Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics

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BACKGROUND: The aim was to identify maternal risk factors in women giving birth to girls with Turner syndrome (TS) and to describe the characteristics of newborns with TS.

METHODS: The Swedish Genetic Turner Register was cross-linked with the Swedish Medical Birth Register. Between 1973 and 2005, 494 children with TS were born. Maternal age, parity, height, smoking habits and neonatal characteristics; mode of delivery, gestational age, size at birth and Apgar score, were compared with women in the general population who gave birth to girls during the same period.

RESULTS: More women with advanced maternal age (40+) delivered girls with TS, 3.2% when compared with 1.8% in the general population [OR 1.83, 95% confidence interval (CI) 1.09–3.08, after adjustment for year of birth]. Maternal height was inversely associated with TS pregnancies (P = 0.005). Late preterm birth occurred in newborns with TS in 10.5% when compared with 4.8% in the general population (OR 2.23; 95% CI: 1.67–2.97, after adjustment for year of birth and maternal age). Newborns with TS had birthweight less than −2SD in 17.8% and birth length less than −2SD in 21.0% when compared with 3.5 and 3.4%, in the general population (OR 6.55; 95% CI: 5.12–8.38 and OR 8.69; 95% CI: 6.89–10.97, after adjustment for year of birth and maternal age).

CONCLUSION: Advanced maternal age and short stature were risk factors for giving birth to a girl with TS. More TS girls were born late preterm and were smaller for gestational age than non-TS girls in the general population.

Key words: Turner syndrome / karyotype / pregnancy / maternal characteristics / neonatal

Introduction

Turner syndrome (TS) is a sex chromosomal aberration found in approximately one in 2000–2500 live born girls (Hook and Warburton, 1983; Nielsen and Wohler, 1991). Short stature, neck webbing, cardiac and renal malformations, primary gonadal failure, infertility, hypertension, osteoporosis, hearing problems and hypothyroidism are all common features in women with TS (Gravholt, 2004). The most common karyotype is monosomy, with a complete loss of one sex chromosome, 45,X. It is found in 40–50% of TS. Mosaicism occurs in 30–40% including 45,X/46,XX with a normal cell line. In some cases the second cell line involves a structurally altered X chromosome, a part of, or an entire Y chromosome (Hanson et al., 2001).

Currently, there is little information about characteristics of pregnant women carrying TS fetuses or giving birth to girls with TS. It is, however, known that women with TS can give birth to a girl with the same syndrome (Uehara et al., 1997; Cools et al., 2004). The literature is inconsistent about the role of maternal age, concerning both spontaneous miscarriages and live born children with TS.

The aim of this retrospective population-based cohort study was to report characteristics of women who gave birth to children with TS and to describe the neonatal data in girls with TS. We used data from the Swedish Genetic Turner Register and cross-linked it with the Swedish Medical Birth Register (MBR).

Materials and Methods

The Swedish Genetic Turner Register is a unique genetic register including Swedish girls and women diagnosed postnatally with TS between 1967 and 2006. The data in the Swedish Genetic Turner Register was collected from
all Swedish cytogenetic laboratories (Umeå, Uppsala, Linköping, Stockholm, Göteborg, Skövde and Lund) and included analysing laboratory, date of birth, information on karyotype and date of diagnosis. In the majority of cases type of tissue (peripheral blood lymphocytes, fibroblasts or buccal cells) and the number of analysed cells were recorded. Chromosomal analysis was mainly performed on cultures of peripheral blood lymphocytes. In some cases the analysis was also performed on buccal cells or in fibroblasts. During the first time period (1967–1994) TS diagnosis was based on a karyotype analysed on 10–25 cells. From 1995 all Swedish Genetic Laboratories analysed at least 30 cells when a TS diagnosis was suspected. Analysis was performed on all TS karyotypes combined and on subgroups of TS karyotypes. Karyotypes were subgrouped into the following four groups:

(i) monosomy 45,X
(ii) mosaics 45,X/46,XX
(iii) isochromosomes 45,X/46,X,i(X) and 46,X,i(X)
(iv) others including 45,X/46XY, 45,X/47,XXX, 45,X/48,XXXX, 45,X/49,XXXXX, 45,X/51,XXXXXX and 45,X/46,Xder(X) (including ring chromosomes, deletions or translocations)

For outcomes with small numbers in each group, analysis was performed on TS pregnancies of any karyotype, on TS pregnancies with monosomy (the subgroup which generally has shorter stature and more additional stigmata later in life) and on a combined group of TS pregnancies with mosaic, isochromosomes and ‘other’ karyotypes. The MBR covers nearly all deliveries in Sweden (a few percent are missing) from 1973 (Chattingius et al., 1990). It contains information about maternal characteristics (i.e. age, parity, height, socioeconomic status, smoking habits), antenatal care, delivery and neonatal data of live births and stillbirths. Data on maternal height and smoking habits were registered from 1983. The Swedish definition of a stillbirth between 1973 and July 2008 was intrauterine fetal death after 28 completed weeks of gestation. Data from the Swedish Genetic Turner Register was linked with the Medical Birth Register via the unique census registration number given to all citizens in Sweden. The study population comprised all women who gave birth to live born girls with TS between 1973 and 2005 and their corresponding newborns with TS. Stillbirths were not included in this study. Maternal age, parity, height, smoking habits in early pregnancy, mode of delivery, gestational age, weight and length at birth and Apgar scores were the outcome measures. Weight and length at birth were calculated as standard deviations (SD) from expected mean birthweight and length according to gestational age in a Swedish reference population (Marsal et al., 1996). The control group consisted of all other women and newborns in the Medical Birth Register during the same time period.

Continuous data were analysed with the Kruskal–Wallis non-parametric tests or ANOVA as specified. Findings with P-values below 0.05 were regarded as statistically significant.

**Ethics**

The study received approval from the Regional Ethic Committee at the University of Gothenburg.

**Results**

Between 1973 and 2005, 494 children with a post-natal diagnosis of TS were born. The 494 TS karyotypes were subgrouped into monosomy 45,X (n = 221), mosaic 45,X/46,XX (n = 62), isochromosome (n = 78) and ‘other’ (n = 133). During the same time period 1 610 754 girls without TS were born in Sweden. The number of TS girls born per year is shown in Fig. 1. The median age for a TS diagnosis of any karyotype was 7.9 years (range 0–34 years). The median age was 5.4 years (0–28 years) for TS monosomy, 7.5 years (0–34 years) for TS mosaic, 9.7 years (0–26 years) for TS isochromosome and 9.7 years (0–30 years) for the ‘other’ TS group (Kruskal–Wallis test for homogeneity, P < 0.0001).

Among the 494 girls with TS, 11 girls were twins (2.2%), which is similar to the overall twin frequency in Sweden during the study period according to the MBR (2.4%). Two of the 11 twins with TS were siblings, the other nine twins with TS had unaffected co-twins. There were no other siblings in the Turner group.

**Maternal characteristics**

The distribution of maternal age is shown in Table I. More women above the age of 40 delivered a girl with TS, 3.2% when compared with 1.8% in the general population (OR 1.83; 95% CI: 1.09–3.08, after adjustment for year of birth). In the analyses regarding maternal age, four women with TS were excluded. The ORs for TS pregnancies of any karyotype in relation to maternal age classes are shown in Fig. 2. Multiple logistic regression analysis with maternal age as the dependent variable using continuous data with one linear and one quadratic term, adjusted for year of birth, is also shown in Fig. 2. A corresponding simultaneous test of the linear and quadratic terms revealed an association between maternal age and TS in the offspring (P = 0.006). In the different subgroups of TS pregnancies, a U-shaped

**Statistical analysis**

All statistical analyses were performed using Gauss (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com). Possible associations between TS (and if specified different subgroups of TS) and maternal and infant characteristics were investigated using simple and multiple logistic regression analyses as specified. Linear, quadratic and polynomial models were tested. The best available models were determined using visual inspection and the Hosmer–Lemeshow test for goodness of fit. Variables with P-values below 0.2 were included in the final models. The Odds Ratios (ORs) with 95% confidence intervals (CIs) obtained from the multiple logistic regression analyses were used to produce graphs.

Tests of homogeneity of the ORs across strata were based on weighted sums of the squared deviations of the stratum specific log-ORs from their weighted means (Hosmer and Lemeshow, 1989).

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**Figure 1** Yearly incidence of individuals born with TS (all karyotypes) in Sweden during the period 1973–2005.
relationship regarding maternal age was indicated for monosomy, but this was not statistically significant ($P = 0.16$). For the mosaic group a statistically significant U-shaped curve was obtained ($P = 0.02$). For isochromosomal TS, a linear model showed the best fit when investigating the relationship with maternal age, and a significant linear association between isochromosomal TS and maternal age was revealed.

**Table I** Characteristics of women who gave birth to a child with TS between 1973 and 2005 when compared with all other women in the MBR during the same time period.

<table>
<thead>
<tr>
<th></th>
<th>All Turner (n = 494) (%)</th>
<th>Monosomy (n = 221) (%)</th>
<th>45,X/46,XX Mosaic (n = 62) (%)</th>
<th>Iso-chromosome (n = 78) (%)</th>
<th>Other (n = 133) (%)</th>
<th>MBR (n = 1 610 754) (%)</th>
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</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>&lt;20</td>
<td>21 (4.3)</td>
<td>12 (5.4)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>8 (6.0)</td>
<td>56 005 (3.5)</td>
</tr>
<tr>
<td>20–24</td>
<td>107 (21.7)</td>
<td>51 (23.1)</td>
<td>14 (22.6)</td>
<td>17 (21.8)</td>
<td>25 (18.8)</td>
<td>353 974 (22.0)</td>
</tr>
<tr>
<td>25–29</td>
<td>165 (33.4)</td>
<td>71 (32.1)</td>
<td>16 (25.8)</td>
<td>28 (35.9)</td>
<td>50 (37.6)</td>
<td>581 583 (36.1)</td>
</tr>
<tr>
<td>30–34</td>
<td>134 (27.1)</td>
<td>56 (25.3)</td>
<td>21 (33.9)</td>
<td>23 (29.5)</td>
<td>34 (25.6)</td>
<td>426 102 (26.5)</td>
</tr>
<tr>
<td>35–39</td>
<td>51 (10.3)</td>
<td>25 (11.3)</td>
<td>6 (9.7)</td>
<td>7 (9.0)</td>
<td>13 (9.8)</td>
<td>163 686 (10.2)</td>
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<td>40+</td>
<td>16 (3.2)</td>
<td>6 (2.7)</td>
<td>4 (6.5)</td>
<td>3 (3.8)</td>
<td>3 (2.3)</td>
<td>29 404 (1.8)</td>
</tr>
<tr>
<td>Parity (n)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>206 (41.7)</td>
<td>94 (42.5)</td>
<td>25 (40.3)</td>
<td>31 (39.7)</td>
<td>56 (42.1)</td>
<td>680 652 (42.3)</td>
</tr>
<tr>
<td>2</td>
<td>170 (34.4)</td>
<td>71 (32.1)</td>
<td>25 (40.3)</td>
<td>24 (30.8)</td>
<td>50 (37.6)</td>
<td>581 066 (36.1)</td>
</tr>
<tr>
<td>3</td>
<td>80 (16.2)</td>
<td>38 (17.2)</td>
<td>10 (16.1)</td>
<td>12 (15.4)</td>
<td>20 (15.0)</td>
<td>244 363 (15.2)</td>
</tr>
<tr>
<td>4+</td>
<td>38 (7.7)</td>
<td>18 (8.1)</td>
<td>2 (3.2)</td>
<td>11 (14.1)</td>
<td>7 (5.3)</td>
<td>104 673 (6.5)</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>219</td>
<td>92</td>
<td>22</td>
<td>43</td>
<td>62</td>
<td>639 864</td>
</tr>
<tr>
<td>&lt;150</td>
<td>1 (0.4)</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>0</td>
<td>0</td>
<td>358 (0.4)</td>
</tr>
<tr>
<td>150–159</td>
<td>42 (15.3)</td>
<td>13 (10.1)</td>
<td>5 (12.5)</td>
<td>8 (22.9)</td>
<td>16 (22.5)</td>
<td>121 943 (12.6)</td>
</tr>
<tr>
<td>160–169</td>
<td>160 (58.2)</td>
<td>72 (55.8)</td>
<td>31 (77.5)</td>
<td>19 (54.3)</td>
<td>38 (53.5)</td>
<td>548 405 (56.5)</td>
</tr>
<tr>
<td>170–179</td>
<td>70 (25.5)</td>
<td>42 (26.6)</td>
<td>4 (10.0)</td>
<td>6 (22.9)</td>
<td>16 (22.5)</td>
<td>282 350 (29.1)</td>
</tr>
<tr>
<td>180+</td>
<td>2 (0.7)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>14 608 (1.5)</td>
</tr>
</tbody>
</table>

Values are n (% of total with unknown excluded).

**Figure 2** Maternal age and OR for a Turner pregnancy (all karyotypes, n = 490). Four mothers with a diagnosis of TS who gave birth to a girl with TS were excluded. Reference group: maternal age 30–34 years.
No association was found between maternal age and the risk of a TS pregnancy in the ‘other’ TS group \((P = 0.62)\). However, no significant heterogeneity regarding the obtained risk estimates for maternal age above 40 years was found between the different TS groups \((P\text{-value for homogeneity} = 0.38)\).

There was no indication of any association between parity and TS. After adjustment for maternal age and year of birth and compared with Parity 2, the \(P\)-values for TS obtained after multiple logistic regression analyses for Parity 1, 3 and 4+ were 0.96, 0.64 and 0.82, respectively. Furthermore, no relation between maternal smoking and TS was found. Information on maternal smoking (from 1983 onwards) was available in 309 TS pregnancies, and in 64 of these (20.7%) maternal smoking was reported. The corresponding percentage in the general population was 20.1%. The OR for any smoking in early pregnancy, adjusted for maternal age and year of birth was 0.88 (95% CI: 0.67–1.17, \(P = 0.38\)). The lack of any association between parity or maternal smoking and TS was valid for all subgroups of TS. Thus, neither parity nor maternal smoking was adjusted for in the multiple logistic regression models.

Table I shows the distribution of maternal height. Data on maternal height were not registered in the Medical Birth Register before 1983; hence data were missing for 44% of TS mothers and 40% of non-TS mothers. Maternal height was inversely associated with TS pregnancies of any karyotype \((P = 0.005\) using maternal height as continuous data with one linear term). Two women with a diagnosis of TS were excluded from the analyses regarding maternal height. Maternal height in TS pregnancies with monosomy is shown in Fig. 3a. No association was found between maternal height and risk of TS pregnancy in the monosomy group \((P = 0.80)\). Maternal height was inversely associated with TS pregnancies in the combined group of mosaic, isochromosome and ‘other’ karyotypes \((P < 0.001)\), Fig. 3b. ORs are adjusted for year of birth as well as the multiple logistic regression analyses using maternal height as continuous data with one linear term.

**Neonatal characteristics**

Preterm birth occurred more often in TS pregnancies than in non-TS pregnancies. Late preterm birth (Week 32–36) occurred in 10.3% of all TS pregnancies when compared with 4.8% in the general population (Table II). Similar results were obtained for TS pregnancies with monosomy and isochromosome. An increased risk of preterm birth <28 weeks was seen for the ‘other’ TS group when compared with non-TS. All TS pregnancies, and each subgroup of TS pregnancies, had lower rates of post-term deliveries. Post-term delivery occurred in 2.8% in all TS pregnancies when compared with 8.2% in the general population. More TS girls were small for gestational age (less than −2SD weight) compared with non-TS girls in the general population, 17.8 versus 3.5% (Table II). Similar results were obtained for each TS subgroup separately. The median (range) SD weight for all TS was −0.99 (−4.55 to 2.74), for TS monosomy −0.99 (−3.86 to 2.74), for TS mosaic −0.64 (−3.23 to 1.83), for TS isochromosome −1.29 (−3.51 to 1.00) and for the ‘other’ TS group −1.21 (−4.55 to 1.70). The results from an analysis of variance revealed differences between the TS subgroups regarding birthweight SD \((P = 0.04)\).

Fewer TS girls were large for gestational age (>2SD weight) compared with non-TS girls in the general population, 0.6 versus 3.1% (Table II). Twenty-one percent of girls with TS had a length at birth less than −2SD, compared with 3.4% in the general population (Table II). Similar results were obtained for the subgroups of TS. The median (range) SD height for all TS girls was −1.17 (−4.69 to 2.01), for TS monosomy −0.97 (−4.69 to 1.96), for TS mosaic −0.72 (−4.13 to 1.21), for TS isochromosome −1.32 (−3.68 to 1.09) and for the ‘other’ TS group −1.26 (−4.47 to 2.01). \(P\)-value for difference between TS subgroups = 0.007 (analysis of variance). The OR for being less than −2SD length for the ‘other’ TS group when compared with the TS monosomy group was 2.21 (95% CI: 1.29–3.80), and for the TS isochromosome group when compared with the TS monosomy group 3.04 (95% CI: 1.65–5.58). Adjustment for maternal age, parity, height and year of birth did not change the results. Apgar score at 5 min did not differ between the TS girls and controls \((P = 0.88)\). Caesarean section was more commonly performed in TS deliveries, 17.0%, when compared with controls, 11.8% (OR adjusted for maternal age and year of birth: 1.59; 95% CI: 1.25–2.01).

**Discussion**

Advanced age of the mother (40+) and short maternal height constituted risk factors for giving birth to a girl with TS. TS girls were more frequently born preterm and small for gestational age compared with children in the non-TS population.

Previously, conflicting results concerning advanced maternal age and the risk of TS have been reported. Bernasconi et al. (1994) found an association between high parental age and the incidence of TS. Carothers et al. (1980) observed a possible paternal age effect for the 45,X/46,X,i(X) or 46,X,i(Xq) karyotype, whereas no association was found between maternal age and 45,X monosomics. In a large study on 88 965 second trimester amniocenteses, an increased incidence of 45,X/46,XX mosaic fetuses was seen in women ≥35 years of age (Forabosco et al., 2009). That finding is in accordance with the hypothesis that 45,X monosomic fetuses do not survive the pregnancy to the same extent as mosaic 45X/46,XX fetuses (Hook and Warburton, 1983). Absence of a parental age effect has also been reported (Loughlin et al., 1991). Further more, other chromosomal aberrations like trisomy 21 are related to higher maternal age (Hassold and Chiu, 1985; Ljung er et al., 2005). Recent studies have shown that the oocyte quality has some age-related dysfunctions which can explain the ‘maternal age effect’, especially disturbances of the mitochondrial function and thereby a loss of the energy necessary for proper oocyte function (Wang et al., 2009).

Short maternal stature is another previously reported risk factor for giving birth to a daughter with TS (Rochiccioli et al., 1994). In most developed countries as in the Western Swedish region, the detection rate for TS is ~50% (El-Mansoury et al., 2007). Estimating an incidence of one girl with TS in 2000–2500 live born girls (Hook and Warburton, 1983; Nielsen and Wohrlt, 1991), the yearly numbers of TS girls in Sweden should be 20–25 and totally during the study period, 1973–2005, 600–700 TS girls should be born. Consequently, about one–third of the expected number of girls with TS are missing in our study. The undiagnosed cases will be diluted among the comparison group girls and is unlikely to influence the observed associations. Generally, it is likely that those cases that remain undiagnosed do so because their phenotype is less pronounced. Therefore, some of the mothers might very well have been Turner mosaic cases themselves. We found four
Figure 3 (a) Maternal height and OR for a monosomy Turner pregnancy \( (n = 113) \). Women not born in Sweden \( (n = 15) \) and women with a diagnosis of TS \( (n = 1) \) were excluded. Reference group: maternal height 165–169 cm. (b) Maternal height and OR for a mosaic/iso/chromosome/other Turner pregnancy \( (n = 121) \). Women not born in Sweden \( (n = 24) \) and women with TS \( (n = 1) \) were excluded. Reference group: maternal height 165–169 cm.
### Table II: Characteristics of newborns with TS born between 1973 and 2005 in Sweden when compared with other newborn girls in the general population born during the same time period.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Turner ((n = 494)) (%)</th>
<th>Monosomy ((n = 221)) (%)</th>
<th>Mosaic ((n = 62)) (%)</th>
<th>Iso-chromosome ((n = 78)) (%)</th>
<th>Other ((n = 133)) (%)</th>
<th>MBR ((n = 1 610 754)) (%)</th>
<th>All Turner versus MBR (OR) (95% CI)</th>
<th>All Turner versus MBR (AOR*) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Unknown</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
<td>3453 (0.2)</td>
<td>0.95 (0.13–6.78)</td>
<td>0.99 (0.14–7.03)</td>
</tr>
<tr>
<td>&lt;28</td>
<td>4 (0.8)</td>
<td>2 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
<td>1 (0.8)</td>
<td>8633 (0.5)</td>
<td>1.52 (0.57–4.08)</td>
<td>1.53 (0.57–4.10)</td>
</tr>
<tr>
<td>28–31</td>
<td>52 (10.5)</td>
<td>24 (10.9)</td>
<td>4 (6.6)</td>
<td>14 (17.9)</td>
<td>10 (7.5)</td>
<td>76 893 (4.8)</td>
<td>2.22 (1.67–2.96)</td>
<td>2.23 (1.67–2.97)</td>
</tr>
<tr>
<td>37–41</td>
<td>422 (85.6)</td>
<td>191 (86.4)</td>
<td>55 (90.2)</td>
<td>57 (73.1)</td>
<td>119 (89.5)</td>
<td>1 386 210 (86.3)</td>
<td>1.0 reference</td>
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<td>42+</td>
<td>14 (2.8)</td>
<td>4 (1.8)</td>
<td>2 (3.3)</td>
<td>6 (7.7)</td>
<td>2 (1.5)</td>
<td>131 202 (8.2)</td>
<td>0.35 (0.21–0.60)</td>
<td>0.32 (0.19–0.55)</td>
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<tr>
<td>SD weight** Unknown</td>
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<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>(n = 10) 153</td>
<td>6.94 (5.43–8.87)</td>
<td>6.55 (5.12–8.38)</td>
</tr>
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<td>less than 87 (17.8)</td>
<td>34 (15.6)</td>
<td>10 (16.4)</td>
<td>15 (19.5)</td>
<td>28 (21.1)</td>
<td>56 663 (3.5)</td>
<td>1.0 reference</td>
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<td>&lt;2</td>
<td>155 (31.7)</td>
<td>69 (31.7)</td>
<td>16 (26.2)</td>
<td>26 (33.8)</td>
<td>44 (33.1)</td>
<td>249 494 (15.5)</td>
<td>2.79 (2.28–3.42)</td>
<td>2.72 (2.22–3.33)</td>
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<tr>
<td>1 to +1</td>
<td>233 (47.6)</td>
<td>107 (49.1)</td>
<td>32 (52.5)</td>
<td>36 (46.8)</td>
<td>58 (43.6)</td>
<td>1 059 672 (66.0)</td>
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<tr>
<td>&gt;2</td>
<td>11 (2.2)</td>
<td>5 (2.3)</td>
<td>3 (4.9)</td>
<td>0 (0.0)</td>
<td>3 (2.3)</td>
<td>185 291 (11.5)</td>
<td>0.27 (0.15–0.49)</td>
<td>0.27 (0.15–0.49)</td>
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<tr>
<td>SD length** Unknown</td>
<td>14</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>(n = 22) 877</td>
<td>8.98 (7.12–11.34)</td>
<td>8.69 (6.89–10.97)</td>
</tr>
<tr>
<td>less than 101 (21.0)</td>
<td>31 (14.6)</td>
<td>8 (13.1)</td>
<td>26 (34.2)</td>
<td>36 (27.5)</td>
<td>53 758 (3.4)</td>
<td>1.0 reference</td>
<td>1.0 reference</td>
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<tr>
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<td>69 (32.5)</td>
<td>15 (24.6)</td>
<td>21 (27.6)</td>
<td>39 (29.8)</td>
<td>166 328 (10.5)</td>
<td>4.14 (3.37–5.09)</td>
<td>4.10 (3.33–5.04)</td>
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<tr>
<td>1 to +1</td>
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<td>111 (52.4)</td>
<td>36 (59.0)</td>
<td>27 (35.5)</td>
<td>52 (39.7)</td>
<td>1 124 770 (70.8)</td>
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<tr>
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<td>2 (3.3)</td>
<td>2 (2.6)</td>
<td>3 (2.3)</td>
<td>203 585 (12.8)</td>
<td>0.19 (0.09–0.38)</td>
<td>0.19 (0.09–0.38)</td>
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</table>
| Values are \(n\) (% of total with unknown excluded). MBR, Swedish Medical Birth Register; OR, odds ratio; CI, confidence interval; *AOR, adjusted OR for maternal age (model with one linear and one quadratic term) and year of birth. SD, standard deviation. For each variable a constant reference group (unexposed) was set to 1.0 (gestational age = 37–41, SD weight = −1 to +1; SD length = −1 to +1).
**SD-scores according to gestational age at birth (Marsal et al., 1996).
mothers with a diagnosis of TS among the mothers who had been giving birth to a girl with TS. Today, it is also possible to determine whether the X chromosome present is derived from the mother or the father. Hopefully, this knowledge together with a more detailed genetic analysis of the parents will provide new knowledge about mechanisms of how short stature is transferred from parent to girls with TS. Even less is known about the association of other maternal characteristics such as parity and the incidence of TS. This study could not confirm such a relationship, but an 1.7–3.8-fold increased risk of having a daughter with TS was observed for a woman who had had three pregnancies or more (Bernasconi et al., 1994), however, it is possible that this finding could be ascribed to increased age.

The other findings of the present study, showing that TS girls were often born preterm and small for gestational age, confirm previous reports (Karlberg et al., 1991; Rongen-Westerlaken et al., 1997; Even et al., 2000; Davenport et al., 2002; Wisniewski et al., 2007). TS babies are more often born preterm and delivered by Caesarean section compared with the rest of the babies in the population (Bernasconi et al., 1994). However, an interesting and unexpected finding in this study was that the isochromosome and “other” TS babies, rather than the monosomy babies, were the shortest. Later in life, monosomy TS women have shorter stature and more stigmata when compared with mosaic TS women. The chromosomal classification and its relationship with phenotype is interesting. In the present study, the median age at diagnosis was significantly lower for the TS monosomy group. A recent study showed that the true mosaics (45,X/46,XX) in TS mitigated both cardiovascular risk factors and stigmata in TS women and was associated with a higher age at diagnosis (El-Mansoury et al., 2007). Hence, it is important to separate the TS babies with 45,X/46,XX from other karyotypes with structural and marker chromosomal aberrations which are phenotypically more like 45,X and isochromosomes.

The strength of the present study was the control group, which was a National Birth Register including all newborns in the general population. Furthermore, the TS cohort was fairly large and included findings from all cytogenetic laboratories in Sweden. Limitations of the present study were that data on maternal height were missing before 1983 and no data were available regarding paternal age and height. A further limitation was that data concerning prenatal diagnosis and its relationship with phenotype is interesting. In the present study, the median age at diagnosis was significantly lower for the TS monosomy group. A recent study showed that the true mosaics (45,X/46,XX) in TS mitigated both cardiovascular risk factors and stigmata in TS women and was associated with a higher age at diagnosis (El-Mansoury et al., 2007). Hence, it is important to separate the TS babies with 45,X/46,XX from other karyotypes with structural and marker chromosomal aberrations which are phenotypically more like 45,X and isochromosomes.

The yearly incidence of individuals born with TS syndrome during the study period showed a decline during the last decade (Fig. 1). An improved diagnostic accuracy is likely after 1995 when karyotyping was based on analysis of more cells when a TS diagnosis was suspected (at least 30 cells when compared with 10–25 cells before 1995). The decline may be explained by both increased and improved prenatal testing resulting in more terminations of pregnancies with TS fetuses. Another explanation is that the median age for a TS diagnosis of any karyotype was 7.9 years with a range up to 34 years.

In conclusion, advanced maternal age and short stature were risk factors for giving birth to a girl with TS. More TS girls were born late preterm and were small for gestational age when compared with non-TS girls in the general population. In newborn girls with a size at birth less than –2SD and from very short statured pregnant women, it is important to consider other stigmata indicative of TS.

Acknowledgements

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References


