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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*

Yon-Ju Kim*, So-Yeon Park†, Jung-Yeol Han*, Moon-Young Kim*, Jae-Hyug Yang*, Kyu-Hong Choi*, Young-Mi Kim†, Jin-Mee Kim†, Hyun-Mee Ryu*,†

Departments of Obstetrics and Gynecology*, Laboratory of Medical Genetics†, Samsung Cheil Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

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Address for correspondence
Hyun-Mee Ryu, M.D.
Department of Obstetrics and Gynecology, Samsung Cheil Hospital, 1-19 Mookjeung-dong, Choong-gu, Seoul 100-380, Korea
Tel : +82.2-2000-7000, Fax : +82.2-2000-7477
E-mail : ryu97@samsung.co.kr

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,XYY. 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,XYY 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 kayotypes of 47,XXY, 47,XXX, and 47,XYY 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 mosaicisms 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 develop gynecomastia. Individuals with 47,XXX and 47, XYY are often taller than the standard, however are usually not associated with other clinical manifestations. Families were informed that individuals with SCA have a normal intelligence. However, they may have an IQ slightly lower than their siblings. Individuals with Klinefelter syndrome are usually infertile, but other conditions have no sexual problems.

When the result was mosaic pattern, the families were counseled regarding a wide spectrum of features ranging from a normal phenotype to classic features of the specific SCA. The individuals with a mosaic 45,X may be associated with a short stature, cardiac problems, primary amenorrhea, lack of secondary characteristics, and may be infertile. In cases with 45,X/46,XY, 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,XYY, 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 ultrasonogram. 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 pregnancies 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

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,XYY	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,XYY/46,XY	AC	17.0	Elderly	C	
16	47,XXX/46,XX	AC	17.4	Previous delivery of acranic baby	C	
17	47,XXX/46,XX	AC/CO	16.1	Elderly	C	
18	47,XXX/46,XX	AC	19.0	Elderly + increased MSAFP	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

Gest. week; Gestational weeks at diagnosis, AC; Amniocentesis, CO; Cordocentesis, NL CO; Normal in cordocentesis, Elderly; Over 35 yr old, Down risk; Positive maternal serum screening for Down syndrome in a triple test, NFT; Increased nuchal fold thickness in ultrasonography, MSAFP; Increased maternal serum alpha-fetoprotein, ICSI; Intracytoplasmic sperm injection, IUI; Intrauterine sperm insemination, GIFT; Gamete intra-fallopian transfer, PPROM; Spontaneous premature rupture of the membranes at 25 weeks of gestational age.

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,XYY	1	1 (100%)	0 (0%)
47,XXX	4	2 (50%)	2 (50%)
45,X/46,XX	4	2 (50%)	2 (50%)
45,X/46,XY	1	1 (100%)	0 (0%)
46,XX/47,XXX	3	3 (100%)	0 (0%)
45,X/47,XXX	2	1 (50%)	1 (50%)
46,XY/47,XXY	3	1 (33%)	2 (67%)
46,XY/47,XYY	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.

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).

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).

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

Table 4. Parental decisions and temporal period

Years	Total	Continued	Terminated
1992-1995	3	1 (33%)	2 (67%)
1996-1998	12	6 (50%)	6 (50%)
1999-2001	10	8 (80%)	2 (20%)
Total	25	15 (60%)	10 (40%)

Table 5. Parental decisions and genetic counseling

Genetic counseling	Number of cases	Continued	Terminated
Genetic counseling	16	12 (75%)	4 (25%)*
No genetic counseling	9	3 (33%)	6 (67%)
Total	25	15 (60%)	10 (40%)

**P*-value 0.04 (Fisher's exact test).

Table 6. Pregnancy continuation rate

	Christian et al. 2000 (9)	Verp et al. 1988 (18)	Meschede et al. 1998 (11)	Perrotin et al. 2000 (19)	The present study
47,XXX	35%	44%	83%	66%	50%
47,XXY	13.5%	25%	83%	58%	50%
47,XYY	80%	43%	90%	50%	100%
Mosaic	50%	–	–	–	64%

results identified following prenatal cytogenetic study (15). 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. Pregnancies with a diagnosis of 47,XYY or 47,XXX 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 nonmosaics may explain this difference (9).

Table 7. Follow-up of the cases with sex chromosome abnormality

Age	Number of cases
Ongoing	3
0-24 months follow-up	3
25-48 months follow-up	1*
5-year follow-up	3
Follow-up until delivery	5
Preterm loss	1†
Total	15

*; Operation due to mitral valve regurgitation.
†; Preterm premature rupture of membranes at 25 gestational weeks.

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.

REFERENCES

1. Abramsky L, Chapple J. *47,XXY (Klinefelter syndrome) and 47, XYY: estimated rates and indication for postnatal diagnosis with implications for prenatal counseling. Prenat Diagn 1997; 17: 363-8.*
2. Linden MG, Bender BG, Harmon RJ, Mrazek DA, Robinson A. *47, XXX: what is the prognosis? Pediatrics 1988; 82: 619-30.*
3. Ohashi Y, Miharu N, Honda H, Samura O, Ohama K. *High frequency of XY disomy in spermatozoa of severe oligozoospermic men. Hum Reprod 2001; 16: 703-8.*
4. Meschede D, Horst J. *Sex chromosomal anomalies in pregnancies conceived through intracytoplasmic sperm injection: a case for genetic counseling. Hum Reprod 1997; 12: 1125-7.*
5. Bonduelle M, Wilikens A, Buysse A, Van Assche E, Devroey P, Van Steirteghem AC, Liebaers I. *A follow-up study of children born after intracytoplasmic sperm injection (ICSI) with epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI. Hum Reprod 1998; 13 Suppl 1: 196-207.*
6. Nielsen J. *Follow-up of 25 unselected children with sex chromosome abnormalities to age 12. Birth Defects Orig Artic Ser 1990; 26: 201-7.*
7. Bender BG, Linden MG, Robinson A. *Neuropsychological impairment in 42 adolescents with sex chromosome abnormalities. Am J Med Genet 1993; 48: 169-73.*
8. Bender B, Fry E, Pennington B, Puck M, Salbenblatt J, Robinson A. *Speech and language development in 41 children with sex chromosome anomalies. Pediatrics 1983; 71: 262-7.*
9. Christian SM, Koehn D, Pillay R, MacDougall A, Wilson RD. *Parental decisions following prenatal diagnosis of sex chromosome abnormality: a trend over time. Prenat Diagn 2000; 20: 37-40.*
10. Evans JA, MacDonald K, Hamerton JL. *Sex chromosome anomalies: prenatal diagnosis and the need for continued prospective studies. Birth Defects Orig Artic Ser 1990; 26: 273-81.*
11. Meschede D, Louwen F, Nippert I, Holzgreve W, Miny P, Horst J. *Low rates of pregnancy termination for prenatally diagnosed sex chromosome polysomies. Am J Med Genet 1998; 80: 330-4.*
12. Abramsky L, Hall S, Levitan J, Marteau TM. *What parents are told after prenatal diagnosis of a sex chromosome abnormality: interview and questionnaire study. BMJ 2001; 322: 463-6.*
13. Linden MG, Bender BG, Robinson A. *Intrauterine diagnosis of sex chromosome aneuploidy. Obstet Gynecol 1996; 87: 468-75.*
14. Chang HJ, Clark RD, Bachman H. *The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. Am J Hum Genet 1990; 46: 156-67.*
15. Park SY, Kim JW, Kim YM, Kim JM, Lee MH, Lee BY, Han JY, Kim MY, Yang JH, Ryu HM. *Frequencies of fetal chromosomal abnormalities at prenatal diagnosis; 10 yr experiences in a single institution. J Korean Med Sci 2001; 16: 290-3.*
16. Robinson A, Bender BG, Linden MG. *Prognosis of prenatally diagnosed children with sex chromosome aneuploidy. Am J Med Genet 1992; 44: 365-8.*
17. Marteau T, Drake H, Reid M, Feijoo M, Soares M, Nippert I, Nippert P, Bobrow M. *Counselling following diagnosis of fetal abnormality: a comparison between German, Portuguese and UK geneticists. Eur J Hum Genet 1994; 2: 96-102.*
18. Verp MS, Bombard AT, Simpson JL, Elias S. *Parental decision following prenatal diagnosis of fetal chromosome abnormality. Am J Med Genet 1988; 29: 613-22.*
19. Perrotin F, Guichet A, Marret H, Potin J, Body G, Lansac J. *Prenatal outcome of sex chromosome anomalies diagnosed during pregnancy: a retrospective study of 47 cases. J Gynecol Obstet Biol Reprod (Paris) 2000; 29: 668-76.*