss, Inc.

Key words: trisomy 13; trisomy 18; spontaneous fetal loss

How to cite this article: Morris JK, Savva GM. 2008. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. *Am J Med Genet Part A* 146A:827–832.

INTRODUCTION

Trisomy 13 (T13; Patau syndrome) and trisomy 18 (T18; Edwards syndrome) are the most common autosomal trisomies other than Down syndrome to be observed in live born infants. Both trisomies lead to abnormalities in multiple systems and both are usually fatal in the first year of life. T13 and T18 are often prenatally detected at routine fetal sonographic examinations because of multiple malformations or intrauterine growth retardation or during Down syndrome screening programs, allowing the option of a termination of the pregnancy.

It is known that T13 and T18 both have high natural fetal loss rates, and it is consistently reported that male fetuses with T18 are more commonly lost than females [Hook et al., 1989; Huether et al., 1996; Niedrist et al., 2006]. However, precise estimates for the risk of loss from specific gestational ages are not currently available. Reliable estimates are needed to counsel women with affected pregnancies. They are also needed for epidemiological analyses, for example to measure the effect of different prenatal

screening protocols on birth prevalence or enable adjustments for varying utilization of prenatal diagnostic services when making comparisons of the prevalence of either trisomy across populations.

The risk of fetal loss of T13 and T18 pregnancies has been estimated using comparisons of prevalences in mothers undergoing fetal karyotyping with the prevalence at birth in a population with no access to prenatal diagnosis [Snijders et al., 1994]. However, such populations are not necessarily comparable, and owing to the rarity of the conditions, estimates of prevalences are imprecise. The risk of loss has also been estimated directly by following relatively small

Grant sponsor: Research Advisory Board of St Bartholomew's; Grant number: RAB04/PJ/03.

*Correspondence to: Dr. Joan K. Morris, Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, St Bartholomew's and the London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK.

E-mail: j.k.morris@qmul.ac.uk

DOI 10.1002/ajmg.a.32220

numbers of pregnancies in a clinical setting, typically recruited from a single center that may not represent the general population [Won et al., 2005; Yamanaka et al., 2006] or at a late median onset of observation [Hook et al., 1989].

Congenital anomaly registers record every cytogenetically confirmed chromosomal anomaly in the populations they cover, and so provide an opportunity to study the outcomes of prenatally diagnosed chromosomal anomalies in an unselected population. In this paper we use the pregnancy outcomes of 175 prenatally diagnosed fetuses with T13 and 475 with T18 recorded by the British Isles Network of Congenital Anomaly Registers (BINOCAR) to provide direct estimates of the risk of loss following a prenatal diagnosis of each condition.

METHODS AND MATERIALS

Congenital Anomaly Registers

BINOCAR is a network of congenital anomaly registers, set up to provide epidemiological monitoring across the UK of all congenital anomalies [Rankin, 2007]. BINOCAR regional registers employ active case finding and use multiple sources of ascertainment. Each register collects information on all congenital anomalies occurring in live births, late miscarriages (≥ 20 weeks) and stillbirths, and in fetuses terminated after prenatal diagnosis. Further details regarding data collection are available on the BINOCAR website (<http://www.binocar.org/>).

We received records of all prenatally diagnosed cases of T13 and T18 diagnosed between January 1st, 1989 and December 31st, 2003 from five BINOCAR registers: the North Thames (West) Congenital Malformation Register, the Northern Congenital Abnormality Survey (NorCAS), the South West Congenital Anomaly Register, the East Midlands & South Yorkshire Congenital Anomaly Register and the Congenital Anomaly Register and Information Service (CARIS) of Wales. These registers together

cover roughly one-third of the population of England and Wales, although not all of the registers have been active since 1989, and the records we received covered roughly 2.3 million of the 10.3 million births registered in England and Wales during this time.

Prenatal Diagnoses of T13 and T18 and Definition of Outcomes

BINOCAR provided information on 411 diagnoses of T13 and 971 diagnoses of T18, of whom 198 (48%) cases of T13 and 538 (55%) cases of T18 were diagnosed prenatally. Mosaics were included in these diagnoses and all the diagnoses had been cytogenetically confirmed. The outcome of each pregnancy was classified as either a live birth, fetal loss (naturally occurring miscarriages and stillbirths), or termination (abortions that were artificially induced). The distribution of pregnancy outcomes is shown in Table I. Pregnancy outcome could not be determined in eight cases of T13 (3%) and 21 cases of T18 (3%). These cases were excluded from our analysis.

NorCAS does not routinely record cases ending in miscarriage before 20 weeks gestation. Therefore, any fetal losses occurring prior to 20 weeks gestation would not be included in the NorCAS dataset, so in order to avoid bias all cases diagnosed prior to 20 weeks gestation were excluded from the NorCAS dataset (13 cases of T13 and 40 cases of T18).

The date of termination of the pregnancy was missing for five cases diagnosed after a CVS and three cases diagnosed after an amniocentesis. In order to include these cases in the analysis the length of time between diagnosis and termination was assumed to be one week for cases diagnosed after having a CVS, and three weeks after having an amniocentesis. The gestational age at diagnosis was missing for 17 cases diagnosed after a CVS and eight cases diagnosed after an amniocentesis. In order to include these cases in

TABLE I. The Number of T13 and T18 Pregnancies According to Pregnancy Outcome and Estimates of the Proportions Resulting in a Fetal Loss According to Gestational Age

	Karyotype	
	Trisomy 13	Trisomy 18
Number of fetuses	175	475
Number of live births	10	24
Number of miscarriages/stillbirths ^a	9	56
Number of terminations ^b	156	395
Proportion of pregnancies resulting in a miscarriage or stillbirth according to gestational age (95% CI)		
12 weeks	49 (29–73)	72 (61–81)
18 weeks	42 (18–72)	65 (57–79)
24 weeks	35 (15–70)	59 (49–77)

^aMiscarriages/stillbirths includes all pregnancies not resulting in a live birth that were not induced.

^bTerminations includes all abortions that were induced.

the analysis the CVS was assumed to have occurred at 12 weeks and the amniocentesis at 15 weeks.

Two cases of T13 (2%) and two cases of T18 (1%) had either the gestational age at diagnosis or the gestational age at outcome missing, with no indication as to whether they had been diagnosed after an amniocentesis or a CVS. These cases were excluded from our analysis.

Analysis

Survival was estimated using Kaplan–Meier survival analysis. Pregnancies were entered into the analysis at the gestation at diagnosis and considered “under observation” until the gestation at outcome. All fetal losses were considered adverse outcomes. Terminations were treated as censored observations, that is as cases for which the natural outcome is unknown, with censoring occurring at the gestational age at termination. Pregnancies ending in live birth were assumed to have survived until 42 weeks gestation. Cases karyotyped subsequent to a miscarriage or stillbirth, which are cases where the diagnosis was made after the pregnancy outcome, were not included in the analysis. The sex difference in loss rates was tested using the log-rank test. All analysis was conducted using the statistical package STATA 9.2.

RESULTS

There were 175 prenatal diagnoses of T13 and 475 of T18 with complete information available. The average maternal age was 35 years with a range from 16 to 51 years. Table I gives the details of the outcomes of these pregnancies and Table II gives the gestational age at which these diagnoses occurred.

Figure 1 shows the Kaplan–Meier survival curve (with 95% confidence intervals) showing the probability of survival of T13 and T18 fetuses from 12 weeks gestation. 49% (95% CI: 29–73%) of fetuses diagnosed with T13 at 12 weeks would not survive to term and of those diagnosed at 18 weeks, 42% (95% CI: 18–72%) would not survive to term. The corresponding figures for T18 pregnancies are 72% (61–81%) and 65% (57–79%).

TABLE II. The Number of T13 and T18 Pregnancies According to Gestational Age at Diagnosis

Gestational age at diagnosis (completed weeks)	Karyotype	
	Trisomy 13	Trisomy 18
<12	1	16
12–15	52	164
16–19	39	80
20–23	69	151
24 +	14	64
Total	175	475

Among the T18 pregnancies there were 212 males, 246 females and 17 fetuses with unknown sex. Figure 2 shows the survival of fetuses with T18 according to sex. Males diagnosed at 12 weeks are more likely to result in a miscarriage or stillbirth [79% (CI: 65–90%)] compared to females 67% (CI: 52–81%). Also the sex ratio in those cases diagnosed by amniocentesis (0.85) was higher than the ratio at birth (0.64). These differences are not statistically significant ($P > 0.1$), but are of the magnitude and direction expected given previous findings. No sex difference was observed in T13 pregnancies.

DISCUSSION

We have provided the most precise estimates currently available for the risk of natural fetal loss following a diagnosis of T13 or T18. This study demonstrates an important use of congenital anomaly registers, in that sufficient numbers of cases are available to investigate the fetal loss rates amongst rare anomalies and to provide estimates that are applicable to the general population.

Comparison between our results and those of previous studies are shown in Table III. Hook et al. [1989] used data from three surveys of cytogenetic laboratories across North America, resulting in a total of 40 fetuses with T18 and 10 fetuses with T13 detected at amniocentesis. The estimates of fetal loss for both trisomies are very similar to our estimates.

Snijders et al. [1994] estimated the fetal loss in T13 and 18 pregnancies by first estimating the fetal loss in Down syndrome pregnancies and then comparing the relative frequencies of the different trisomies at the time of CVS and amniocentesis to the relative frequencies at birth. However, Snijders' estimates of the relative frequencies of the trisomies at birth were based on only three cases of T13 and seven of T18 resulting in very imprecise estimates [Hook and Hammerton, 1977].

Won et al. [2005] followed 106 cases of T18 where termination had been declined from 20 weeks to birth. Of these, 32% (95% CI: 23–42) ended in fetal loss between 20 weeks gestation and term, lower than our estimate of 59% (49–77%) at 20 weeks. Their study was set in a single center and included only cases karyotyped following abnormal serum screening results, whereas our dataset included all prenatal diagnoses, a large proportion of whom were diagnosed due to an anomaly being detected on an ultrasound scan. This suggests that those cases detected following an ultrasound scan may be more likely to result in a miscarriage or stillbirth than those detected through serum screening. This is also indicated by Yamanaka et al. [2006] who followed up a cohort of T18 fetuses diagnosed at a mean gestation of 28 weeks, with the majority being identified due to abnormal ultrasound findings and found that 45% (95% CI: 32–58) were lost, higher

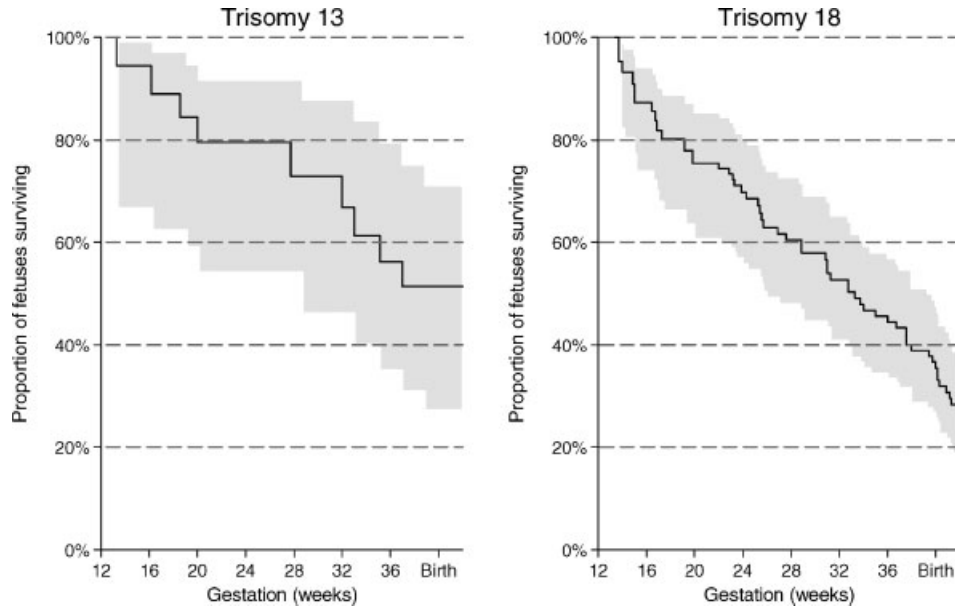


FIG. 1. Proportion of T13 and T18 fetuses surviving from 12 weeks gestation with 95% confidence intervals (shaded in gray).

than the proportion lost in the study by Won et al. [2005] despite the diagnosis being at a later gestation.

We also found a suggestion that T18 is more lethal for male fetuses than for female fetuses, a finding that is supported by published sex ratios at different gestational ages [Hook et al., 1989; Huether et al., 1996; Niedrist et al., 2006]. These studies observed the ratio of males to females in T18 births to be around 0.69 (in our study it is 0.64), whereas the ratio at amniocentesis was roughly 0.9 (in our study it is 0.85). This implies a greater risk of loss between

amniocentesis and birth for male fetuses with T18 than for females. No sex difference was observed in the T13 loss rate. The prenatal and postnatal sex ratios in T13 reported by Huether et al. [1996] were both 0.88, also indicating no sex difference in the loss rate.

Survival analysis including all prenatal diagnoses has been previously established as the best way in which to directly estimate fetal loss rate. Pregnancies ending in termination are 'under observation' for the time between diagnosis and the termination,

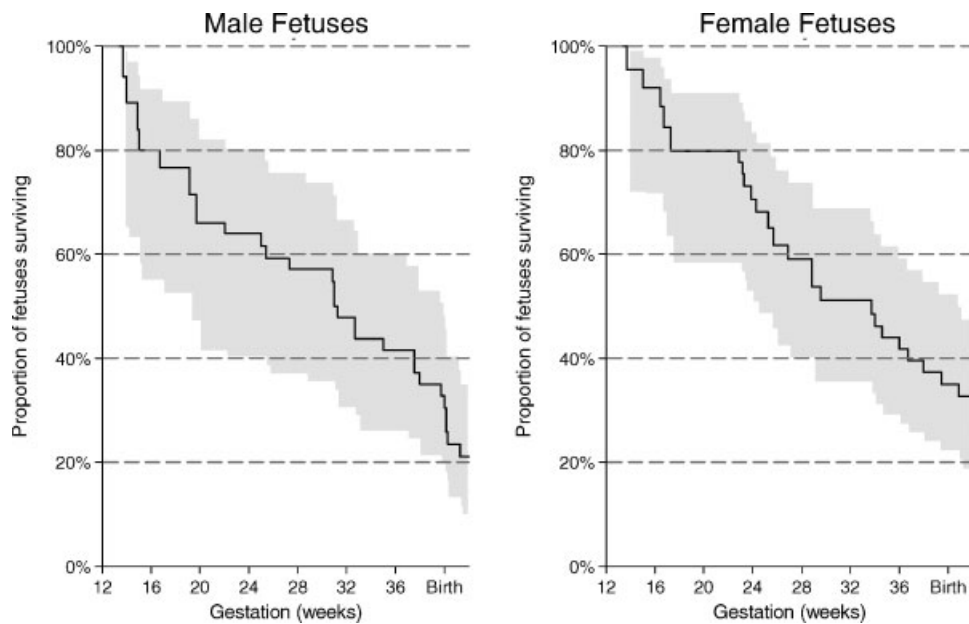


FIG. 2. Proportion of T18 fetuses surviving from 12 weeks gestation according to sex of the fetus with 95% confidence intervals (shaded in gray).

TABLE III. The Proportions of T13 and T18 Pregnancies Resulting in a Fetal Loss According to Gestational Age at Diagnosis

Study	Gestational age at diagnosis (weeks)	Trisomy 13 (95% CI)		Trisomy 18 (95% CI)	
		Published estimates	Estimates from current study at same age	Published estimates	Estimates from current study at same age
Snijders et al. [1994]	9–14	80 (42–97)	49 (29–73)	86 (66–95)	72 (61–81)
Hook et al. [1989]	15–20	37 (11–70)	42 (18–72)	64 (49–80)	65 (57–79)
Snijders et al. [1994]	15–20	57 (0–91)	42 (18–72)	70 (35–89)	65 (57–79)
Won et al. [2005]	>20			32 (23–42)	59 (49–77)
Yamanaka et al. [2006]	28			45 (32–58)	52 (41–65)

because if a fetal loss occurs in this time, the case would be recorded as a fetal loss. Excluding pregnancies ending in terminations would therefore significantly inflate the estimates of fetal loss rate. A numerical illustration of the consequences of excluding terminated pregnancies is provided by Morris et al. [1999]. Won et al. avoid this bias by including only pregnancies where termination had been actively refused. Information regarding mother's intentions was not available from our congenital anomaly registers.

We have recently conducted a study to determine the ascertainment and accuracy of BINOCAR regional registers (paper in preparation). Cases of trisomy 21 recorded by BINOCAR were compared using probabilistic record linkage with cases recorded by the National Down Syndrome Cytogenetic Register (NDSCR). Capture-recapture methods were used to estimate the ascertainment of the registers. Ascertainment of BINOCAR registers was around 95% complete, and was found to be independent of the pregnancy outcome, so ascertainment bias is unlikely to occur in the calculation of the risk of fetal loss. Comparisons of the matched records revealed that pregnancy outcome was successfully recorded in around 99% of cases. Furthermore, cases in which the pregnancy outcome was not recorded by BINOCAR registers were not substantially more likely to have ended in fetal loss. In our data, we excluded eight cases of T13 (3%) and 21 cases of T18 (3%) in which the outcome was not recorded. This is therefore unlikely to affect our results.

The date of termination was missing for five cases diagnosed after a CVS and three cases diagnosed after an amniocentesis. The length of time between diagnosis and termination was assumed to be one week for cases diagnosed after having a CVS, and three weeks after having an amniocentesis. The sensitivity of the results on these assumptions was investigated by repeating the analysis assuming different lengths of time between diagnosis and termination ranging from one day to four weeks. The results did not materially alter.

This paper provides the most precise gestation-specific estimates currently available for the risk of fetal loss in a general population. The worldwide increase in both prenatal screening for Down syndrome and fetal anomaly ultrasound scans at around 20 weeks gestation is leading to an increase in the numbers of women referred for prenatal diagnoses. This combined with increasing maternal age will lead to an increase in the number of cases of T13 and T18 and in the proportion that are detected prenatally. It is essential that women who are found to be carrying a fetus with T13 or T18 be given reliable prognoses for their pregnancy, and that accurate epidemiological information is available to meet the demand from healthcare services and policy makers.

ACKNOWLEDGMENTS

We thank the following BINOCAR registers for allowing us to use their data: the North Thames West Congenital Malformation Register, the Northern Congenital Abnormality Survey (NorCAS), the South West Congenital Anomaly Register, the East Midlands & South Yorkshire Congenital Anomaly Register and the Congenital Anomaly Register and Information Service (CARIS) of Wales. JM is Director of The National Down Syndrome Cytogenetic Register, funded by the United Kingdom National Screening Committee. GS is supported by grant RAB04/PJ/03 from the Research Advisory Board of St Bartholomew's and The Royal London Charitable Foundation. NorCAS is funded by the UK Department of Health (Disease Register Call). We also thank Lenore Abramsky, Judith Budd, Judith Rankin and Eva Alberman for help with preparation of the manuscript.

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