Performance of non-invasive prenatal screening for sex chromosome aneuploidies and parental decision-making

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To the Editor: Sex chromosomal aneuploidies (SCAs) are common chromosomal aberrations that are normally diagnosed after birth. It results in abnormal physical development or infertility. The prenatal incidence is as high as 1/435 and is usually identified by karyotyping. SCAs are characterized by an abnormal number of sex chromosomes and include monosomy (45, X), trisomy (47, XXX, 47, XXY, and 47, XYY), other aneuploidies and various forms of sex chromosome mosaicism. The phenotypes of SCA patients are diverse. The prenatal diagnosis of fetal SCAs affects the parents and there is a need for clinical counseling. What’s more, early diagnosis is important as it provides opportunities for early treatment and future healthcare for children with SCAs.

With the development of molecular detection techniques, non-invasive prenatal testing (NIPT) has been widely used for detection of fetal T21, T18, and T13 aneuploidies due to its high accuracy and sensitivity. It has been recommended by the majority of obstetrics & gynecology professional associations. Hence, SCA screening has been made available and is compared to routine serological and ultrasound screening. However, there is controversy as to whether SCAs results should be reported. In this study, the diagnosis of SCA identified using NIPT in our diagnosis center was retrospectively analyzed together with the decisions of the parents in the hopes of providing reference for clinical consulting.

This study was approved by the Ethics Committee in our hospital. Written informed consent was obtained from the parents. NIPT was performed using the BGISEQ-500 (Wuhan MGI Tech Co., Ltd., Wuhan, China) following the manufacturer’s instructions. Data were processed using Excel 2016 and were analyzed using Chi-square statistics.

A total of 20,637 singleton pregnancies agreed to undergo NIPT between January 2017 to December 2017, of which, 20,601 cases had reportable results. Patients were divided into groups based on the following characteristics: advanced maternal age (5111, 24.81%), high risk of serological screening (1925, 7.42%), and intermediate-risk (2830, 13.74%), abnormal ultrasound findings (1734, 8.42%) such as a slight thickening of the nuchal translucency (NT) (<3.5 mm), echogenic intracardiac foci and additional characteristics. In addition, cases who underwent in-vitro fertilization (901, 4.37%), lack of routine prenatal screening (431, 2.09%), and those with none of the above indicators and voluntarily selected NIPT (7669, 37.27%) were included in the study.

Of the cases screened, 64 pregnant women (0.31%) had positive SCAs NIPT results, of which, 25 patients were positive for 45, X (39.06%, 25/64), 15 for 47, XXX (23.44%, 15/64), 16 for 47, XXY (25.00%, 16/64), and eight for 47, XYY (12.50%, 8/64). Genetic information was available for 44 cases (68.75%) who agreed to undergo invasive prenatal diagnosis (IPD) for fetal karyotyping, of which, 24 had consistent results with SCAs were observed (P < 0.05). The overall PPV for SCAs screening was 54.55% (24/44). Of these, four positive cases with monosomy X were validated, including one case with 45, X and 3 cases with mosaic 45, X/46, XN. The PPV for 45, X was 23.53% (4/17), while the PPV for 47, XXX, 47, XXY, and 47, XYY was 70.00%, 75.00%, 80.00%, respectively. The remaining 20 cases refused further...
underwent karyotyping with six cases confirmed to be true positives. The total PPV was 85.71% (6/7). The PPV for 45, X, 47, XXX, and 47, XXY was 100%, 100%, 100%, respectively. The overall PPV in the serological screened high-risk group was 75.00%. The PPV for 45, X, 47, XXX, and 47, XXY was 0%, 100%, 100%, respectively. For abnormal ultrasonographic findings, five cases had positive NIPT results and the PPV was 40.00% (2/5). The PPV for 45, X and 47, XXY was 25.00% and 100%. The overall PPV in the other groups was 50.00%. The PPV for 45, X, 47, XXX, 47, XXY, and 47, XYY was 20.00%, 57.14%, 83.33%, and 66.67%, respectively. The positive rate of SCAs in the serological screened intermediate-risk group was 0.

After genetic counseling, 24 out of the 64 positive SCAs cases were confirmed. Among them, seven cases selected to continue the pregnancy, 13 cases selected termination and four cases refused follow-up. Pregnant women with 45, X or 47, XXY babies were more likely to select termination (100% and 83.33%). Of the 20 cases who refused prenatal testing selected to continue their pregnancy. One case had a pregnancy loss, three cases refused follow-up and the remaining 16 cases had healthy babies without physical abnormalities based on prenatal ultrasound and postnatal clinical examinations for at least 1 year after birth.

In this study, the positive SCAs detection rate was 0.31% and the overall PPV of SCAs was 54.55%. This was similar to previous reports and was higher compared to common trisomies.15 NIPT has lower accuracy and a higher false-positive rate for sex chromosomal abnormalities compared to other common trisomies, particularly for monosomy X. If classified based on the different detection characteristics, advanced maternal age group and high-risk prenatal screening group had higher PPV (ie, 85.71% and 75.00%, respectively). The PPV for the no-high-risk group who selected NIPT voluntarily was 30.00%. However, no true positive results were observed for the serological intermediate-risk group. This indicates that prenatal screening of the low-risk population is also necessary and should not be ignored. NIPT for SCAs is more complicated compared to common autosomal aneuploidies. It can be confounded by a variety of maternal or fetal biological factors and by technical limitations.

The current clinical application for SCAs screening using NIPT is controversial in China. Patients with SCAs very rarely show severe phenotypes and their clinical manifestations vary widely. Fetuses with SCAs rarely have severe malformations or have high mortality during pregnancy (except for spontaneous abortion during the first trimester). Most patients do not show symptoms until adolescence during secondary development. The main clinical characteristics are mental disorders, short stature, infertility, sex development retardation or abnormalities. A few patients have various degrees of intellectual disabilities. Early diagnosis of SCAs and appropriate treatment could improve the patient’s height, cognition, and behavioral ability. This will help with the patient’s overall mental health and social adaptation. With regard to prenatal care, hospitals should offer prenatal screening and diagnosis to pregnant women. However, the PPV of NIPT screening for SCAs is lower compared to other common chromosomal aneuploidies.

With regard to medical ethics considerations, providing SCAs screening may cause fetal sex selection and excessive pregnancy terminations. Hence, some clinicians have suggested that SCA should not be reported for NIPT. At present, there are no clear prenatal screening programs for SCAs. In addition, clinical manifestations of SCAs vary significantly and this complicates genetic counseling.

The percent of patients with positive NIPT results for SCAs who were willing to undergo IPD was similar to the results published by Ronzoni et al (61%) and Kornman et al (65.5%), but was higher compared to Ramdaney et al (34%).16,44 However, the overall termination rate (65%, 13/20) for pregnancies with defined SCAs diagnosis in this study was higher compared to previous studies.5 Women were more likely to terminate their pregnancies if their fetal diagnosis was 45, X and 47, XXY (100% and 83.33%) compared to other types of SCAs. Parental decision-making may be influenced by several confounding factors, including the type and severity of the disease, culture, the local policy, parental education, anxiety, family support, financial support, consideration of life quality and reproductive ability. Genetic counseling may have a significant influence on the decision-making process.

The limitation of this retrospective cohort study was that the sensitivity, specificity, and negative predictive value were not calculated due to difficulties in screening newborns and pregnancies with false-positive outcomes using karyotype analysis. Most parents refused IPD and decided against having a postnatal confirmation.

These findings suggest that SCAs screening is necessary and highlights the critical need for professional pre- and post-test counseling by multidisciplinary teams. Women who undergo NIPT should fully understand the significance and limitations of this technique and determine whether SCAs should be performed. Medical geneticists have a crucial role to provide prenatal counseling for family decision-making and postnatal follow-ups.

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**Conflicts of interest**

None.
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