feeding and will improve the prospects of early hospital discharge. We are carrying out further work to determine the effects on long term quality of life in such patients, and our preliminary results have so far been encouraging. In addition, further work is required to determine the ideal timing at which to institute gastrostomy feeding after an acute dysphagic stroke.

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# Prenatal and postnatal prevalence of Turner's syndrome: a registry study

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## Abstract

***Objective*—To study prevalence of Turner's syndrome in Denmark and to assess validity of prenatal diagnosis.**

***Design*—Study of data on prenatal and postnatal Turner's syndrome in Danish Cytogenetic Central Register.**

***Subjects*—All registered Turner's syndrome karyotypes (100 prenatal cases and 215 postnatal cases) during 1970-93.**

***Main outcome measures*—Prevalence of Turner's syndrome karyotypes among prenatally tested fetuses and Turner's syndrome among liveborn infants.**

***Results*—Among infant girls, prevalence of Turner's syndrome was 32/100 000. Among female fetuses tested by amniocentesis, prevalence of Turner's syndrome karyotypes was 176/100 000 (relative risk of syndrome, 6·74 compared with prevalence among untested pregnancies). Among female fetuses tested by chorion villus sampling, prevalence of syndrome karyotypes was 392/100 000 (relative risk, 16·8). We excluded prenatal tests referred because of results of ultrasound scanning: among fetuses tested by amniocentesis revised relative risk was 5·68, while revised relative risk among fetuses tested by chorion villus sampling was 13·3. For 29 fetuses with prenatal diagnosis of possible Turner's syndrome, pregnancy was allowed to continue and 24 children were live born. Thirteen of these children were karyotyped postnatally, and diagnosis of Turner's syndrome had to be revised for eight, seven being normal girls and one boy. This gives tentative predictive value of amniocentesis in diagnosing Turner's syndrome of between 21% and 67%. There was no significant relation between mother's age and risk of Turner's syndrome.**

***Conclusions*—Discrepancy between prenatal and postnatal prevalence of Turner's syndrome challenges specificity of prenatal examination in diagnosing Turner's syndrome.**

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## Introduction

Turner's syndrome is a disorder of female patients that is typically associated with the absence of one sex chromosome (45,X), although structural abnormality of one sex chromosome or mosaicism may also be responsible. The prevalence of Turner's syndrome at birth has been studied, so far, only in large scale chromosome surveys of children. In white populations it has been estimated to be 25-55 per 100 000 females[1-3] and in Japanese populations to be 70-210 per 100 000.[4] The high prevalence of 210 per 100 000 was found in a small study of only 2400 females. It has recently been suggested that advanced maternal age may be a risk factor for giving birth to a child with Turner's syndrome,[5] while other workers have found that maternal age is inversely related to the occurrence of monosomy X (45,X) in offspring.[6-8]

All cytogenetic laboratories in Denmark report all prenatal and postnatal karyotype examinations to the Danish Cytogenetic Central Registry. The register is excellent for studying epidemiological aspects of Turner's syndrome. There has recently been a rise in the numbers of fetuses with prenatally diagnosed Turner's syndrome in Denmark. We used data from the Danish Cytogenetic Central Register to try to estimate whether this reflected a true rise in the prevalence of Turner's syndrome; if it was simply a reflection of the increased use of amniocentesis, chorion villus sampling, and ultrasonography; or if it was related to other factors.

## Subjects and methods

In Denmark seven laboratories perform postnatal karyotyping, and four of these also perform prenatal karyotyping. All results are reported to the Danish Cytogenetic Central Register. The register includes information on maternal age, whether prenatal results were obtained by amniocentesis or chorion villus sampling, if amniocentesis or chorion villus sampling was preceded by ultrasonography (information about

ultrasonography has been available since 1989), and the outcome of the pregnancy (induced abortion, spontaneous abortion, live birth). The register does not include information on the number of cells analysed. However, when a normal karyotype is encountered at least 10 cells are analysed, and when a Turner's karyotype is suspected at prenatal examination at least 50 cells, but normally 100 cells or more, from two different cultures are analysed. The register has issued an annual report since 1978.[9]

In Denmark all pregnant women aged over 35 are given the opportunity of having a prenatal examination. For a pregnant woman aged under 35 to be offered a prenatal examination, there would have to be an indication: these include advanced age of father (>50); previous child with chromosomal abnormality, mental retardation, or congenital abnormality; family history of chromosomal abnormality or mental retardation; habitual abortions; parental exposure to mutagens or teratogens; decreased concentration of serum α fetoprotein in maternal serum; abnormal findings at ultrasonography; parental anxiety; parents carrying a chromosome aberration; increased risk of monogenic inheritable diseases; increased risk of open defects (spina bifida, anencephaly, etc). Postnatal karyotyping of infants is performed on the basis of clinical signs.

We studied the period 1970-93 as amniocentesis was introduced in Denmark in 1970 and looked for all possible Turner's syndrome karyotypes affecting the X chromosome. (We did not include karyotypes affecting the Y chromosome, since the karyotype 45,X/46,XY is known to result in an array of phenotypes such as phenotypic females with or without virilising features, Turner's syndrome, intersex with ambiguous genitalia, and phenotypic males with or without genital malformations.[10,11]) Our study was approved by the local ethics scientific committee and by the national registry authorities.

### STATISTICAL METHODS

We used the binomial distribution to calculate confidence limits; the Mantel-Haenszel method to calculate relative risk stratifying by year, or the Pearson $\chi^2$ test when stratification was not feasible; logistic regression to test whether a change was taking place in the prevalence of Turner's syndrome diagnosed over the years; and the $\chi^2$ test for trend (Mantel-Haenszel test for linear association) to test for any maternal age effect. The statistics were done with SPSS for Windows, version 6.0.1 (SPSS, Chicago IL, USA).

**Table 1**—*Distribution of all prenatal and postnatal Turner's syndrome karyotypes. Values are numbers of cases*

| Karyotype | Prenatal | Postnatal* |
|---|---|---|
| 45,X | 62 | 109 |
| 45,X/46,XX | 22 | 29 |
| 45,X/46,X,i(Xq); 46,X,i(Xq); 45,X/46,X,i(Xq)/47,X,i(Xq),i(Xq); etc | 6 | 27 |
| 45,X/46,X,del(X); 46,X,del(X) | 5 | 18 |
| 45,X/46,XX/47,XXX; 45,X/47,XXX; 45,X/46,XX/47,XXX/48,XXXX | 3 | 7 |
| 45,X/46,X,r(X) | 2 | 14 |
| 45,X/46,XY | | 6 |
| Others with Y material | | 5 |
| Total | 100 | 215 |

*Though some of the prenatally diagnosed cases of Turner's syndrome came to term, they are not included in the postnatal group.

## Results

Table 1 shows all the Turner's syndrome karyotypes recorded in the cytogenetic register during 1970-93. There was a higher proportion of the 45,X karyotype in prenatal diagnoses compared with postnatal findings, but the difference was not significant ($\chi^2$=3·51, df=1, P=0·06). There were no differences between prenatal and postnatal diagnoses for the other groups of karyotypes.

Table 2 shows the number and prevalence of prenatal and postnatal diagnoses of Turner's syndrome. The overall proportion of liveborn infant girls with Turner's syndrome was 32 (95% confidence interval 28 to 37) per 100 000. The overall proportion of liveborn infant girls with the syndrome after untested pregnancies was also 32 (27 to 36) per 100 000. The overall

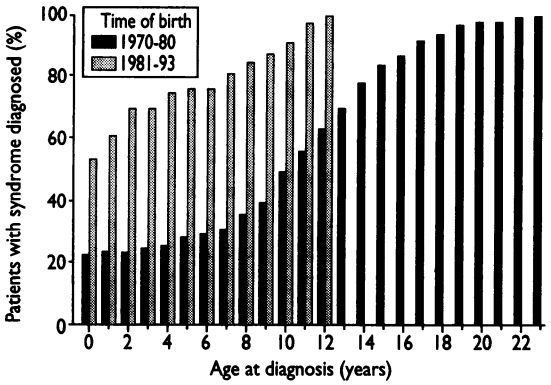
**Table 2**—*Prenatal and postnatal diagnosis of Turner's syndrome by year*

| Year | Prenatal diagnosis (year of diagnosis) | Liveborn infants with syndrome (year of birth) | Prenatal diagnosis in females | | Postnatal diagnosis among untested girls (year of birth) | Prevalence per 100 000 | | |
|---|---|---|---|---|---|---|---|---|
| | | | Amniocentesis | Chorion villus sampling | | Amniocentesis | Chorion villus sampling | Untested liveborn girls |
| 1970 | 0 | 12 | 0/3 | | 12/34417 | 0 | | 35 |
| 1971 | 0 | 15 | 0/10 | | 15/36394 | 0 | | 41 |
| 1972 | 0 | 16 | 0/31 | | 16/36782 | 0 | | 43 |
| 1973 | 0 | 16 | 0/52 | | 16/34944 | 0 | | 46 |
| 1974 | 0 | 17 | 0/169 | | 17/34602 | 0 | | 49 |
| 1975 | 0 | 14 | 0/312 | | 14/34948 | 0 | | 40 |
| 1976 | 0 | 7 | 0/380 | | 7/31153 | 0 | | 22 |
| 1977 | 0 | 5 | 0/606 | | 5/29449 | 0 | | 17 |
| 1978 | 2 | 14 | 2/973 | | 14/29190 | 206 | | 48 |
| 1979 | 3 | 10 | 3/1402 | | 10/27510 | 214 | | 36 |
| 1980 | 4 | 10 | 4/1759 | | 10/26186 | 227 | | 38 |
| 1981 | 6 | 10 | 6/2025 | | 9/23953 | 296 | | 38 |
| 1982 | 4 | 4 | 4/2366 | | 4/23233 | 169 | | 17 |
| 1983 | 5 | 7 | 5/2826 | 0/4 | 6/21996 | 177 | 0 | 27 |
| 1984 | 2 | 6 | 2/2736 | 0/64 | 6/22430 | 73 | 0 | 27 |
| 1985 | 2 | 7 | 1/2634 | 1/110 | 6/23542 | 38 | 909 | 25 |
| 1986 | 5 | 5 | 3/2886 | 2/300 | 3/23697 | 104 | 667 | 13 |
| 1987 | 4 | 7 | 2/2735 | 2/510 | 6/23901 | 73 | 392 | 25 |
| 1988 | 6 | 9 | 5/3001 | 1/604 | 6/24921 | 167 | 166 | 24 |
| 1989 | 8 | 10 | 7/2775 | 1/685 | 7/26424 | 252 | 146 | 26 |
| 1990 | 6 | 8 | 4/2678 | 2/924 | 6/27217 | 149 | 216 | 22 |
| 1991 | 11 | 10 | 4/2612 | 7/1264 | 8/27489 | 153 | 554 | 29 |
| 1992 | 20 | 13 | 12/2770 | 8/1352 | 6/28812 | 433 | 592 | 21 |
| 1993 | 12 | 7 | 7/2616 | 5/1582 | 6/28485 | 268 | 316 | 21 |
| Total | 100 | 239 | 71/40357 | 29/7399 | 215/681475 | 176 | 392 | 32 |

proportion of cases of prenatally and postnatally diagnosed Turner's syndrome combined was 43 (39 to 48) per 100 000 females. When diagnoses of Turner's syndrome were pooled regardless of ascertainment there was a significant rise in the prevalence over the years (logistic regression: yearly change in odds 1·016 (1·0004 to 1·031), P=0·045).

POSTNATAL DIAGNOSES

About 46% of all postnatal diagnoses of Turner's syndrome were made within the first five years of life, 60% were made within the first 10 years, and 90% were made within the first 15 years. Turner's syndrome was diagnosed significantly later among children who were born during 1970-80 than among those who were born in 1981-93 (figure): for those born in 1970-80, 28% (38/136) of all postnatal diagnoses of Turner's syndrome were found during the first five years of life, while, for those born in 1981-93, 76% (60/79) of diagnoses were found during the first five years.




*Age at which Turner's syndrome was postnatally diagnosed in patients born in 1970-80 and 1981-93*

The prevalence of postnatally diagnosed Turner's syndrome in each birth cohort declined over the years (logistic regression: yearly change in odds 0·969 (95% confidence interval 0·950 to 0·987), P=0·001). These comparisons are, however, biased, since some cases of Turner's syndrome in the recent birth cohorts would not have yet been diagnosed.

PRENATAL DIAGNOSIS

*Diagnosis by amniocentesis*

Among female fetuses tested by amniocentesis, the prevalence of Turner's syndrome karyotypes was 176 (134 to 215) per 100 000. The relative risk of the diagnosis, compared with the prevalence of postnatal diagnoses after untested pregnancies, was 6·74 (5·21 to 8·73) (Mantel-Haenszel method: $\chi^2=211$, df=1, P<0·0001). The proportion of amniocentesis tests with positive results increased non-significantly over the years (logistic regression: yearly change in odds 1·050 (0·996 to 1·107), P=0·07). Amniocentesis was on average performed in the 16th week of pregnancy.

**Table 3**—*Prevalence of prenatal diagnosis of Turner's syndrome by method of testing and by referral after ultrasonography. Values are numbers of subjects unless stated otherwise*

| Test used | Test for Turner's syndrome: Positive | Test for Turner's syndrome: Negative | Total | Prevalence per 100 000 | Relative risk (95% confidence interval)* |
|---|---|---|---|---|---|
| Amniocentesis: | 71 | 40 286 | 40 357 | 176 | 6·74 (5·21 to 8·73) |
| Without ultrasonography | 60 | 40 169 | 40 230 | 149 | 5·68 (4·30 to 7·50) |
| Preceded by ultrasonography | 11 | 117 | 128 | 8 594 | 276 (144 to 467) |
| Chorion villus sampling: | 29 | 7 370 | 7 399 | 392 | 16·8 (11·9 to 23·7) |
| Without ultrasonography | 23 | 7 350 | 7 373 | 312 | 13·3 (9·06 to 19·5) |
| Preceded by ultrasonography | 6 | 20 | 26 | 23 077 | 741 (315 to 1347) |
| None | 215 | 681 460 | 681 675 | 32 | 1·00 |
| Total | 315 | 728 993 | 729 431 | 43 | |

*Compared with no test used.

**Table 4**—*Fate of fetuses with prenatal diagnosis of Turner's syndrome. Values are numbers of subjects*

| | Method of testing: Amniocentesis | Method of testing: Chorion villus sampling |
|---|---|---|
| Diagnosed | 71 | 29 |
| Legally aborted | 47 | 24 |
| Continued pregnancy: | 24 | 5 |
| Live born | 22 | 2 |
| Spontaneous abortion | 2 | 3 |

*Diagnosis by chorion villus sampling*

Among female fetuses examined by chorion villus sampling, the prevalence of Turner's syndrome karyotypes was 392 (252 to 538) per 100 000. The relative risk of the diagnosis, compared with the prevalence of postnatal diagnoses after untested pregnancies, was 16·8 (11·9 to 23·7) (Mantel-Haenszel method: $\chi^2=258$, df=1, P<0·0001). There was no change in the proportion of tests with positive results over the years. Chorion villus sampling was on average performed in the 11th week of pregnancy.

*Adjustment for ultrasonography*

Since findings at ultrasonography can raise suspicion of Turner's syndrome, we made a revised calculation excluding women referred to prenatal karyotyping because of ultrasonographic findings. Prenatal examinations preceded by ultrasonography have been recorded at the Danish register since 1989. A total of 154 women carrying female fetuses were referred for amniocentesis or chorion villus sampling, and 17 of these fetuses had a Turner's syndrome karyotype.

After exclusion of these cases, the revised relative risk among amniocentesed compared with untested pregnancies was 5·68 (4·30 to 7·50) (Mantel-Haenszel method: $\chi^2=150$, df=1, P<0·0001). The increase over the years in the proportion of amniocentesis tests with positive results vanished when pregnancies referred due to ultrasonography were excluded (logistic regression: yearly change in odds 1·011 (0·957 to 1·068), P=0·70). The revised relative risk among pregnancies tested with chorion villus sampling was 13·3 (9·1 to 19·5) (Mantel-Haenszel method: $\chi^2=175$, df=1, P<0·0001). Table 3 summarises these results.

*Fate of fetuses with diagnosis of Turner's syndrome*

Table 4 shows the fate of fetuses that had Turner's syndrome diagnosed prenatally. About 75% of all fetuses with the syndrome diagnosed are terminated legally in Denmark, with the proportion declining during recent years. During 1978-85, 86% (24 of 28) of such fetuses were aborted, while 72% (51 of 72) were aborted during 1986-93.

For 29 fetuses with a possible prenatal diagnosis of Turner's syndrome, the parents chose to let the pregnancy continue, and 24 were live born. Table 4 shows the prenatal and postnatal status for these children. Of the 24 pregnancies that were allowed to continue after a positive amniocentesis test, 22 (92% (73% to 99%)) successfully came to term and no deaths were recorded during the first year after birth. Of the five pregnancies that were allowed to continue after a positive result from chorion villus sampling, two survived to term.

Among the 24 liveborn infants, six had a prenatal 45,X karyotype while 18 had a mosaic Turner's syndrome karyotype (table 5). Thirteen of the liveborn children were karyotyped postnatally, and the diag-

**Table 5**—*Prenatal and postnatal karyotypes of 24 liveborn infants that had prenatal diagnosis of Turner's syndrome*

| Prenatal examination | | Postnatal examination | |
|---|---|---|---|
| **Karyotype** | **No of subjects** | **Karyotype** | **No of subjects** |
| 45,X | 6 | Not examined* | 5 |
| | | 45,X/46,X,idic(Y)† | 1 |
| 45,X/46,XX | 15 | Not examined* | 5 |
| | | 45,X/46,XX | 3 |
| | | 46,XX | 6 |
| | | 45,X | 1 |
| 45,X/47,XXX | 1 | 45,X/47,XXX | 1 |
| 46,XX/46,X,del(X)(pterq24) | 1 | 46,XX | 1 |
| 46,XX/46,X,i(Xq) | 1 | Not examined* | 1 |
| Turner's syndrome | 24 | Not examined* | 11 |
| | | Turner's syndrome | 5 |
| | | Male (45,X/46,X,idic(Y)) | 1 |
| | | Normal female (46,XX) | 7 |

*Legally registered as female, but nothing known of phenotype or genotype.
†Male.

**Table 6**—*Prevalence of detection of Turner's syndrome karyotypes at prenatal testing by age of mother. Values are numbers of subjects*

| | Method of testing | | |
|---|---|---|---|
| **Maternal age (years)** | **Amniocentesis** | **Chorion villus sampling** | **Total** |
| ≤24: | 7/3473 | 2/451 | 9/3924 |
| Prevalence* | 202 (81 to 415) | 443 (54 to 1593) | 229 (105 to 435) |
| 25-29: | 16/7076 | 7/1222 | 23/8298 |
| Prevalence* | 226 (129 to 367) | 573 (231 to 1177) | 277 (176 to 416) |
| 30-34: | 17/9388 | 5/1710 | 22/11098 |
| Prevalence* | 181 (106 to 290) | 292 (95 to 681) | 198 (124 to 300) |
| 35-39: | 26/17822 | 14/3359 | 40/21181 |
| Prevalence* | 146 (95 to 214) | 417 (228 to 698) | 189 (135 to 257) |
| ≥40: | 5/2598 | 1/657 | 6/3255 |
| Prevalence* | 192 (63 to 449) | 152 (4 to 845) | 184 (68 to 401) |
| $\chi^2$ Test for trend (df=1) | 1·17 (P=0·28) | 0·78 (P=0·38) | 1·50 (P=0·22) |
| Total: | 71/40357 | 29/7399 | 100/47856 |
| Prevalence* | 176 (137 to 219) | 392 (263 to 562) | 209 (170 to 254) |

*With 95% confidence interval.

nosis of Turner's syndrome was revised for eight (62% (32% to 86%)): seven had normal female karyotypes (45,X/46,XX revised to 46,XX for six children; 46,XX/46,X,del(X) revised to 46,XX for one) and one was male (45,X revised to 45,X/46,X, idic(Y)). Furthermore, one Turner's syndrome karyotype was revised at postnatal examination (45,X/46,XX revised to 45,X). Among the other 11 children, we know that they were all legally females, but no further information was obtained about their phenotype. The probability of a fetus with a mosaic karyotype for Turner's syndrome surviving to term was significantly higher than that of a fetus with 45,X karyotypes surviving ($\chi^2=18·4$, df=1, $P<0·0001$).

Table 6 shows the prevalence of Turner's syndrome karyotypes at prenatal examinations by the age of the mother. There was no relation between the age of the mother and overall risk of Turner's syndrome. There was also no relation between the age of the mother and the 45,X karyotype. Excluding cases referred after ultrasonography did not change this (data and results not shown).

## Discussion

### DANISH CYTOGENETIC CENTRAL REGISTER

This register represents a unique opportunity for studying abnormal karyotypes, because all prenatal and postnatal examinations performed in Denmark are recorded here. The register can be considered complete, though administrative errors can never be excluded. The data we have extracted from the register cannot be thought of as representative of the Danish population of pregnant women, as most prenatal examinations are carried out on older women. This is not, however, a source of bias, as maternal age apparently is not a risk factor for giving birth to a female infant with Turner's syndrome, though conflicting results have been presented over the years. One study found no maternal age effect among a group of 288 girls with the 45,X karyotype of Turner's syndrome.[6] Recently, another study showed a positive maternal age effect in a group of 772 girls with Turner's syndrome (all karyotypes pooled together).[5] Our results show that there is no relation between maternal age and risk of Turner's syndrome (both overall and for the 45,X karyotype only) at prenatal diagnosis.

Studies on spontaneous abortions, on the contrary, have shown that young maternal age is associated with aborting Turner's syndrome (45,X) fetuses more frequently.[7,8] It remains to be seen whether this finding can be extrapolated to the population with postnatally diagnosed Turner's syndrome, and we are currently investigating this. We had no information on paternal age.

The prenatal and postnatal groups were not completely comparable, as postnatal diagnosis is mainly based on clinical suspicion while prenatal diagnosis is mainly based on the age of the mother. This will of course, presuming that the postnatal diagnosis of Turner's syndrome is not complete, tend to underestimate the postnatal prevalence of Turner's syndrome. It is important to note that the information in the register is about karyotypes and not phenotypes. A Turner's syndrome karyotype might not necessarily result in a Turner's syndrome phenotype.

### PRENATAL AND POSTNATAL PREVALENCE OF TURNER'S SYNDROME

We found that Turner's syndrome in Denmark was diagnosed prenatally at a rate that was much higher than the observed postnatal rate. The result was highly significant for both amniocentesis and chorion villus sampling, and when cases referred after ultrasonography were excluded. The rate of spontaneous abortion in the first trimester is estimated to be 99%, but this high rate of abortion can only partially explain our findings.[2,12] The fact that 91% of all fetuses with the syndrome detected by amniocentesis (and 40% of those detected by chorion villus sampling) survived until term when the pregnancy was not terminated suggests that other factors may play a role and that most fetuses with Turner's syndrome detected by amniocentesis are viable.

Hook and Warburton presented data from the New York State Chromosome Registry, where, for every 100 000 female fetuses tested by amniocentesis, about 85 (95% confidence interval 54 to 127) cases of Turner's syndrome were detected. We found 176 (134 to 215) cases of Turner's syndrome for every 100 000 amniocenteses and 392 (252 to 538) cases for every 100 000 chorion villus samples, which are significantly higher figures. Hook and Warburton estimated the postnatal prevalence of Turner's syndrome to be 22·2 per 100 000 females without intervention; they explained the difference in prevalence by an expected survival of the fetuses with Turner's syndrome (45,X) of only 31% after an amniocentesis had been performed, based on the well known high lethality of especially the 45,X karyotype, peaking according to their data at week 13.[13] This is contrary to our finding that 92% of all fetuses with Turner's syndrome detected by amniocentesis, and 75% (35% to 97%) of fetuses with the 45,X karyotype, survived to term if the

pregnancy was not terminated. Some researchers have claimed that a degree of mosaicism must be present, at least in very early life, for survival in utero and that pure 45,X, as such, does not exist.[14] In our study amniocentesis was performed on average in the 16th week of pregnancy, which is after the period of high intrauterine lethality during the first trimester. The high viability of fetuses with prenatally diagnosed Turner's syndrome, especially after amniocentesis, might be biased by the older age of the women undergoing prenatal examination compared with the rest of the pregnant population and might not be applicable to younger age groups.

The higher number of diagnoses of Turner's syndrome with amniocentesis cannot be explained by the increased use of ultrasonography. Ultrasonography seemed to be a rather good method of identifying some fetuses with Turner's syndrome (table 3), but only few cases of Turner's syndrome were found as a result of suspicious ultrasonographic findings.

The prevalence of Turner's syndrome has never been established, but cytogenetic studies have given estimates ranging from 25 to 210 per 100 000 females,[1-4] and most researchers seem to agree on a hypothetical proportion of 50 per 100 000 girls in white populations. If the true proportion of Turner's syndrome is 50 per 100 000 females, then not all females with Turner's syndrome were postnatally diagnosed in the period 1970-93 (relative risk 0·65). When adding the prenatally diagnosed Turner's syndrome, we find a relative risk of 0·86 (0·77 to 0·96), still a little lower than the expected proportion of 50 per 100 000, keeping in mind that the prenatal figure was contaminated by a number of karyotypically normal girls and boys.

The prevalence of cases of Turner's syndrome not found prenatally but diagnosed postnatally seemed to be decreasing in recent birth cohorts (logistic regression: yearly change in odds 0·969 (0·950 to 0·987), P=0·001). This finding can partially be explained by ascertainment bias: not all liveborn infants with Turner's syndrome from recent cohorts have yet been diagnosed. It must also be noted that some cases found prenatally and subsequently aborted tend to lower the postnatal prevalence, though never more than 15% of pregnant women with female fetuses underwent prenatal examination each year. How to explain, then, that the total prevalence of diagnoses of Turner's syndrome (prenatal and postnatal) was increasing (logistic regression: yearly change in odds 1·016 (1·0004 to 1·031), P=0·045) in spite of the aforementioned bias? We conclude that this increase was either a genuine reflection of a real increase or a biased result. Recently, several reports have indicated that sperm quality might be deteriorating.[15,16] Furthermore, a significant positive correlation between structural abnormalities in sperm karyotypes and age has been demonstrated.[17] As the X in 45,X Turner's syndrome is of maternal origin in 85% of cases,[18-24] indicating an error in the paternal sperm, it is tempting to speculate that this might be the basis for the apparent rise in the prenatally detected Turner's syndrome. On the other hand, the result might be biased by two mechanisms. One is that increased awareness among clinicians and the introduction of prenatal examinations increase the likelihood of a child or fetus with Turner's syndrome to be detected. The other is that the specificity of prenatal examinations is less than perfect, leading to false positive diagnoses.

### SPECIFICITY OF PRENATAL TECHNIQUES IN DIAGNOSIS OF TURNER'S SYNDROME

The finding of a much higher prevalence of Turner's syndrome at prenatal karyotyping than postnatally raises doubts about the specificity of prenatal examinations for Turner's syndrome. We have tried to estimate the predictive value of a positive prenatal Turner's syndrome karyotype by comparing the prenatal and postnatal prevalences of Turner's syndrome, correcting for the risk of spontaneous abortion after the time of prenatal examination.

We found a spontaneous abortion rate after amniocentesis of 8% (1% to 27%). If the rate of spontaneous abortions after amniocentesis is 30%, a prevalence of 176 fetuses with Turner's syndrome karyotypes per 100 000 at the time of amniocentesis corresponds to a prevalence at birth of 123 liveborn infants with Turner's syndrome per 100 000 females. If the true prevalence at birth (without intervention) is 50 infants with Turner's syndrome per 100 000 females the false positive rate is 73 per 100 000 tests, yielding a specificity of 0·9993. Because of the rarity of Turner's syndrome, this apparently satisfactory specificity corresponds to a predictive value of 41%. If the true prevalence at birth is higher or lower than 50 per 100 000 females the estimates of the specificity and the predictive value change accordingly.

### REVISION OF KARYOTYPES: FALSE POSITIVE CASES

Another way of estimating the predictive value of the prenatal examination techniques is by studying the prenatal and postnatal karyotypes of the 24 liveborn children diagnosed prenatally. Table 5 shows that an appreciable number of prenatal karyotypes were revised after birth. Six newborn infants with the prenatal karyotype 45,X/46,XX turned out to be girls with the normal female karyotype 46,XX, and one infant with the prenatal karyotype 46,XX/46,X, del(X)(pterq24) was also normal (46,XX). Amniocytes are a mixture of ectodermal and endodermal cells, while postnatal karyotyping is performed on leucocytes; thus continued mosaicism—for example, in the skin or other parts of ectodermal and endodermal tissues—cannot theoretically be ruled out. It is of course important to stress that, from the registry data, we are not able to say anything of the relative distributions of the different cell lines in mosaic cases. We have previously shown that the percentage of mosaicism can change dramatically over time when examined postnatally, perhaps suggesting that similar changes can take place during fetal development.[25]

One fetus with a prenatal diagnosis of 45,X turned out to be a male with the karyotype 45,X/46,X,idic(Y), while in another case a prenatal diagnosis of 45,X/46,XX was revised postnatally to 45,X. Such problems of specificity have been reported only sporadically.[26,27] Although placental mosaicism is a well recognised problem in the use of chorion villus sampling,[28-32] this cannot explain the findings concerning amniocentesis. These data question the specificity of amniocentesis in the prenatal diagnosis of Turner's syndrome, and especially the predictive value of mosaicism at prenatal examination.

We found that, of the 24 fetuses with a prenatal diagnosis of Turner's syndrome that survived to term, five definitely had the syndrome, yielding a predictive value of 21%. If the 11 girls that did not get karyotyped after birth are assumed to have had Turner's syndrome, the predictive value was 67%. The mosaic karyotypes are particularly responsible for the low predictive value. If the 45,X cases are discounted, the predictive value of Turner's syndrome mosaicism was 28%-61%. It can be concluded that the predictive value of prenatal testing was between 21% and 67% in this population. It should be noted that possible Turner's syndrome karyotypes affecting the Y chromosome were not included in this study.

We tried to estimate the predictive value of a positive test in two different ways from the data available. Both ways led to similar estimates. The implication of this is

## Key Messages

- There has recently been a rise in the numbers of fetuses with prenatally diagnosed Turner's syndrome in Denmark
- We used data from the Danish Cytogenetic Central Register to try to estimate whether this reflected a true rise in the prevalence of Turner's syndrome
- Karyotypes of Turner's syndrome were diagnosed prenatally at a much higher rate than the observed postnatal rate of the syndrome
- Of 24 children who were live born after prenatal diagnosis of possible Turner's syndrome, 13 were karyotyped postnatally and diagnosis of Turner's syndrome had to be revised for eight, seven being normal girls and one a boy.
- Discrepancy between prenatal and postnatal prevalence of Turner's syndrome challenges specificity of prenatal examination in diagnosing Turner's syndrome

that one may assume that perfectly healthy fetuses could have been legally aborted over the years because of false positive prenatal diagnoses of Turner's syndrome.

### CONCLUSION

Our study challenges the predictive value and the specificity of prenatal examination techniques (especially amniocentesis) in the diagnosis of Turner's syndrome. In Denmark geneticists recommend that aborted fetuses should be karyotyped, but unfortunately this does not always happen. Future research on this area should focus on every fetus with a prenatally diagnosed Turner's syndrome karyotype. Of particular interest would be the distribution of cells in cases of mosaic karyotypes, results from karyotyping of aborted fetuses, and karyotyping of infants with the syndrome who have not yet been examined postnatally.

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## ONE HUNDRED YEARS AGO

### THE EMBARRASSMENT OF GUY'S HOSPITAL.

The authorities of Guy's Hospital are now making a determined attempt to raise a sum of £500,000 for investment, to make good the depreciation in income from the endowments, which almost wholly consist of agricultural property. That an appeal from a great institution like Guy's is a matter of national importance is evidenced by the warm interest which the Prince of Wales is taking in the movement for re-endowment, and H.R.H. will preside on May 20th next at the only festival dinner ever held in connection with this hospital. A feature of the movement of much interest, more especially to the medical profession, is the manner in which old Guy's men and present students are rallying to the support of their Alma Mater. Already Guy's men in practice have influenced several munificent donations, while it is believed that the majority are doing something. The present members of the Medical School have voluntarily organised themselves into a collecting committee, and, if Providence helps those who help themselves, then it may safely be prophesied that Guys Hospital will not only maintain its present position, but also reopen its closed beds. (*BMJ* 1896;i:682.)