Parental Decisions of Prenatally Detected Sex Chromosome Abnormality

Because of the widespread use of amniocentesis, the prenatal recognition of sex chromosome abnormality (SCA) has become increasingly common. Recent literature provided an insight into the understanding of the natural history and prognosis for individuals with SCA. Our study was designed to review the parental decision on pregnancy with SCA. Over the last 10 yr, we diagnosed 38 cases (0.50%) with SCA out of 7,498 prenatal cases. We reviewed the records and the results of the pregnancies. We included the cases (n=25) of apparently normal anatomic fetus to analyze the factors influencing parental decision. We excluded 13 cases with obvious anomaly or presumably bad outcome. Fifteen (60%) couples continued their pregnancies and ten (40%) terminated theirs. Nine couples (64%) out of fourteen mosaicism cases continued their pregnancies. All five pregnancies assisted by reproductive technique continued their pregnancies. More pregnancies were continued when counseling was done by an MD geneticist rather than by an obstetrician. A significant trend was observed with a higher rate of pregnancy continuation in recent years. The genetic counseling is important to give appropriate information to the parents. Establishing guidelines and protocols will help both obstetricians and parents to make a decision.

Key Words : Sex Chromosome Aberrations; Prenatal Diagnosis; Genetic Counseling

INTRODUCTION

Most people with an extra sex chromosome are not identified because there are no exact indications for karyotyping (1). However, they are sometimes prenatally diagnosed by chances since the use of invasive prenatal techniques, such as amniocentesis and chorionic villus sampling, has become widespread (2). Furthermore, the rate of sex chromosomal abnormality (SCA) is higher after treatment with intracytoplasmic sperm injection (ICSI), which has improved the chances of treatment of male factor infertility, than in naturally conceived pregnancy (3-5). The increased rate of SCA after ICSI calls for intensified efforts to provide adequate and realistic genetic counselling for parents (3-6). SCA includes 45,X (Turner syndrome), 47,XXX (triple X syndrome), 47,XXY (Klinefelter syndrome), and 47,XY Y. Mosaic and structural variants of chromosome X and Y are also included. Although the chances for a live birth in prenatally diagnosed Turner syndrome are low, most fetuses with SCA survive to term. Major malformations may occur in some Turner syndrome, but not in Klinefelter, triple X, and the XYY syndromes (7). Mosaic patients are affected mildly or phenotypically normal, compared with nonmosaics (8).

Despite the relatively good prognosis, the knowledge that their baby may have an abnormality make parents feel uncomfortable to continue the pregnancy (1). The reports based on studies on individuals in mental and penal institutions in the 1960s were proven to be ascertained. This demonstrated men with Klinefelter syndrome had a tendency to be homosexual and mentally retarded; women with 47,XXX were infertile and psychotic; and men with 47,XY Y had a tendency for criminal behaviors (9). By 1990, information on individuals with SCA aged 20 yr or older became available (10), showing an even optimistic prognosis. Although some variations existed among the types of SCA, the individuals with SCA showed only a little deterioration in verbal IQ, compared to their siblings. Furthermore, the condition is compatible with a productive and well adjusted social life (11). The intelligence of the children with SCA was average or above average at school, if they had a good home with parents willing and able to follow the counseling (12).

Given that no major malformations or severe mental handicaps are to be expected, prospective parents are confronted with a difficult decision. It is not easy for the parents to make a decision when they incidentally know their baby has a SCA. Previous studies show that a major proportion of such gestations were terminated (6, 13), presumably because of fears
about how the condition in question would manifest itself. However, recent studies suggest that a formal genetic counseling provide more information to the parents and increase the chances of live births (7-13).

Over the past 10 yr in our hospital, prenatal karyotyping was done in 7,498 cases. We found 39 cases with SCA incidentally and performed a retrospective analysis of the post-counseling outcomes of the cases.

MATERIALS AND METHODS

Over the last 10 yr between 1992 and 2001, we diagnosed 39 cases (0.52%) with SCA out of 7,498 prenatal cases. All cases with SCA (karyotypes 45,X, 47,XXY, 47,XXX, and 47,XYY in nonmosaic or mosaic state) were identified through searching our database. The diagnosis of SCA was verified from the original patient charts and laboratory sheets. Thirty-eight cases were prenatally diagnosed at our hospital, and one case had been referred from an outside institution, and was confirmed by cordocentesis in our institution. Diagnostic methods were amniocentesis and cordocentesis. We included the cases (n=25) of apparently anatomically normal fetuses to analyze the factors influencing the parental decision. We excluded 13 cases, nonmosaic Turner syndrome (n=11), because it is commonly associated with fetal hydrops and/or cystic hygroma, a case of 47,XXY with multiple anomalies (lobar holoprosencephaly, corpus callosum agenesis, ventriculomegaly, heart anomaly with double outlet of the right ventricle, and polyhydramnios), a case of 48,XXXX.

After excluding all these 13 cases, the remaining 25 cases were analyzed. The karyotypes of 47,XXY, 47,XXX, and 47,XXY in nonmosaic or mosaic state were included. Mosaic Turner syndromes were included, too. Cases of presumed pseudomosaicism because of culture artifact or maternal cell contamination were excluded. Presumed confined placental mosaicism were included.

Families (mother, father, and if needed, other relatives) were counseled by ten different obstetricians. Obstetricians recommended further genetic counseling with MD geneticists. Families were generally informed that individuals with SCA have a normal phenotype: individuals with Klinefelter syndrome may be associated with a tall stature and secondary characteristics, and may be infertility. In cases with 45,X/46,XXY, the possibility of mixed gonadal dysgenesis was explained, too. The families were generally told that 95% of pregnancies with a prenatal diagnosis of mixed gonadal dysgenesis result in a normal phenotypic male with a possibility of infertility and an increased risk of gonadal tumors. The remaining 5% of the pregnancies result in an infant with some degree of ambiguous genitalia, which may require surgery or a normal phenotypic female with some Turner syndrome features (14).

The courses and outcomes of the pregnancies were reviewed from the patient charts. The parental age, previous pregnancy history, the presence or absence of infertility, the performed assisted reproductive technology procedure, the presence or absence of a fetal structural anomaly on ultrasonographic examination, the type of SCA, and the prenatal procedure performed were reviewed. The outcomes of 4 patients delivered at other hospitals were confirmed by telephone interviews.

Statistical analysis was done by Fisher's exact test.

RESULTS

Six cases were 47,XXY, four cases were 47,XXX, one case was 47,XXY, and 14 cases were several types of mosaicism. Details of the cases are summarized in Table 1. Twenty five pregnancies with the diagnosis of SCA were included in our analysis. Twenty four cases were a singleton, and one was a twin whose karyotype was 47,XXX, while the other twin had a normal karyotype. The diagnoses were made between the 14.6th and 26.6th gestational weeks, which were confirmed or corrected by early gestational ultrasound. The mean gestational age with ±2 standard deviation at the time of diagnosis was 18.7±2.8 weeks.

The indications for invasive prenatal diagnosis were advanced maternal age (>35 yr) (n=13), abnormal maternal serum triple screen result (n=8), increased nuchal fold thickness on fetal ultrasonography (n=3), and previous abnormal pregnancy (n=2).

All 25 cases were diagnosed by amniocentesis. Among 14 mosaicism cases, six were confirmed by cordocentesis. Two cases were normal in cordocentesis, however, a skin biopsy of the fetus was not performed.

Table 2 summarizes the cytogenetic findings and the parental decision of the 25 analysed gestations with SCA. Ten couples (40%) terminated their pregnancy and 15 (60%) continued theirs.

Nine couples (64%) out of 14 mosaicism cases continued their pregnancy (Table 3) and there was no statistical significance (p=0.69). All five couples (100%) who were infertile.
and made through the assisted reproductive technique continued their pregnancies (Cases 4, 6, 10, 11, and 14; Table 1).

Parental decisions differed depending on the period in which the prenatal diagnoses of SCA were made. A higher number of couples chose to continue their pregnancies in recent years (Table 4). More pregnancies with a SCA were continued when counseling was done by an MD geneticist rather than by an obstetrician ($p=0.04$; Table 5).

**DISCUSSION**

With an increasing number of pregnancies being subjected to prenatal karyotyping because of abnormal ultrasound findings and positive screening results on maternal serum screening, it is inevitable that a large proportion of fetuses with SCA are detected prenatally as an incidental finding. SCA represent more than 10% of abnormal chromosome

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**Table 1. Details of 25 cases with prenatally diagnosed sex chromosome abnormality**

| Case | Karyotype   | Diagnostic Method | Gest. weeks | Indication          | Decision | Remarks |
|------|-------------|-------------------|-------------|---------------------|----------|---------|
| 1    | 47,XXY      | AC                | 22.6        | Down risk           | T        |         |
| 2    | 47,XXY      | AC                | 21.9        | Elderly             | T        |         |
| 3    | 47,XXY      | AC                | 15.0        | Previous delivery of Down baby | T        |         |
| 4    | 47,XXY      | AC                | 18.3        | Down risk           | C        | IUI     |
| 5    | 47,XXY      | AC                | 16.1        | Down risk           | C        |         |
| 6    | 47,XXY      | AC                | 20.0        | Elderly             | C        | ICSI    |
| 7    | 47,XXY      | AC                | 21.0        | NFT                 | C        |         |
| 8    | 47,XXX      | AC                | 16.1        | Elderly             | T        |         |
| 9    | 47,XXX      | AC                | 21.4        | Increased MSAFP     | T        |         |
| 10   | 47,XXX      | AC                | 14.6        | Elderly             | C        | IUI     |
| 11   | 47,XXX      | AC                | 16.4        | Elderly             | C        | ICSI, Twin |
| 12   | 47,XXY/46,XY| AC/CO             | 25.0        | Down risk           | T        |         |
| 13   | 47,XXY/46,XY| AC                | 22.4        | Down risk           | T        |         |
| 14   | 47,XXY/46,XY| AC/CO             | 15.4        | NFT                 | C        | GIFT    |
| 15   | 47,XXY/46,XY| AC                | 17.0        | Elderly             | C        |         |
| 16   | 47,XXY/46,XX| AC                | 17.4        | Previous delivery of acranic baby | C        |         |
| 17   | 47,XXY/46,XX| AC/CO             | 16.1        | Elderly             | C        |         |
| 18   | 47,XXY/46,XX| AC                | 19.0        | Elderly             | C        |         |
| 19   | 45,X/46,XY  | AC                | 22.7        | NFT                 | T        |         |
| 20   | 45,X/46,XY  | AC                | 20.4        | Down risk           | T        |         |
| 21   | 45,X/46,XY  | AC                | 16.2        | Elderly             | C        | PPROM   |
| 22   | 45,X/46,XY  | AC/CO             | 18.7        | Down risk           | C        |         |
| 23   | 45,X/46,XX  | AC                | 18.9        | Elderly             | T        |         |
| 24   | 45,X/46,XX  | AC/CO             | 19.0        | Elderly             | C        | NL CO   |
| 25   | 45,X/46,XX  | AC/CO             | 17.0        | Elderly             | C        | NL CO   |

**Table 2. Cytogenetic diagnoses and outcomes in 25 pregnancies with sex chromosome abnormality**

| Karyotype   | Number of cases | Continued | Terminated |
|-------------|-----------------|-----------|------------|
| 47,XXY      | 6               | 3 (50%)   | 3 (50%)    |
| 47,XXY      | 1               | 1 (100%)  | 0 (0%)     |
| 47,XXX      | 4               | 2 (50%)   | 2 (50%)    |
| 45,X/46,XX  | 4               | 2 (50%)   | 2 (50%)    |
| 45,XXY/47,XXX| 3              | 3 (100%)  | 0 (0%)     |
| 45,XXY/47,XX| 2               | 1 (50%)   | 1 (50%)    |
| 46,XY/47,XXY| 3               | 1 (33%)   | 2 (67%)    |
| 46,XY/47,XY | 1               | 1 (100%)  | 0 (0%)     |
| Total       | 25              | 15 (60%)  | 10 (40%)   |

*The aneuploid cell line accounted for 6% to 82% of the analysed metaphase cells in cases of mosaicism.

**Table 3. Parental decisions and mosaicism**

| Mosaicism   | Number of cases | Continued | Terminated |
|-------------|-----------------|-----------|------------|
| Non-Mosaic  | 11              | 6 (55%)   | 5 (45%)    |
| Mosaic      | 14              | 9 (64%)   | 5 (36%)    |
| Total       | 25              | 15 (60%)  | 10 (40%)   |

*p-value=0.69 (Fisher's exact test).*
The couples are faced with a very difficult and personal decision when a SCA is identified prenatally. The study by Abramsky and Chapple showed that the most undiagnosed 47,XXY and 47,XYY males do not look or behave in a manner that prompts testing for a chromosome abnormality (1).

The present study showed that 60% of couples at our center continued pregnancy following a prenatal diagnosis of SCA except nonmosaic Turner syndrome. Most reports from other institutions present termination rates between 32% and 66%. Christian et al. (2000) reported that among the couples with normal fetal ultrasound findings, the overall continuation rate was 40% (9). Meschede et al. (1998) showed low rates (12.7%) of pregnancy termination for prenatally diagnosed Klinefelter syndrome and other sex chromosomal polysomies.

The decision by parents to continue or terminate a pregnancy with SCA is dependent on many factors including economic, social, and psychological ones, and influenced by the type of information presented by an obstetrician or a counselor. In this study, several factors were found to have a significant influence on the parental decision making including the type of SCA, counseling with geneticists, having infertility, and the temporal period.

The type of SCA may influence parental decision. Pregnanacies with a diagnosis of 47,XXX or 47,XXY were continued significantly more often than those with a diagnosis of 47,XXY (9). This difference might have resulted from parental concerns over having a child with infertility. Parents also perceive a larger burden for a child with Klinefelter syndrome because of its association with physical manifestations such as lack of secondary sexual characteristics and gynecomastia. In our study, 50% of cases pregnancies with 47,XXX and 47,XXY were continued (Table 6). The parents’ perception of the expected disability was believed to play an important role (17).

Although the presence or absence of mosaicism does not significantly influence the couples’ decisions regarding their pregnancy (Table 3), the data suggest that couples are more likely to continue their pregnancy with a mosaic karyotype. Counseling regarding a milder phenotype than in the nonmosics may explain this difference (9).

Temporal period showed a significant difference over time. Parental decisions significantly differed depending on the temporal period in which the prenatal diagnosis of SCA was made (Table 4). The trend toward a higher rate of continuation may be a consequence of the publication of studies on long-term prospective outcomes in both newborns and pregnancies diagnosed with SCA (9). The results of these studies proposed a more optimistic prognosis than previously predicted (6, 13, 16).

Usually, parents are given initial information about their fetus with a SCA from an obstetrician. Such information significantly influences the attitude of the parents toward their fetus. Also, the speciality of the medical professional providing the counseling may have an impact. Clearly, more pregnancies with a SCA were terminated when the post-diagnosis counseling was done by an obstetrician rather than by an MD geneticist (Table 5). The first communication with parents is important because it may affect how later information is interpreted or even whether it is sought (12).

It is essential for an obstetric unit to have an established protocol for giving results and for all members of the staff who...
communicate with parents to give accurate, up-to-date information about the condition identified.

Follow-up of a small number of children with SCA showed the prognosis was even more optimistic (10). Although our study was done on a very limited number of cases, most of them showed a good growth (Table 7). Longer term studies on such children and their families are needed.

The overall termination rate of 40% appears low in comparison with the literature data. The genetic counseling is important to give appropriate information to parents. Establishing guidelines and protocols will help both obstetricians and parents to make a decision. It appears that the development of consensual guidelines in pluridisciplinary fetal care centers would help reduce the disparities in the management of fetuses with SCA.

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