The Karyotype Analysis of Sex Chromosome Mosaicism in Prenatal Diagnosis and Their Clinical Outcomes

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Research article

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Abstract

Objective To analyze the karyotype of sex chromosome mosaicism in our prenatal diagnosis of 14034 pregnant women in their second trimester, and report the rate of sex chromosome mosaicism and their clinical outcomes.

Methods A retrospective analysis of cytogenetic studies of 14043 cases of pregnant women from the Genetic Counseling Clinic from May 2017 to January 2020 by amniocentesis, were performed.

Results A total of 46 cases of sex chromosome mosaicism were found, and the sex chromosome mosaicism rate was 0.328%, mainly including four types of mosaicism: mos45,X/46,XX(12); mos45,X/46,XY (11); mos47XXX(or XXY or XYY)/46XX(or XY)(11); and other types of complex abnormal karyotype mosaic(12). Among the 46 fetuses with sex chromosome mosaicism, the indications of prenatal diagnosis includes the numerical abnormality of sex chromosome by NIPT(23/46)the high risk of trisomy 21 by serum screening(12/46)abnormal ultrasound(4/46), the advanced maternal age(age ≥ 35)(4/46), and the histories of abnormal pregnancy(3/46). According to the results of cytogenetic analysis and genetic counseling, the pregnant women would decide to continue or terminate their pregnancy.

Conclusion Prenatal cytogenetic diagnosis by amniocentesis is an accurate and convenient method and helps to avoid the delivery of fetuses with chromosomal diseases and reduce the risk of fetal malformation.

Introduction

It has been reported that sex chromosome mosaicism involving a numerical abnormality is the most common type of mosaicism¹. The phenomenon of chromosomal mosaicism often occurs in prenatal diagnosis, including autosomal and sex chromosomal mosaicism. Sex chromosome abnormality may cause fetal sexual organ hypoplasia, usually accompanied by other organ structure aberrant and dysfunction², or with mental retardation, mental and neurological disorders³. Therefore, it is very important to diagnosis fetus with chromosome aberrants.

Nowdays, it is a prevailing trend to perform prenatal screening and diagnosis, which could effectively reduce the born of children with abnormal chromosome. The karyotype analysis of amniotic fluid cells was the main strategy for detecting fetal chromosomal abnormalities, and was regard as the gold standard for cytogenetic diagnosis currently.

Here in our study, we retrospectively collect 14034 cases of pregnant women with specific prenatal diagnostic indications or of their own accord. Karyotype analysis of the amniotic fluid cells were performed. Of them, karyotype of 46 fetuses were sex chromosome mosaicism. Different proportions of mosaicism may have different effects on fetal prognosis, which makes increased difficulty in prenatal genetic counseling^{4,5}.

This study was approved by the Medical Ethics Committee in the First Affiliated Hospital of Zhengzhou University. All of the analysed samples were obtained with signed informed consent.

Materials And Methods

Subjects

Our study recruits 14034 pregnant women with the need of prenatal cytogenetic diagnosis who came to the clinic of the prenatal diagnosis center of the First Affiliated Hospital of Zhengzhou University between May 2017 and January 2020. Then amniotic fluid samples were successfully extracted and cultured, at last, all of the fetuses received karyotype diagnosis. All of the pregnant women performed amniocentesis with specific prenatal diagnostic indications or of their own accord. There are a variety of indications for genetic amniocentesis, including abnormal ultrasound finding, the numerical abnormality of sex chromosome by NIPT(Non-Invasive Prenatal Testing), the high risk of trisomy 21 by serum screening, abnormal ultrasound finding, the advanced maternal age(age ≥ 35), and the histories of abnormal pregnancy. The pregnant women were at 17–24 weeks' gestation undergoing amniocentesis to get amniotic fluid samples.

Methods

Amniotic fluid specimens (15 ml) was collected by amniocentesis under the guidance of ultrasonography, then centrifuged at 1500r/min for 8 minutes. After discarding the supernatant, the remaining liquid was mixed and incubated with two 5 ml of amniocyte culture medium (Gibco,USA, and Isreal). The cells grew in an incubator at 37 °C and 5% CO₂ for about 9 days. When cell colonies reached more than 15, these cells were collected followed by making sections and conventional Giemsa banding, then scanned by Zeiss Automated Nuclear Scanning System. For each sample, 5 mitotic figures were analyzed with 30 counts (abnormal karyotype with 100 counts). For these abnormal karyotypes, the second line cells were also managed as the first line.

Results

Out of the 14034 pregnant women recruited in our research, a total of 46 cases of sex chromosome mosaicism were found, and the sex chromosome mosaicism rate was 0.328%, mainly including four types of mosaicism: mos45,X/46,XX(12); mos45,X/46,XY (11); mos47XXX(or XXY or XYY)/46XX(or XY) (11); and other types of abnormal karyotype mosaic(12). The detailed information is in the Table 1.

Table 1
Karyotype analysis of 46 cases with sex chromosome mosaicism

No.	karyotype	indications	Follow-ups
1	45X[37]/46XX[63]	high risk of trisomy 21 by serum screening	abort
2	45X[26]/46XX[74]	the numerical abnormality of sex chromosome by NIPT	abort
3	45X[47]/46XX[53]	the numerical abnormality of sex chromosome by NIPT	abort
4	45X[63]/46XX[37]	high risk of trisomy 21 by serum screening	abort
5	45X[54]/46XX[46]	the numerical abnormality of sex chromosome by NIPT	abort
6	45X[56]/46XX[44]	age ≥ 35	abort
7	45X[83]/46XX[17]	the numerical abnormality of sex chromosome by NIPT	abort
8	45X[82]/46XX[18]	the numerical abnormality of sex chromosome by NIPT	abort
9	45X[49]/46XX[51]	age ≥ 35	abort
10	45X[5]/46XX[95]	the numerical abnormality of sex chromosome by NIPT	continue
11	45X[16]/46XX[84]	high risk of trisomy 21 by serum screening	lose contact
12	45X[61]/46XX[39]	the histories of abnormal pregnancy	abort
13	45X[24]/46XY[76]	the histories of abnormal pregnancy	continue
14	45X[4]/46XY[96]	high risk of trisomy 21 by serum screening	continue
15	45X[46]/46XY[54]	abnormal ultrasound	continue
16	45X[77]/46XY[23]	high risk of trisomy 21 by serum screening	abort
17	45X[54]/46XY[46]	the numerical abnormality of sex chromosome by NIPT	abort
18	45X[66]/46XY[34]	the numerical abnormality of sex chromosome by NIPT	lose contact
19	45X[17]/46XY[83]	the numerical abnormality of sex chromosome by NIPT	abort
20	45X[12]/46XY[88]	high risk of trisomy 21 by serum	continue

		screening	
21	45X[12]/46XY[88]	the numerical abnormality of sex chromosome by NIPT	continue
22	45X[14]/46XY[86]	the numerical abnormality of sex chromosome by NIPT	continue
23	45X[27]/46XY[73]	high risk of trisomy 21 by serum screening	continue
24	47XXX[7]/46XX[93]	age ≥ 35	continue
25	47XXX[83]/46XX[17]	age ≥ 35	abort
26	47XXX[23]/46XX[77]	the numerical abnormality of sex chromosome by NIPT	continue
27	47XXX[6]46XY[94]	the numerical abnormality of sex chromosome by NIPT	continue
28	47XXY[38]/46XY[62]	high risk of trisomy 21 by serum screening	abort
29	47XXY[6]/46XY[94]	the numerical abnormality of sex chromosome by NIPT	continue
30	47XXY[38]/46XY[62]	the histories of abnormal pregnancy	abort
31	47XXY[13]/46XY[87]	abnormal ultrasound	continue
32	47XYY[4]/46XX[96]	abnormal ultrasound	continue
33	47XYY[87]/46XX[13]	the numerical abnormality of sex chromosome by NIPT	abort
34	47XYY[18]/46XY[82]	high risk of trisomy 21 by serum screening	continue
35	45X[53]/47XXX[47]	the numerical abnormality of sex chromosome by NIPT	abort
36	45X[70]/47XYY[30]	the numerical abnormality of sex chromosome by NIPT	abort
37	46XX[8]/46XY[92]	high risk of trisomy 21 by serum screening	lose contact
38	46XY[95]/46XX[5]	abnormal ultrasound	continue
39	45X[80]/46Xi(X)(q10)[20]	the numerical abnormality of sex chromosome by NIPT	abort
40	45X[61]/46Xi(X)(q10)[39]	the numerical abnormality of sex chromosome by NIPT	abort
41	45Xinv(9)(p11q13)[33]/46XXinv(9)(p11q13)[67]	the numerical abnormality of sex chromosome by NIPT	abort

42	45X ^{inv} (9)(p11q13)[53]/46XY ^{inv} (9)(p11q13)[47]	the numerical abnormality of sex chromosome by NIPT	abort
43	47XXY ^{22pstk+} [22]/46XY ^{22pstk+} [78]	the numerical abnormality of sex chromosome by NIPT	abort
44	45X[18]/46XX ^t (3;7)(q21;q22)[5]/46XX[77]	the numerical abnormality of sex chromosome by NIPT	abort
45	47XXX[42]/48XXXX[2]/46XX[56]	high risk of trisomy 21 by serum screening	abort
46	45X[43]/46X ^{dic} (X;X)(q28;q28)[6]/46XX[51]	high risk of trisomy 21 by serum screening	abort

Among the 46 fetuses with sex chromosome mosaicism, the indications of prenatal diagnosis are different, 23 cases were the numerical abnormality of sex chromosome by NIPT(23/46), 12 pregnant women had the high risk of trisomy 21 by serum screening(12/46),the other indications like abnormal ultrasound(4/46), the advanced maternal age(age ≥ 35)(4/46), and the histories of abnormal pregnancy(3/46), are less than the former two indications. The detailed proportion is shown as Fig. 1 indicated obviously.

Follow ups

For all the 46 cases with mosaic sex chromosome karyotype, 27 pregnant women had the abortion, 16 pregnant women had a normal delivery, 3 cases lost contact. The overall rate of pregnancy termination is 58.7%.

Discussion

Chromosome abnormality are common genetics disorders causing spontaneous abortion, fetus aberration or birth defects^{6,7}. However, there are no effective methods to treat this kind of abnormal chromosome disorders. Nowadays with the rapid development of technology, amniocentesis and subsequent karyotype analysis is the gold standard for prenatal diagnosis, which is an important way to confirm and prevent aberrant pregnancies^{8,9}. Chromosome mosaicism would cause varying degrees of fetal abnormalities according to the mosaic proportion. Sex chromosome mosaicism will lead to hermaphroditism and psychiatric disorders¹⁰.

Early work indicated that sex chromosome mosaic is the most common type of mosaicism, which involved either a loss or gain of one sex chromosome, with the proportion of nearly a half of all kinds of mosaicism, including sex chromosome mosaicism, autosomal mosaicism and marker chromosome mosaicism¹. Out of the 14046 cases of fetal karyotype analysis, 46 fetus were found sex chromosome

mosaicism, the sex chromosome mosaicism proportion is 0.327%, which is a little lower than that of others' research in China reported in 2018¹¹.

For all these 46 cases, their prenatal diagnostic indications are different, a half of them were the numerical abnormality of sex chromosome by NIPT, which could increase the sex chromosome mosaicism proportion among general pregnant women, because of the high accuracy rate of NIPT. 26% of the 46 pregnant women were grouped into high-risk serum screening, other high risk indications are less than or only 8.7%. In lights with these findings, we would summarize that of the proportion of sex chromosome mosaicism is less than 0.327% of all the pregnant women in China. So when they had high risk in the numerical abnormality of sex chromosome by NIPT, they must perform the amniocentesis to get accurate cytogenetic diagnosis to exclude sex chromosome abnormality due to its definite pathogenicity.

Among these mosaic cases, 45,X(Turner Syndrome) is the most common chromosome abnormality. 31 out of 46 were 45, X mosaicism, which usually causes infertility, cardiac and kidney malformation, and ear and hearing problems¹². Sex chromosome trisomies mosaicism, including 47,XXY, 47,XXX, 47,XYY, that is an extra X or Y chromosome in karyotype, are less than 45,X mosaicism.

47,XXY(Klinefelter syndrome) usually leads to varying clinical manifestation, like infertility, small testes, and problems with psychological development, lower IQ, and delayed speech development¹³.

47,XXX(Triple X) girls are at high risks for difficulties in language, neuromotor and learning skills and behavior problems¹⁴. 47,XYY usually shows worldwide attention deficit hyperactivity disorder symptoms, comprised language development, psychotic disorder^{15, 16}. Among all these mosaicisms, only one fetus have 48,XXXX mosaicism karyotype. It was reported that girls with tetrasomy X had dysmorphic facial features, varying degrees of cognitive dysfunction, speech and language disorders and skeletal and connective tissue disorders¹⁷. There are sex chromosomal or autosomal structure abnormality for 6 cases, including inversion, translocation, isochromosome, dicentric X chromosome. One case is the short arm of chromosome 22 increased with the length of the body stalk (22sptk+), which is normal chromosome variation.

It has been indicated that Turner syndrome, Klinefelter syndrome, and 45,X mosaicism were main factors associated with parental decisions to terminate an affected pregnancy¹⁸. In our study, most pregnant women prenatal diagnosed 45,X/46,XX mosaicisms choose to abort their pregnancies, except one case with 45,X[5]/46,XX[95] karyotype, because of high proportion of normal karyotype. However, as regard to 45,X/46,XY karyotype,when the proportion of 46,XY was higher than 80%, almost all women choose to continue the pregnancy. This may be due to the traditional Chinese demand for boys. Especially for one pedigree the abnormal karyotype was 45,X/46,XX, and the mosaic proportion was 46% and 54%, respectively, the family urged to continue the pregnancy even the doctor advised them to abort.

If the karyotypes of the three sex chromosomes(47,XXX,47,XXY,47,XYY) are chimeric with the normal two sex chromosomes(46,XX,46,XY), pregnant women usually choose to induce labor,but when the proportion

of normal karyotypes are higher than 80%, pregnant women would continue the pregnancies. When the karyotypes of the chimeras are all abnormal karyotypes, that is, either the number or structure of sex chromosomes are abnormal or the structure of autosomes is abnormal, pregnant women would choose to induce labor. When there are three types of karyotypes in the chimera, pregnant women choose to induce labor. Three pedigrees lost contact, and we could not know their choices.

In lights with these findings, we would suggest the fetus with mosaic sex chromosome karyotype abort their pregnancies if the abnormal karyotype was higher than 80%.

However, there are many potential factors associated with parental decisions regarding abnormal sex chromosome pregnancy in our research, we just did a simple follow-up, more studies need to be explored.

Concluding, if the pregnant women have clear incidences of prenatal diagnosis, they had better to follow the doctors' advices to conduct prenatal cytogenetic diagnosis. Prenatal cytogenetic diagnosis by amniocentesis is an accurate and convenient method and helps to avoid the delivery of fetuses with chromosomal diseases and reduce the risk of fetal malformation.

Declarations

Ethics approval and consent to participate:

This study was approved by the Medical Ethics Committee in the First Affiliated Hospital of Zhengzhou University. All of the analysed samples were obtained with signed informed consent.

Consent for publication:

All of the analysed samples were obtained with signed informed consent.

Availability of data and material:

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

XK and SH conceived the study, SH and NL summarized all the data and involved in histological analysis, XK provided expertise for data interpretation and suggestions for manuscript preparation. SH wrote the manuscript.

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Figures

Figure 1

the proportion of different indications of prenatal diagnosis