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Title: Survival of Trisomy 18 (Edwards Syndrome) and Trisomy 13 (Patau Syndrome) in England and Wales: 2004 – 2011

Running title: Survival of trisomy 18 and trisomy 13

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Abstract

The aim of this study is to determine the survival of live births with trisomy 18 and trisomy 13 and their variants. Information on live births with trisomy 18 or trisomy 13 recorded in the National Down Syndrome Cytogenetic Register (NDSCR) was linked by the NHS Information Centre to obtain information about survival. Survival was known for 326 (88%) of live births with trisomy 18 and 142 (82%) of live births with trisomy 13 born in England and Wales between 2004 and 2011. The median survival time for live births with full trisomy 18 was 14 days and with full trisomy 13 was 10 days, the 3-month survival was 20% and 18% respectively, and the 1-year survival for both syndromes was 8%. The 1 year survival for live births with trisomy 18 mosaicism (n = 17) was 70%, for those with trisomy 13 mosaicism (n=5) was 80% and for those with partial trisomy 13 (Robertsonian translocations) (n = 17) was 29%.

This study is based on the largest data set on survival for live births with trisomy 18 and trisomy 13. Although median survival for these children is two weeks or less, about 1 in 5 survive for 3 months or more and about 1 in 12 survive for 1 year or more. We suggest that these survival rates are used in counselling as well as the median survival time.

Keywords: Trisomy 18, Trisomy 13, Survival, Mosaicism, Robertsonian Translocation

INTRODUCTION

Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are the second and third most common autosomal trisomies in live births. Although long term survivors have been reported [Mankinen and Sears, 1976; Mehta et al., 1986; Smith et al., 1989; Zoll et al., 1993], most infants with trisomy 18 or trisomy 13 usually die in the first few days or weeks of life[Brewer et al., 2002; Goldstein and Nielsen, 1988; Irving et al., 2011; Nembhard et al., 2001; Niedrist and Riegel, 2006; Rasmussen et al., 2003; Vendola et al., 2010], with studies reporting median survival times varying from 2 days to 14.5 days. About 1% of trisomy 18 and trisomy 13 cases have mosaicism and 8% of trisomy 13 cases are partial trisomies (they have Robertsonian translocations)[Alberman et al., 2012]. Case reports suggest these individuals live longer than those with full trisomy, but no cohort study has reported the survival of live births with trisomy 18 mosaicism or partial trisomy 13.

Information on factors associated with long-term survival is limited, although some studies have suggested that girls live longer than boys[Lin et al., 2006; Nembhard et al., 2001; Niedrist and Riegel, 2006; Rasmussen et al., 2003; Weber, 1967]. Studies also suggest that gestational age at delivery ethnicity and the presence of heart defects can also affect survival[Niedrist and Riegel, 2006; Rasmussen et al., 2003].

In this study we investigate the survival of all live births with trisomy 18 and trisomy 13 in England and Wales from 2004 to 2011. We evaluate the impact of gender, gestational age and the presence of a heart defect on survival. We also report the survival of live births with trisomy 18 mosaicism, trisomy 13 mosaicism or with partial trisomy 13.

MATERIALS AND METHODS

Data Collection

The National Down Syndrome Cytogenetic Register (NDSCR) has collected data on all diagnoses of trisomy 18 or trisomy 13 since January 2004 from all clinical cytogenetic laboratories in England and Wales[Morris, 2011]. The laboratories were asked to complete a form for each diagnosis of trisomy 18 or trisomy 13 and their variants. The form contains details of the outcome of the pregnancies (live birth/stillbirth/spontaneous abortions/terminations), the gestational age at delivery, the presence of a heart defect, the date of delivery and the NHS number of the baby.

Data Matching

All live births with trisomy 18 or trisomy 13 that were diagnosed prenatally or postnatally from 2004 to 2011 were identified in the NDSCR database. Information on the baby's NHS number, date of birth, gender, gestational age at delivery, postcode and the first three characters of the mother's surname were extracted. These data were sent to the NHS Information Centre (NHSIC) for data linkage after excluding any case missing two or more of NHS number, date of birth, or postcode. The NHS Information Centre provided information on matching status, date of death, and cause of death.

Ethics Approval

The NDSCR as a part of the British Isles Network of Congenital Anomaly Registers (BINOCAR) has been given permission to operate without informed consent. The NDSCR has ethics approval from the Trent multi-centre research ethics committee (MREC) to undertake studies involving the use of its data.

Statistical Analyses

We estimated the survival probability, including the median survival time where possible, from birth by the Kaplan-Meier product-limit method for the entire study period. For live

births with full trisomy 18 and full trisomy 13, we also estimated the survival probability at 1-week, 1-month, 3-month and 1-year time points and stratified for gender, gestational age at delivery and the presence of a heart defect. We used the log-rank test to examine the association between prognostic factors and survival. For gestational age at delivery, we only compared the variation between 32-36 weeks and 37 weeks and over, because the number of live births born before 32 weeks was small and clearly had much higher mortality rates. A baby was judged to have a heart anomaly if there was a mention of a heart anomaly on the NDSCR form or a mention of one on the death certificate. The information on the NDSCR forms may not be complete as it is a free text box and information on specific anomalies is not requested.

RESULTS

Trisomy 18

Table I shows the outcomes of the 4028 recorded cases with diagnoses of trisomy 18. Survival information was available for 326 (88%) live births with trisomy 18; 309 with full trisomy 18 and 17 with trisomy 18 mosaicism. None of the trisomy 18 cases were partial. Of the 309 children with full trisomy 18, 285 (92%) died during the first year of life, 10 (3%) died between the age of 1 and 5 years and 14 (5%) were alive by the date of data extraction. Among the 14 children alive 3 were at least 5 years old.

Table II shows that the median survival time for infants with full trisomy 18 was 14 days (95% CI: 10 - 20) with 20% surviving 3 months (95%CI: 16% - 24%) and 8% surviving a year (95% CI: 5% - 11%). Figure 1 and table II show that survival was significantly longer among girls than among boys (log-rank test, $p = 0.044$). Survival was longer for births after 36 weeks compared with those between 32 to 36 weeks gestation ($p = 0.002$). Of the 309 children with full trisomy 18, 58% had a heart anomaly (43% according to the death

certificate and 34% from the NDSCR form). The presence of a heart defect was not associated with survival (p = 0.262).

Among the 17 children with trisomy 18 mosaicism, 6 (35%) died during the study period and 11 children (65%) were alive by the date of data extraction and 7 (41%) were more than 5 years old. The median survival time was over 1 year and 70% survived over a year (95% CI: 42% - 86%) (table II).

Trisomy 13

Table I shows the outcomes of the 1662 recorded cases with diagnoses of trisomy 13. Survival information was available for 142 (82%) live births with trisomy 13; 120 with full trisomy 13, 17 with partial trisomy 13 (Robertsonian translocations) and 5 with trisomy 13 mosaicism. There was one partial that was not Robertsonian: 47,XX,der(13)t(4;13)(p16;q12.3). Of the 120 children with full trisomy 13, 110 (92%) died during the first year of life, 3 (3%) died between the age of 1 and 5 years and 7 (6%) were still alive by the date of data extraction (4 of whom were more than 5 years old).

Table III shows that the median survival time for infants with full trisomy 13 was 10 days (95% CI: 7 - 19) with 18% surviving 3 months (95% CI: 11% - 25%) and 8% surviving at least a year (95% CI: 4% - 14%). Figure 2 and table III show that survival was significantly longer among girls than among boys (log-rank test, p = 0.038), but that there was no association with gestational age at birth (p = 0.135). Of the 120 children with full trisomy 13, 43% had a heart anomaly (28% according to the death certificate and 23% from the NDSCR form). The presence of a heart defect was not associated with survival (p = 0.526).

For the 17 children with partial trisomy 13 (Robertsonian translocations), 14 (82%) died during the study period. The three children (18%) who were still alive were all over 5 years old. Table III shows that 29% survived over 1 year (95% CI: 11% - 51%).

For the 5 children with trisomy 13 mosaicism, only one died at 4 months of age and the other four children were aged 1, 3, 3, and 4 years at the date of data extraction; 80% survived at least one year.

DISCUSSION

This population-based study on live births with trisomy 18 and 13 is the largest study of its kind. It is unlikely that many live-born children with trisomy 18 or 13 were excluded from the analysis since the data were collected both pre- and postnatally and the NDSCR has been shown to be over 94% complete[Savva and Morris, 2009]. It is also unlikely that births were incorrectly included as all the births were karyotyped.

In our study the median survival for live births with trisomy 18 was 14 days, slightly longer than that reported by most of the earlier studies (table IV). This may reflect improvements in survival. The proportion surviving at least one year (8%) was also slightly higher than that reported in other studies. Our study confirmed that girls with trisomy 18 live longer survival than affected boys [Baty et al., 1994; Carter et al., 1985; Embleton et al., 1996; Lin et al., 2006; Niedrist and Riegel, 2006; Root and Carey, 1994; Weber, 1967], but the 1-year survival rates were similar in boys and girls. None of the previous studies had sufficient power to compare longer term survival in boys and girls. Our study showed gestational age at delivery was a strong predictor of the median survival time in agreement with a Swiss study[Niedrist and Riegel, 2006] (<1 day, 2 days and 10 days). Rasmussen et al[Rasmussen et al., 2003] reported that children without heart defects had a higher 1-year survival rate than those with heart defects, but in our study there was no statistically significant difference.

This may be due to the classification of those with heart defects being inaccurate as we relied on either a mention of a heart anomaly on the NDSCR form or on the death certificate and both sources of data were incomplete. It was expected that children with trisomy 18 mosaicism have a longer survival and this is confirmed; 70% of the 17 such children lived for more than 1 year and 41% lived for at least 5 years.

In our study the survival of live births with trisomy 13 was also slightly longer than that reported in earlier studies (table V). We again found evidence that girls have live longer than boys as reported in other studies[Ferguson-Smith, 1962; Rasmussen et al., 2003]. We did not find that gestational age had a statistically significant association with survival, but our study did not have enough power to fully investigate this association. Also we found no significant association of survival with the presence of a heart defect, but as noted above this may reflect the inaccuracy of classifying heart defects. Our study confirmed the longer survival of live births with partial trisomy 13 and trisomy 13 mosaicism compared with those with full trisomy 13 which was also reported by Magenis et al.[Magenis et al., 1968] (This study was excluded in table V due to selection bias of cases). The 1-year survival of children with partial trisomy 13 was much higher than that of full trisomy 13 (29% vs. 8%, $p = 0.009$). Although we only collected data on 5 children with trisomy 13 mosaicism, the 1-year survival was significantly greater than those with full trisomy 13 (80% vs. 8%, $p < 0.001$).

A limitation of our study is that we do not have information about the treatment or surgical interventions that the children receive; these were likely to vary across England and Wales. In particular we were unable to assess if the infants with cardiac anomalies received any cardiac interventions, which are known to improve survival of children with trisomy 18 or trisomy 13 in Japan and the USA[Graham et al., 2004; Kaneko et al., 2008; Kosho et al., 2006; Maeda et al., 2011].

The median survival time (2 weeks) is an incomplete description of survival and may imply that 50% will not survive much more than a further two weeks. This would be incorrect as almost a fifth survive for 3 months and almost a tenth survive a year. We suggest that as well as the median survival time the proportions of these children surviving both 3-month and 1-year should be quoted in information provided to parents, genetic counsellors and health professionals involved in caring for affected children.

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Conflict of interests: The authors declare no conflict of interests.

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Table I The outcomes of cases diagnosed with trisomy 18 and trisomy 13 in England and Wales between 2004 and 2011

	No (%) of cases diagnosed in England and Wales	
	Trisomy 18	Trisomy 13
Total	4028	1662
Miscarriages (20-23 weeks gestation)	424 (11%)	278 (17%)
Stillbirths (24+ weeks gestation)	185 (5%)	36 (2%)
Terminations of pregnancy	2574 (64%)	1053 (63%)
Prenatal diagnoses with unknown outcome*	473 (12%)	122 (7%)
Live births	372 (9%)	173 (11%)
For the live births		
Insufficient information for matching	36 (9%)	20 (12%)
Sufficient information but match not achieved by NHSIC	10 (3%)	11 (6%)
Matched by NHSIC	326 (88%)	142 (82%)

*Diagnoses with unknown outcomes were likely to have been terminations of pregnancy

Table II Median survival time, 1-week, 1-month, 3-month, and 1-year survival of live births with full trisomy 18 according to gender, gestational age and the presence of heart defects and of live births with trisomy 18 mosaicism.

	Number of live births	Median survival time (days, 95% CI)	Percentage Surviving (95% CI)				P-value for survival
			1-week	1-month	3-month	1-year	
Full Trisomy 18	309	14 (10-20)	60 (55-65)	39 (34-45)	20 (16-24)	8 (5-11)	
Gender							
Male	101	7 (5-11)	48 (38-57)	29 (20-38)	14 (8-21)	7 (3-13)	0.044
Female	208	21 (14-32)	66 (59-72)	44 (37-51)	23 (17-28)	8 (5-12)	
Gestational age*							
≥ 37 weeks	165	35 (23-53)	67 (59-74)	53 (45-61)	28 (21-35)	10 (6-15)	0.002†
32-36 weeks	79	9 (6-14)	54 (43-65)	27 (17-37)	13 (6-21)	5 (2-11)	
< 32 weeks	31	2 (0-5)	23 (10-38)	0	0	0	
Heart defect							
Absent	129	17 (7-26)	57 (48-65)	40 (31-48)	19 (13-27)	14 (9-21)	0.262
Present	180	13 (10-22)	62 (55-69)	39 (32-46)	20 (15-26)	3 (1-7)	
Trisomy 18 mosaicism	17	-	82 (55-94)	76 (49-90)	70 (42-86)	70 (42-86)	

*34 (11%) children with unknown gestational age

†P-value represents the comparison between gestational age at 32-36 weeks and ≥ 37 weeks

Table III Median survival time, 1-week, 1-month, 3-month, and 1-year survival of live births with full trisomy 13 according to gender, gestational age and the presence of heart defects and of live births with partial trisomy or trisomy 13 mosaicism.

	Number of live births	Median survival time (days, 95% CI)	Percentage Surviving (95% CI)				P-value for survival
			1-week	1-month	3-month	1-year	
Full Trisomy 13	120	10 (7-19)	59 (50-67)	29 (21-37)	18 (11-25)	8 (4-14)	
Gender							
Male	52	7 (4-18)	50 (36-63)	23 (13-35)	10 (4-19)	4 (1-12)	0.038
Female	68	12 (8-25)	66 (54-76)	34 (23-45)	24 (14-34)	12 (6-21)	
Gestational age*							
≥ 37 weeks	66	21 (10-32)	73 (60-82)	39 (28-51)	21(12-32)	11 (5-19)	0.135†
32-36 weeks	32	5 (3-19)	50 (32-66)	22 (10-37)	19 (8-34)	6 (1-18)	
< 32 weeks	11	0 (0-2)	9 (1-33)	0	0	0	
Heart defect							
Absent	68	9 (5-21)	55 (43-66)	30 (20-41)	23(14-34)	12 (5-20)	0.526
Present	52	15 (6-25)	65(50-76)	27 (16-40)	10(4-20)	4 (1-12)	
Partial trisomy 13	17	6 (0-653)	41 (19-63)	29 (11-51)	29 (11-51)	29 (11-51)	
Trisomy 13 mosaicism	5	-	100	100	100	80 (20-97)	

*11 (9%) children with unknown gestational age

†P-value represents the comparison between gestational age at 32-36 weeks and ≥ 37 weeks

Table IV Survival of live births with full trisomy 18

Trisomy 18 study	[Carter et al., 1985]	[Young et al., 1986]	[Goldstein and Nielsen, 1988]	[Root and Carey, 1994]	[Embleton et al., 1996]	[Naguib et al., 1999]	[Nembhard et al., 2001]	[Brewer et al., 2002]	[Rasmussen et al., 2003]	[Vendola et al., 2010]	[Niedrist and Riegel, 2006]	[Lin et al., 2006]	[Hsiao et al., 2009]	[Irving et al., 2011]	Current study
Study period	1972 - 1982	1980 - 1985	1977 - 1986	1979 - 1988	1986 - 1992	1980 - 1997	1995 - 1997	1974 - 1997	1968 - 1999	1999- 2003	1964 - 2003	1988 - 2004	1991 - 2006	1985 - 2007	2004 - 2011
Geographical region	Queensland	England	Denmark	Utah	England	Kuwait	Texas	Scotland	Georgia	Texas	Switzerland	Taiwan	Taiwan	Northern England	England and Wales
Sample size	43	21	76	64	34	118	68	84	114	200	161	39	31	67	309
Age	Proportion Surviving (%)														
1 week	43	32	44	45	26	47	56	43	63	52	40	46	58	36	60
1 month	26	18	21	34	15	NR	NR	25	39	30	22	16	32	NR	39
3 month	13	10	9	20	6	1	NR	NR	21	NR	14	5	NR	NR	20
1 year	4	0	NR	5	0	NR	10	2	8	3	6	3	6	6	8
Median survival (days)	5	2.5	6	4	3	NR	NR	6	14.5	7	4	6	12	NR	14

NR, not reported in study.

Two studies [Baty et al., 1994; Weber, 1967] were excluded because their selection of cases was from parents or patient support groups replying to questionnaires, which are biased towards longer survival.

Table V Survival of live births with full trisomy 13

Trisomy 13 study	[Goldstein and Nielsen, 1988]	[Wyllie et al., 1994]	[Nembhard et al., 2001]	[Brewer et al., 2002]	[Rasmussen et al., 2003]	[Vendola et al., 2010]	[Lin et al., 2007]	[Irving et al., 2011]	Current study
Study period	1977 - 1986	1985 - 1992	1995 - 1997	1974 - 1997	1968 - 1999	1999 - 2003	1985 - 2004	1985 - 2007	2004 - 2011
Geographical region	Denmark	Northern England	Texas	Scotland	Georgia	Texas	Taiwan	Northern England	England and Wales
Sample size	19	16	27	26	70	140	28	30	121
Age	Proportion Surviving (%)								
1 week	38	38	59	50	50	42	61	43	59
1 month	19	13	NR	28	30	20	29	NR	29
3 month	14	6	NR	NR	18	NR	14	NR	17
1 year	NR	0	7	3	9	3	4	3	8
Median survival (days)	2.5	3	NR	8.5	7	4.5	9	NR	10

NR, not reported in study.

Two studies [Magenis et al., 1968; Weber, 1967] were excluded because the selection of cases was biased towards longer survival.

Figure 1 Trisomy 18: Kaplan-Meier survival curves (truncated at 1 year). Panel a also contains 95% confidence interval.

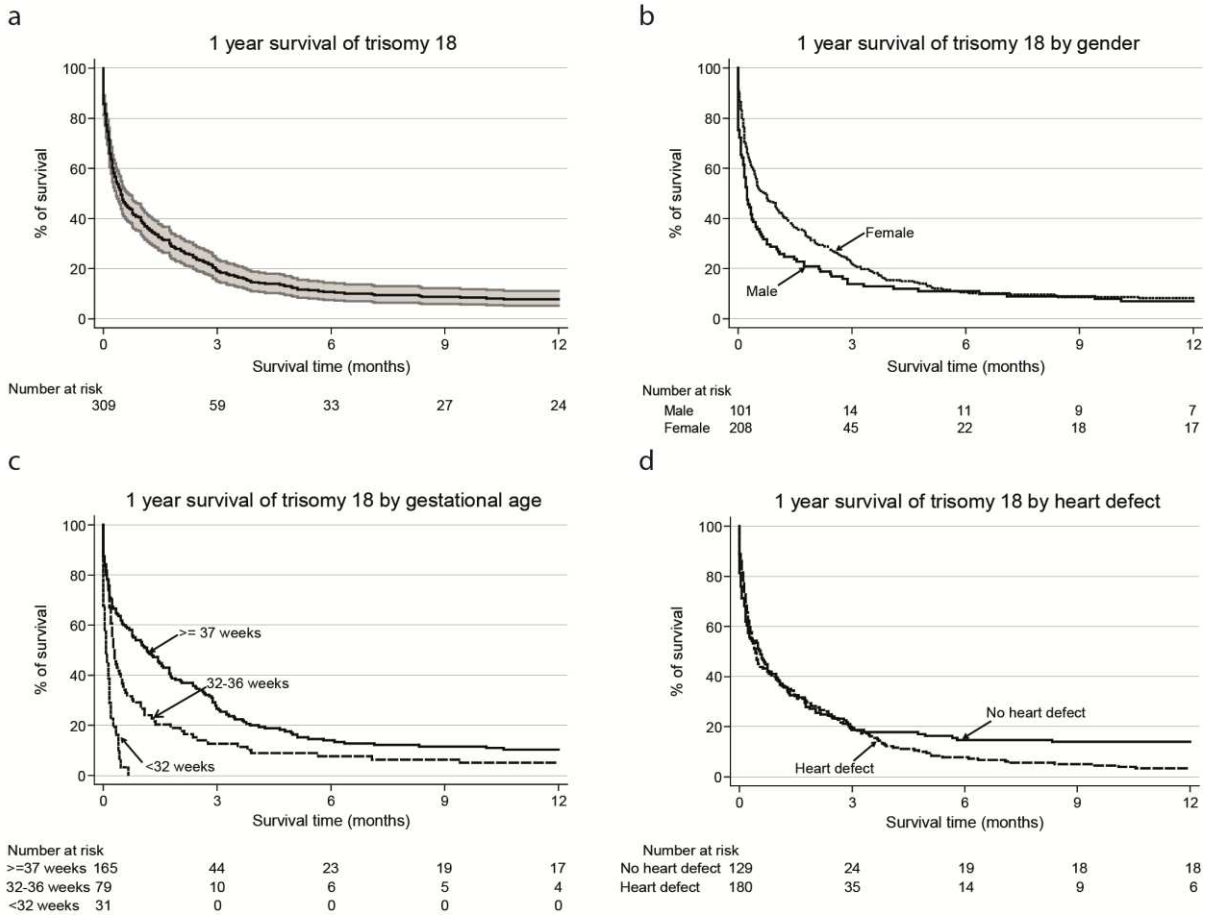

Figure 2 Trisomy 13: Kaplan-Meier survival curves (truncated at 1 year). Panel a also contains 95% confidence interval.