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Prenatal and Postnatal Prevalence of Klinefelter Syndrome: A National Registry Study

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The objective of this study was to describe the prevalence of Klinefelter syndrome (KS) prenatally and postnatally in Denmark and determine the influence of maternal age.

All chromosomal examinations in Denmark are registered in the Danish Cytogenetic Central Registry. Individuals with KS diagnosed prenatally or postnatally were extracted from the registry with information about age at the time of diagnosis and mother's age.

In the period 1970–2000, 76,526 prenatal examinations on male fetuses resulted in the diagnosis of 163 fetuses with KS karyotype, corresponding to a prevalence of 213 per 100,000 male fetuses. Standardization according to maternal age resulted in a prevalence of 153 per 100,000 males. Postnatally, 696 males of 2,480,858 live born were diagnosed with KS, corresponding to a prevalence among adult men of approximately 40 per 100,000. Less than 10% of the expected number was diagnosed before puberty. Advanced maternal age had a significant impact on the prevalence.

KS is severely underdiagnosed in Denmark. Only approximately one fourth of adult males with KS are diagnosed. There is a marked delay in diagnosis of the syndrome. A delay in treatment with testosterone may lead to decreased muscle and bone mass with subsequent risk of osteoporosis. (*J Clin Endocrinol Metab* 88: 622–626, 2003)

KLINEFELTER SYNDROME (KS) is a sex chromosomal syndrome in males with an extra X chromosome (47,XXY), but additional X chromosomes (48 or more chromosomes) can be present as well as mosaicism (47,XXY/46,XY).

The phenotype varies, but the typical male suffering from the syndrome is characterized by eunuchoid body proportions, abnormally long legs and arm span, feminine distribution of adipose tissue including gynecomastia, absent or decreased facial and pubic hair, small hyalinized testes and small penis (1), a verbal IQ frequently below normal, and learning difficulties (2, 3).

Elevated gonadotropins are found in all men with KS, but the degree of hypogonadism is variable with the vast majority below the normal range (1).

It is recommended to start supplementation with testosterone at the beginning of puberty to secure at proper development of sexual characteristics and normal peak bone and muscle mass (1).

The only prospective, longitudinal study with follow-up through to adulthood of an entire cohort of KS found at birth shows that almost all KS boys have significant medical, psychological, or social problems (4). Furthermore, mortality in KS is significantly increased, with excess deaths due to diabetes, cardiovascular, respiratory, and gastrointestinal diseases (5).

The prevalence of the syndrome has been studied in representative chromosome surveys in newborn children (a total of 84 diagnosed subjects with KS in 55,212 boys), resulting in an estimated mean prevalence of 152 per 100,000 [95% confidence interval (CI), 121–188 per 100,000], ranging from 85–223 per 100,000 males (6–10, 12–14).

Abbreviations: CI, Confidence interval; CVS, chorion villus sampling; DCCR, Danish Cytogenetic Central Registry; KS, Klinefelter syndrome.

Recently, a discrepancy has been described between the prenatal and postnatal prevalence estimates of another sex chromosome disorder, Turner syndrome, suggesting false positive prenatal diagnoses (15–17), although no studies have dealt with the possibility of false positive prenatal diagnosis of KS.

The aim of this study was to estimate the prevalence of KS among prenatally examined and live-born boys in Denmark and compare it with the prevalence estimated from representative studies on chromosomes in the newborn. In addition, the maternal age effect on prevalence was also studied, both in the prenatal group and in a subgroup of postnatally diagnosed.

Subjects and Methods

In Denmark, seven laboratories perform postnatal karyotyping, and five of these also perform prenatal karyotyping. All results are reported to the Danish Cytogenetic Central Registry (DCCR). The registry includes information on maternal age, method [amniocentesis or chorion villus sampling (CVS)], and the outcome of the pregnancy (induced abortion, spontaneous abortion, or live birth). There is no information on karyotypes of aborted fetuses.

The registry contains virtually all cytogenetic examinations performed in Denmark since 1961, or approximately 200,000 cytogenetic examinations (160,000 prenatal and 40,000 postnatal); the annual number of examinations is approximately 10,000 (data available at the website, www.auh.dk/dccr). Reasons for performing prenatal examinations have been described earlier (18). The registry contains only information regarding karyotype and no information regarding phenotype.

In the periods 1969–1974 and 1980–1988, a study on chromosome disorders in live births was made in Aarhus County, enrolling 34,910 live births contributing to the total number of postnatal examinations (6). Apart from this study, no other chromosome examinations have been made in representative samples of live births in Denmark.

All karyotypes 47XXY, 48XXXY, 49XXXXY, and mosaics 47XXY/46XY diagnosed prenatally or postnatally were included. The karyotype 48XXYY was excluded because classification of this karyotype is not clear.

Amniocentesis has been performed since 1970, and CVS since 1983. For prenatal examinations, the age of the mother at the time of diagnosis and the year of diagnosis were extracted from the database. For postnatal

examinations, the age of the subject at the time of diagnosis, year of examination, and whenever possible the age of the mother at time of birth were extracted. The prevalence of KS in the prenatal and postnatal groups was compared, after stratification for maternal age at the time of prenatal examination or at the time of birth. Among the prenatally diagnosed KS subjects, there was no difference in the prevalence in the amniocentesis group compared with the CVS group (relative risk, 0.91; 95% CI, 0.65–1.29; Mantel-Haenszel method, $\chi^2 = 0.261$; $P = 0.61$), and these two groups were pooled for all further statistical computations.

The study was approved by the local scientific ethical committee in Aarhus County and by the Danish Data Protection Agency.

Statistics

We used binomial distribution to calculate confidence limits and the Mantel-Haenszel method to calculate relative risk, stratifying by maternal age; logistic regression was used to test for effect of mothers' age on the prevalence and for a time trend analysis. *P* values less than 5% were considered significant.

Results

Karyotypes

The distribution of karyotypes can be seen in Table 1. There was no difference in prevalence of mosaicism in the prenatally and postnatally diagnosed subjects with KS (Pearson's $\chi^2 = 1.842$; $P = 0.175$).

Prenatal examinations

A total of 163 fetuses were diagnosed as having a KS karyotype in a total of 76,526 prenatal examinations on Y chromosome positive fetuses (males), resulting in a prevalence of 213 per 100,000 males (95% CI, 182–248; Table 2). Of the 163 fetuses positive for KS, 114 were legally aborted (70%). There were no spontaneous abortions or stillbirths among the nonterminated fetuses. Twenty-three of the 49 live-born KS subjects diagnosed prenatally were karyotyped postnatally, and none had their diagnosis revised.

Extrapolating the prevalence of prenatal examinations to the whole population of live-born boys (standardization according to maternal age) resulted in a prevalence of 153 per 100,000 males (95% CI, 145–161).

Postnatal diagnoses

In males born between 1931 and 2000, 696 boys and men among 2,480,858 males not tested prenatally were diagnosed with KS. The prevalence of postnatal diagnosis of KS is described in 5-yr groups (age at the end of yr 2000; Table 3 and Fig. 1). The prevalence of diagnosed KS among the boys aged 10–14 yr was only 14.2 per 100,000 males, less than 10% of the expected number. At the ages of 25–54 yr, the prevalence of diagnosed KS was in the range of 35–40 per 100,000 males, representing approximately 25% of the expected.

TABLE 1. Distribution of karyotypes in prenatal and postnatal examinations

Karyotype	Prenatal	Postnatal	Total
47 XXY	147 (90.2)	714 (89.7)	861 (89.8)
46 XY/47XXY	15 (9.2)	48 (6.0)	63 (6.6)
48 XXXY	0	11 (1.4)	11 (1.1)
49 XXXXY	1 (0.6)	16 (2.0)	17 (1.8)
47 XXY/48 XXXY	0	2 (0.3)	2 (0.2)
48 XXY +18	0	5 (0.6)	5 (0.5)
Total	163 (100.0)	796 (100.0)	959 (100.0)

Percentage of total in each group is shown in *parentheses*. The total number of postnatal examinations is all KS subjects diagnosed (years of birth, 1900–2000).

Impact of mother's age on the prevalence of KS

Maternal age showed a significant and similar effect on the prevalence of KS diagnosed by CVS and amniocentesis (logistic regression: annual change in odds, 1.081; 95% CI, 1.044–1.120; $P < 0.0001$), but a nonsignificant effect of maternal age on prevalence was found in the postnatally diagnosed KS (logistic regression: annual change in odds, 1.017; 95% CI, 0.985–1.051; $P = 0.30$; Fig. 2).

The distribution of maternal age in the prenatal and postnatal groups differed. The mean age of mothers tested prenatally was higher than the mean age of mothers in the whole population of pregnant women (34.0 yr *vs.* 28.1 yr; data from the Statbank Denmark and DCCR).

The effect of time (Table 2 and Fig. 2)

The prevalence of KS among subjects prenatally diagnosed with KS did not change significantly during the period 1970–2000 (logistic regression, $P = 0.386$).

Discussion

Postnatal diagnosis

This report shows a low rate of postnatal diagnosis; postnatal examination resulted in much lower prevalence than expected; the highest prevalence was around 40 per 100,000; only about one fourth of the expected number was diagnosed.

Less than 10% of the expected KS diagnoses were made in the population of 10- to 14-yr-old boys, a period in life when testosterone is crucial for a proper development of muscle and bone, as well as secondary sexual characteristics. Part of the reason for this delay is probably that prepubertal boys suffering from KS do not exhibit severe physical stigmata, and in most men with KS, diagnoses are made because of infertility or hypogonadism (19). The decline in prevalence of KS diagnoses after age 54 probably reflects a low diagnostic activity in the older generations.

The DCCR contains no information about reasons for referring to cytogenetic examination. Abramsky and Chapple (19) showed that in the North Thames (west) health region (UK) from 1990–1993, 26% of the expected numbers with KS were diagnosed postnatally; of these, 29% (8 of 28) were diagnosed before the age of 20 yr, and only 4% (one) were diagnosed before the age of 10 yr. Our data corroborate their findings.

Prenatal diagnosis

By prenatal examinations, the prevalence of KS in Denmark was 213 per 100,000 male fetuses. Standardization according to maternal age yields an adjusted prevalence of 153 per 100,000, which is almost exactly the same as the prevalence found in the Danish cytogenetic survey among newborns (151 per 100,000; Ref. 6) and the estimated mean prevalence from the representative chromosome studies (152 per 100,000; Refs. 6–10, 12–14).

Previous reports have described a discrepancy between the prenatal and postnatal karyotypes in Turner syndrome,

TABLE 2. Annual frequency and prevalence of KS diagnoses in the period 1970–2000 diagnosed prenatally or postnatally

Year	Prenatal diagnosis of KS	Postnatal diagnosis of KS	All prenatal examinations (male fetuses)	Live-born boys not tested prenatally	Prevalence per 100,000 prenatal examinations (male fetuses)	Prevalence per 100,000 untested live-born boys
1970	0	12	1	36,381	0	33
1971	0	25	13	38,942	0	64
1972	0	17	26	38,666	0	44
1973	0	13	54	36,843	0	35
1974	1	12	129	36,427	775	33
1975	0	6	229	36,582	0	16
1976	0	12	362	33,372	0	36
1977	1	7	619	31,204	162	22
1978	4	7	1,123	30,752	356	23
1979	2	5	1,471	29,084	136	17
1980	4	10	1,874	27,478	213	36
1981	4	8	2,230	24,887	179	32
1982	2	5	2,493	24,570	80	20
1983	10	7	2,952	23,049	339	30
1984	3	8	2,850	23,722	105	34
1985	9	2	3,014	24,451	299	8
1986	5	3	3,465	24,969	144	12
1987	10	4	3,541	25,538	282	16
1988	11	5	3,711	26,613	296	19
1989	8	3	3,731	27,744	214	11
1990	2	4	3,841	28,779	52	14
1991	7	2	4,108	28,897	170	7
1992	9	0	4,405	30,407	204	0
1993	9	1	4,380	30,229	205	3
1994	7	3	4,287	31,353	163	10
1995	12	0	3,970	31,916	302	0
1996	9	0	3,580	31,239	251	0
1997	6	3	3,546	31,195	169	10
1998	8	0	3,457	30,598	231	0
1999	12	1	3,481	30,404	345	3
2000	8	0	3,583	30,848	223	0
Total	163	185	76,526	937,139	213	19

In the prenatally diagnosed subjects, the year represents the year of diagnosis. In the postnatally diagnosed subjects, the year represents the year of birth.

TABLE 3. Raw data on postnatal prevalence of KS diagnoses clustered in 5-yr groups from 1931–2000

Age in 2000 (yr)	Year of birth	Live-born boys at risk (not tested prenatally)	XXY diagnosed	Prevalence per 100,000 males (95% CI)
0 to 4	1996–2000	154,284	4	2.6 (0.7–6.6)
5 to 9	1991–1995	152,802	6	3.9 (1.4–8.5)
10 to 14	1986–1990	133,643	19	14.2 (8.6–22.2)
15 to 19	1981–1985	120,679	30	24.9 (16.8–35.5)
20 to 24	1976–1980	151,890	41	27.0 (19.4–36.6)
25 to 29	1971–1975	187,460	73	38.9 (30.5–48.9)
30 to 34	1966–1970	198,945	69	34.7 (27.0–43.9)
35 to 39	1961–1965	208,465	82	39.3 (31.5–48.8)
40 to 44	1956–1960	193,780	73	37.7 (29.5–47.4)
45 to 49	1951–1955	198,775	79	39.7 (31.5–49.5)
50 to 54	1946–1950	222,700	81	36.4 (28.9–45.2)
55 to 59	1941–1945	216,990	65	30.0 (23.1–38.2)
60 to 64	1936–1940	174,715	44	25.2 (18.3–33.8)
65 to 69	1931–1935	165,730	30	18.1 (12.2–25.8)
Total		2,480,858	696	28.1 (26.0–30.2)

with false positive tests prenatally (15–17). No such discrepancy was found among the prenatally diagnosed KS patients, because no prenatally diagnosed KS patient had his diagnosis revised postnatally (however, less than half were tested), and furthermore, the agreement between the extrapolated prenatal prevalence and the true prevalence obtained from representative studies suggests that false positive testing is not a major problem in KS.

A possible explanation of the low rate of postnatal diagnosis compared with prenatal diagnosis could be an excess of intrauterine deaths; however, no intrauterine deaths were reported in the registry. Intrauterine deaths would also reduce the true prevalence compared with the prenatal prevalence, which in this report matches the true prevalence.

A substantially raised intrauterine mortality has been reported for several chromosomal aberrations (Turner syndrome, trisomy 13, 18, and 21) but not for KS, XXX, and XYY (20).

Prenatal diagnosis of KS leads to induced abortion in 70% of

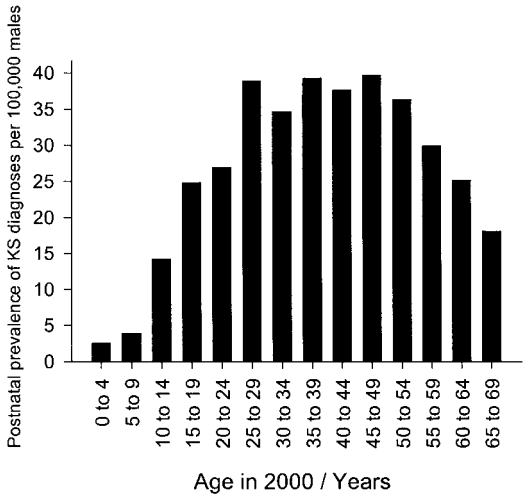

FIG. 1. Postnatal prevalence of KS diagnosis per 100,000 males in the year 2000 in 5-yr age groups (age in the year 2000). The reference prevalence is 153 per 100,000 males.

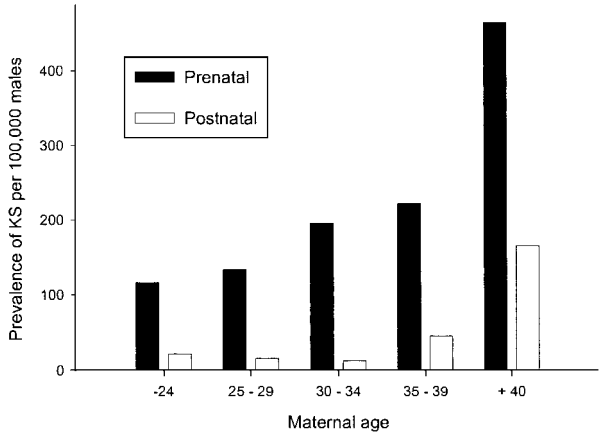

FIG. 2. The impact of maternal age on the prevalence of KS. A significant rise in prenatal prevalence of KS was found with increasing maternal age. In the postnatally diagnosed subjects, a nonsignificant rise was found.

the cases, a rather high proportion when considering that the syndrome has a very variable phenotype and many will only be diagnosed due to infertility. It is very difficult for expectant parents to decide whether a risk of a minor handicap should lead to a termination of the pregnancy, when proper guidance and medical care can ameliorate many of the expected problems. It has recently been shown that the parents' decision to terminate the pregnancy is influenced by the health professional providing the counseling. The affected pregnancy was more likely to continue if the counseling was given by a genetic specialist (21, 22).

Karyotypes

Seven percent of KS subjects had a mosaic karyotype. Only one prospective study included data regarding mosaicism (6), and all of these subjects are included in our material. In all of the other prospective studies, too few cells (three to five cells) have been examined to diagnose a substantial number of KS subjects with mosaicism.

Maternal age effect

Among prenatally examined subjects, there was an approximately 4-fold increase in prevalence, from a maternal age less than 24 yr to an age above 40 yr (Fig. 2). Although not significant, a steep rise in prevalence was seen among postnatally diagnosed subjects with a 10-fold increase in prevalence from a maternal age less than 35 yr to above 40 yr. Previous reports have described a significant effect of maternal age on prevalence of KS in both postnatally tested (23) and prenatally tested subjects (24).

Quality of the data

The DCCR can be considered complete, and it represents a unique opportunity for studying abnormal karyotypes.

The data we have extracted from the registry are not representative of the whole Danish population of pregnant women, because most prenatal examinations are carried out among older women who have a higher risk of KS. The age standardized prevalence is similar in the present study to the known true prevalence from prospective chromosome studies on live borns; when taking into consideration that no increased risk of intrauterine death has been ascribed to the KS karyotype, it seems reasonable to extrapolate the data to the whole Danish population and to populations of Caucasians and Japanese, because the previous cytogenetic surveys mainly included Caucasians and Japanese.

Consequence of missing the diagnosis

Early studies of KS revealed an increased risk of psychiatric disturbances, criminal behavior, and mental retardation (25–27), but this could not be confirmed by later prospective studies based on chromosome surveys (6, 28).

Prospective studies have shown that boys with KS often suffer from language and academic difficulties and psychological distress, which may be reduced by early diagnosis, guidance of parents and teachers, and proper medical management (2, 4, 29).

Proper masculinization with a normal development of bone, muscle, and secondary sexual characteristics is dependent on a normal testosterone level, and most subjects with KS are suffering from hypogonadism and are typically described with eunuchoid body proportions. Supplementation with testosterone from early puberty can secure a proper development of male sexual characteristics, and probably also a peak bone mass sufficient to prevent osteoporosis later in life (30). Testosterone treatment may also influence attention, self-esteem, and cognitive functions (3, 31).

We probably only see the worst and best functioning men with KS, the former being diagnosed early because of language and behavioral problems, the latter because of infertility. The average man with KS may not show severe stigmata, but may be suffering from hypogonadism severe enough to keep him from mating and therefore not leading him to the infertility clinic and to our knowledge.

Currently the indications for performing prenatal karyotyping are changing, increasingly being based on pathological findings during ultrasonography and the triple test, rather that the former major indication "advanced maternal

age" (>35 yr) (at least in Denmark). As a consequence, one can predict that the number of prenatally diagnosed KS subjects will decline, because no stigmata are seen on ultrasonography and no biochemical markers are present in the pregnant mother's blood. This will lead to a small rise in the prevalence among live borns, because fewer pregnancies with KS fetuses will be diagnosed and hence terminated.

Neonatal chromosome screening would be helpful, not only to diagnose KS but also other syndromes in which early treatment and guidance are beneficial for optimal development (*e.g.* Turner syndrome, where GH therapy is necessary for a normal adult height, and estrogens for a normal development of sexual characteristics and bone formation). It may be discussed whether simple screening measures, at birth or later in life, should be implemented. Chromosomal karyotyping is probably too expensive, but PCR-based solutions could be more cost effective (32).

General practitioners, pediatricians, speech therapists, and school medical officers should pay more attention to this rather common but overlooked syndrome, to diagnose more boys with KS at an earlier age.

In a population like the Danish of approximately 5 million people, with approximately 60,000 births per year, the annual number of newborn boys with KS will be around 46 per year (without correction for prenatal examinations).

Conclusions

KS is severely underdiagnosed in Denmark. Only approximately one fourth of adult males with KS are diagnosed. There is a delay in diagnosis of the syndrome, with less than 10% being diagnosed before puberty. The prenatal prevalence (adjusted for maternal age) confirms that the true prevalence is in fact around 150 per 100,000 (one in 667 males). No cases of false positive KS diagnoses were found among prenatally examined subjects who underwent postnatal examination. Advanced maternal age has a significant impact on the prevalence of KS.

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