INTRAUTERINE DIAGNOSIS OF SEX CHROMOSOME ANEUPLOIDY

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Objective:

To provide current information on sex chromosome aneuploidies to obstetricians who encounter such diagnoses and who counsel prospective parents faced with the prenatal diagnosis of a sex chromosome aneuploidy.

Data Sources:

Unbiased information about the natural course of sex chromosome aneuploidy has become available only in the last few years. Current knowledge is based on seven prospective studies on unselected individuals with sex chromosome aneuploidy identified 20-30 years ago. All literature on sex chromosome aneuploidy was reviewed, Karyotypes specifically addressed included the following: 47,XXY, 47,XXX, 47,XYY, 45,X, 45,X/46/XX, 46,XX/47,XXXX, and 46,XY/47,XXY.

Methods of Study Selection:

The international studies followed the effected subjects from birth to young adulthood. All published reports, case studies, and articles were reviewed.

Tabulation, Integration, and Results:

All prospective studies from birth to young adulthood. All prospective studies were included in the course of determining necessary information for obstetricians and prospective parents. Points addressed for each of the aneuploid karyotypes included expected phenotype, reproductive competence, developmental risks, and intervention therapies.

Conclusion:

Information about sex chromosome aneuploidy can assist obstetricians in providing accurate and comprehensive genetic counseling to parents of affected fetuses, and thereby facilitate the process of making an informed decision about pregnancy management. (Obstet Gynecol 1996;87:468-75)

The prenatal diagnosis of sex chromosome aneuploidy occurs frequently, and many obstetricians are faced with questions about the clinical implications. Prospective parents must receive current information about the prognosis of individuals with X and Y chromosome aneuploidy so that they can make informed

decisions regarding the continuation or termination of pregnancy. Knowledge about sex chromosome aneuploidy has been increasing over the last few years based on several prospective studies of individuals who had sex chromosome aneuploidy diagnosed at birth and who were followed-up into young adulthood. Despite this, parents often receive inaccurate or incomplete information based on outdated and biased reports or textbook summaries that often stereotype these conditions. Little information is written specifically for parents, who often rely solely on communication with the obstetrician, especially when a genetic counselor is not available. This paper summarized current knowledge about sex chromosome aneuploidy and offers suggestions for prenatal counseling.

BACKGROUND AND METHODS

Sex chromosome aneuploidy is the most common chromosome abnormality present at birth, with an overall incidence of 1/400, making it approximately twice as frequent in newborns as trisomy 21. Its incidence at amniocentesis is even greater and is estimated to be 1/250 in woman over 35 years of age. Twenty-five percent of all chromosome abnormalities detected at amniocentesis in women older than 35 involve the sex chromosomes. In one early amniocentesis study, the incidence of sex chromosome aneuploidy before 14 weeks gestation was 1/85, and two chorionic villus sampling (CVS) studies have suggested the incidence to be increased or equivalent to that of amniocentesis. There have been few studies on women under 35, but sex chromosome aneuploidy has been shown to comprise a significant proportion of chromosome abnormalities in younger mothers. One study found the percentage of sex chromosome aneuploidy in aneuploid fetuses to be larger than that of trisomy 21 in women age 39 or younger. Sex chromosome aneuploidy is defined as a numeric abnormality of an X or Y chromosome, with addition or loss of an entire X or Y chromosome, with addition or loss of an entire X or Y chromosome resulting in 47,XXX, 47,XXY, 45,X, and 47,XYY karyotypes. Sex chromosome mosaicism, in which one or more populations of cells have lost or gained a sex chromosome, also is common. The most commonly occurring sex chromosome mosaic karyotypes include 45,X/46XX, 46XX/47,XXX, and 46,XY/47,XXY. All of these aforementioned aneuploidies are discussed later. Other less frequent sex chromosome abnormalities, which are considered elsewhere, involve the addition of more than one sex chromosome, a structural variant of an X or Y chromosome, and other X and Y mosaicism.

For many years, information about these conditions was dependent on case reports or screenings of abnormal individuals ascertained on the basis of aberrant phenotypes and/or behavior. When chromosome identification techniques became routinely available in the 1960's, many studies used the easily accessible populations of mental and penal institutions to screen for chromosome abnormalities. The incidence of 47,XXY men and 47,XXX women was found to be four to five times greater than the newborn population incidence.

Among prison populations, an increased representation of 47,XYY men was noted. As a result, a series of stereotypes about sex chromosome aneuploid individuals evolved in which 47,XXY men were characterized as mentally retarded and homosexual, 47,XXX women as infertile and psychotic, and 47,XYY men as "super males" possessing the "murder chromosome." The fact that over 99% of all living individuals with sex chromosome aneuploidy were not included in these studies was overlooked, and the possibility that some could be normal was not generally considered. Unfortunately, these stereotypes still exist in some reference books.

Such biased portraits of sex chromosome aneuploidy are being displaced by information from long-term prospective studies on individuals with X and Y aneuploidy. These studies were begun in the 1960's and have provided an opportunity to document the developmental course of these conditions and to dispel past myths. Seven study groups in different parts of the world (Denver, Colorado; New Haven, Connecticut; Boston, Massachusetts; Edinburgh, Scotland; Aarhus, Denmark; Toronto, Canada; and Winnipeg, Canada) commenced studies independently between 1964 and 1975 to determine the incidence and course of sex chromosome aneuploidy in newborn populations. Researchers screened 199,898 consecutive newborn live births by examination of amniotic membranes, buccal smear, or cord blood, and all discrepancies were confirmed by chromosomal analysis of blood leukocytes. As a result, 307 individuals were identified in these worldwide populations, representing various cultures, ethnic groups, and socioeconomic groups. The families were then invited to join a prospective study of the development of these children. The ensuing studies were free of the selection bias of earlier investigations. Controls consisted of chromosomally normal siblings or matched newborns. Our own study has followed more than 40 such individuals from birth to young adulthood. From the Denver study and the other six prospective studies, an appreciation for the variability of these conditions is now becoming established concurrent with the knowledge that most of these individuals with sex chromosome aneuploidy fall within the normal range in development and that marked abnormality is not usually seen.

RESULTS

47,XXY

The addition of an extra X chromosome to a normal male 46,XY karyotype results in a 47,XXY chromosome constitution, often referred to as Klinefelter syndrome. It occurs in 1/600 to 1/800 male births. Infants are physically normal. Tall stature (above the 75th percentile) may become evident in childhood and is consistent with the adult phenotype. Boys with the 47,XXY karyotype enter puberty normally, but become hypergonadotropic by mid puberty as testicular growth ceases and testosterone production decreases. Testes are small in adulthood, and testosterone supplementation is desirable. Males with the

47,XXY karyotype are infertile but can have normal sexual relations because the genitals are otherwise normal. There is no evidence of increased homosexuality. The literature reports that about one-third of men with the 47,XXY karyotype develop gynecomastia; when severe, it can be surgically corrected with mammoplasty. Mental retardation is not associated with the 47,XXY karyotype. Usually, the intelligence quotient (IQ) is in the average range but can be 10-15 points less than that of siblings. Among 105 47,XXY males in the combined prospective studies who were 10-24 years old, the full-scale IQ mean was 85-90 (range 67-133). In most cases, the verbal IQ was significantly less than the performance IQ, which manifested as reading deficiencies and poor spelling skills in about two-thirds of the sample. Speech and language delays were noted in about half of the boys, which could be predictive of later learning problems. Educational intervention, usually part-time, was provided for approximately 70% of the boys. Motor skills were assessed only by the Denver group, who noted slight delays in eight of 14 boys, as evidence by a later age of independent walking compared with siblings and established norms. Poor gross motor coordination was noted throughout adolescence, and individual sports (biking, hiking, swimming) were observed to be more satisfying than team sports (baseball, football, basketball). Among the 105 males in the entire 47,XXY population, behavior characteristics frequently noted by the research teams included tendencies toward passive and unassertive behaviors; antisocial behavior and psycho pathology were not increased over controls. The variability among 47,XXY males has been discussed by most investigators. Many boys exhibit delays in several of the developmental areas, whereas some appear to be relatively unaffected by the presence of the extra X chromosome, except for tall stature and infertility.

47,XXX

The 47,XXX karyotype is known as triple X, and its incidence is approximately 1/1000 to 1/1200 female births. The only consistent physical characteristics is tall stature (above the 80th percentile) by adolescence. Sexual development and puberty are normal. Fertility has not been reduced in the prospectively followed group, and thus the earlier stereotype on infertility is no longer considered correct. The mean full-scale IQ score for the 46 females followed prospectively was between 85 and 90 (range 53-112). Mental retardation is not associated with 47,XXX, but IQ scores are usually 10-15 points below that of siblings. Approximately half of the group experienced receptive and expressive language delays. Learning disabilities that necessitated educational intervention, either part-time or full-time, were documented in 71% of the group. All delays were global in nature rather than being confined to specific academic areas. Gross motor skills were not ascertained for the entire sample, but many investigators have commented on awkwardness, clumsiness, and poor coordination. Of the 11 girls in the Denver study, six walked late, and only one scored above the tenth percentile on tests of motor proficiency. Behavior is generally not aberrant, but several centers have noted that some 47,XXX girls

have had difficulty with interpersonal relationships. Wide phenotypic variability has been observed; some 47,XXX girls have difficulty in all developmental areas and are unable to achieve high school graduation, whereas others are relatively free of X aneuploidy effects, and some have attended college.

47,XYY

The 47,XYY karyotype occurs in 1/1000 male births. Physical phenotype is normal, with tall stature (75th percentile) by adolescence. There are no problems associated with puberty or fertility. Among the 39 boys followed prospectively, full-scale IQ averaged 105 (range 65-129). Speech delay was noted in approximately half of the boys, and half of the sample needed part-time or full-time educational intervention. There was no consistent behavioral phenotype. Several investigators reported an increase in temper tantrums and distractibility among boys. Aggression was not frequently observed in children and adolescents.

45,X

Turner syndrome is most commonly the result of an absence of an entire X chromosome resulting in a 45,X karyotype. The Turner phenotype can also be produced by various partial X deletions or other structural abnormalities. Its incidence is approximately 1/2500 newborn females, and thus it occurs considerably less frequently than the other sex chromosome aneuploidies. At least 99% of all 45,X pregnancies are are aborted spontaneously in early pregnancy. Usually, the phenotype is obvious in infancy and childhood, and thus most cases are identified at an early age. Because only a few girls were identified in the unselected screenings, Turner syndrome has not been included in prospective study summaries. However, there is considerable information about Turner syndrome in the medical literature. Short stature is a hallmark of Turner syndrome. These females are usually small at birth, do not experience an adolescent growth spurt, and reach an adult height of approximately 4'6" (144 cm, below the fifth percentile). Using current therapy, most of these girls can now be treated with recombinant human growth hormone injections, usually beginning in childhood, and can expect to reach an average height of at least 4'11" (150 cm, fifth percentile). The other significant feature of Turner syndrome is gonadal dysgenesis. In general, women with Turner syndrome are infertile because their ovaries usually are fibrous streaks. Supplemental estrogen-progesterone therapy can be initiated in early adolescence to achieve secondary sexual characteristics and establish menses. Current assisted reproductive techniques using donated oocytes have made it possible for many Turner syndrome women to sustain pregnancies.

Other somatic features of Turner syndrome can include cardiac and kidney abnormalities, webbed neck, and lymphedema. These females are at an increased risk of otitis media, cardiovascular disease, hypertension, diabetes

mellitus, thyroid disorders, and obesity. Careful medical management can assist in identifying and treating most of these problems. Mental retardation is not prevalent in Turner syndrome, and most girls have normal IQ's. Usually, verbal IQ is significantly greater than performance IQ, resulting in a visual-spatial deficit. Many investigators have noted deficits in left-right orientation, copying shapes, handwriting, and solving math problems. In general, speech is normal, but expression can be compromised if recurrent otitis media has not been treated successfully. Motor skills can be delayed slightly, and poor gross and fine motor coordination has been observed frequently. Behavior characteristics are variable, with no tendencies toward psychopathology.

MOSAICISM

Sex chromosome mosaic karyotypes are most often 45,X/46,XX, 46,XX/47,XXX or 46,XY/47,XXY, but many other combinations are possible. In general, the presence of a normal 46,XX or 46,XY cell line tends to modify the effects of the aneuploid cells. Twenty-two mosaics have been followed prospectively, including 11 45,X mosaics, six 47,XXY mosaics, and five 47,XXX mosaics. On evaluations of intelligence, educational intervention, motor skills, and behavioral problems, those with mosaicism scored similarly to controls, and no significant differences were determined. Fertility may vary, depending on the chromosomal constitution. Although 46,XX/47,XXX females usually can be assumed to be fertile, the prognosis for 45,X/46,XX mosaics and 46,XY/47XXY mosaics is less definitive. Although many may have normal reproductive competency, appropriate tests must be performed at puberty or later to establish fertility status.

The international investigators have long recognized that an element of the self-fullfilling prophecy could affect the study results. In question is whether early identification and disclosure of a sex chromosome aneuploidy to parents, physicians and affected individuals would influence development and behavior over the course of infancy and into adulthood. Two observations have emerged that lend to refute the effects of a self-fulfilling prophecy. First, the seven international centers used similar methods to ascertain the subjects in an unbiased fashion but used different methods of disclosure. In some instances, parents were told of the chromosome abnormality within a few days of birth, whereas other groups withheld such information for several years. Each group also used various test procedures and evaluations over the course of the studies (ie, the evaluation tools were not homogenous across international groups). Despite these two different approaches, all of the groups have produced similar results and conclusions. A second consideration involves the results of the sex chromosome mosaic group, who have been found to be similar to controls on all measures. These 22 propositi were identified at birth and followed in the same way as the individuals with pure karyotypes. Although is it known that mosaicism usually produces a more normal phenotype, the fact that their incidence of developmental and behavioral problems is not increased refutes the

effects of a self-fulfilling prophecy.

GENETIC COUNSELING

Based on the results of these international prospective studies, several features common to all of the sex chromosome aneuploid karyotypes have been documented, all of which should be included in the genetic counseling of parents with affected fetuses. These are discussed below. The specific features for each of the most frequently diagnosed sex chromosome aneuploid karyotype are outlined in Table 1 and should be discussed with parents. More extensive information on each karyotype can be found in several current references.

When a diagnosis of sex chromosome aneuploidy is made prenatally, genetic counseling of parents should include the following information:

1) Usually, physical appearance is normal, although there are exceptions in the case of Turner syndrome.

2) Mental retardation, defined as an IQ less than 70, is not typically associated with sex chromosome aneuploidy. Most individuals with sex chromosome aneuploidy have IQs in the normal range, but IQ is often somewhat less than that of siblings. There is a normal distribution of full-scale IQs for each karyotype.

3) The presence of X or Y chromosomal aneuploidy confers a moderate risk for developmental problems in the areas of speech, motor skills, and learning abilities. Speech delays are common and can contribute to school difficulties if untreated. Motor delays are observed occasionally, and decreased coordination can be present; consequently, individual sports are usually more rewarding than competitive team sports. Learning disabilities are frequent among sex chromosome aneuploidy school-age children, and most are mainstreamed with part-time education assistance. Anticipatory guidance can be most useful in identifying early delays and providing appropriate therapy. There are no specific remedial programs designed for children with sex chromosome aneuploidy who have learning problems. Intervention is not different from that given to children with normal 46,XX and 46,XY karyotypes when similar developmental problems are present. Although there may be an increased association between the presence of sex chromosome aneuploidy and these difficulties, some sex chromosome aneuploid children demonstrate normal development.

4) The impact of the environment is particularly significant. Our studies have concluded that these individuals adapt less well to environmental adversity (alcoholism, family conflict, economic instability) than do their karyotypically normal siblings. For this reason, a strong and supportive home environment is especially important. Sex chromosome aneuploid children from stable and nurturing families have no more psychological disorders than do their siblings.

5) A specific prognosis based on karyotype for any affected child is not possible. As with eukaryotic children, the variability is extensive. Although some develop serious difficulties, other do not and may adapt fairly well despite some developmental problems. Many individuals with sex chromosome aneuploidy are never identified throughout their lifetimes.

The decision by parents to continue or terminate a sex chromosome aneuploid pregnancy is dependent on many economic, social, and psychologic factors, and by the type of information presented to the parents by the obstetrician or counselor. The difference between the decisions of parents given current information versus those who used older medical literature is striking. Holmes-Siedle et al reported a termination rate of 62% in reports from the early 1980's. They also noted that there was a greater tendency to terminate when parents were counseled by obstetricians rather than geneticists. A similar report by Verp et al indicated a 67% termination rate, based on 24 studies from the period 1976-1987. Observations derived from more recent counseling sessions have shown a reversal of these numbers. Only one-third of couples faced with this decision chose termination in the 60 families counseled by Donnai and our own study reflects the same trend. In the last decade, our group has counseled over 800 cases of sex chromosome aneuploidy in the western hemisphere. Such inquiries have come from physicians and parents concerned about the prognosis for a prenatally ascertained child. Genetic counseling included a discussion of all of the points listed in the text and Table1, with emphasis on the variability of these conditions and the importance of a strong environment. The counseling was non directive. We observed that many parents contacted us after their primary care physician (usually an obstetrician) had little information to offer or after termination was recommended without extensive discussion or prognosis. The results of our counseling sessions indicate that slightly over one-third chose to terminate, and two-thirds continued the pregnancies.

Follow-up of a small number of these children has indicated that their development appears to surpass that of those sex chromosome aneuploid individuals from the earlier studies diagnosed through postnatal newborn screening. The reasons for this are not well defined at this point, but the fact that these parents made a conscious decision to continue their pregnancies appears to have a very positive bearing on the development of their children. Furthermore, these parents have had the advantage of anticipatory guidance in knowing of a risk for developmental problems and offering early intervention. More long-term studies of such children and their families are needed.

TABLE 1. Selected Features of Common Sex Chromosome Abnormalities

Karyotype	Name	Expected Phenotype
47,XXY	Klinefelter Syndrome	Normal at birth, Normal genetalia

or XXY		Normal puberty, testicular size reduced, need for testosterone supplementation beginning in adolescence and continued through adulthood, infertility, risk for gynecomastia, Heterosexual orientation Tall stature, Risk of learning disabilities, especially in reading and writing-50% may have dyslexia.
47,XXX	Triple X	Normal in appearance, tall stature normal puberty and reproductive competence. Risk for speech delays and global learning disabilities.
47,XYY	XYY	Normal in appearance, tall stature Normal puberty and reproductive competence, risk for learning disabilities and hyperactivity, No increased incidence of aggression.
45,X	Turner syndrome	At birth may have congenital lymphedema; risk for cardiac malformations (which may require surgery), webbing of neck, kidney malformations, growth delay, short stature-consideration of human growth hormone therapy. Ovarian dysgenesis and absence of sexual development-hormone supplementation usually begun in adolescence, assited reproductive techniques can assist some in pregnancy. At risk for otitis media, cardiovascular disease, hypertension, diabetes mallitus, thyroid disorders, obesity, risk for learning disabilities, especially those involving spatial relations and perception.
45,X/46,XX	Turner mosaic	Often normal appearance, may have slightly short stature. Fertility possible in many cases, at risk for spontaneous abortions and early menopause
46,XX/47,XXX	Triple X Mosaic	Usually normal in appearance, fertility is likely, developmental risks reduced compared with 47,XXX
46,XY/47,XXY	Klinefelter	Usually normal in appearance, Fertility

Mosaic	possible in many cases, developmental risks reduced compared to 47,XXY

DISCUSSION

The prenatal diagnosis of a chromosome abnormality is always emotionally complex for the obstetrician and parents. For autosomal aneuploidy, the prognosis for a well-defined syndrome such as trisomy 21 or an unbalanced translocation usually includes known clinical significance for that disorder, and many are severely affected. Such is not the case for sex chromosome aneuploidy, for which the phenotype is not as severe and development is more mildly affected. The situation is further intensified in the cases in which prenatal counseling before CVS or amniocentesis has not included a discussion of sex chromosome aneuploidy, and thus parents are faced with a totally unfamiliar diagnosis. Most women are referred because of maternal age, so the emphasis of such counseling has been on the increased occurrence of trisomy 21. However, because sex chromosome aneuploidy is encountered so frequently across all age groups, a discussion of these chromosome abnormalities should be included for parents who receive a diagnosis of sex chromosome aneuploidy, this preparation can enable them to under standard use the information more effectively. The importance of including a discussion of sex chromosome aneuploidy in prenatal counseling should not be overlooked.

The increased use of prenatal diagnosis resulting in frequent identification of sex chromosome aneuploidy fetuses requires that obstetricians become familiar with sex chromosome abnormalities in order to begin the counseling process with prospective parents. In many instances, a referral to a clinical geneticist or a genetic counselor who is more familiar with the phenotype and prognosis of individuals with sex chromosome aneuploidy can be helpful for parents. Written resources for parents on Turner syndrome and 47,XXY can provide further information on these two karyotypes.

Usually, the initial information a parent receives about a fetus affected with a sex chromosome aneuploidy is from the obstetrician. Such information significantly influences the attitude of the parents toward their child. It also provides the intellectual and emotional background on which all future information will be compared and evaluated. The knowledgeable obstetrician can thus provide prospective parents with information about sex chromosome aneuploidy that will assist them in their attempts to make informed decisions about pregnancy management.

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