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Original Article

The role of ultrasound in women with a positive NIPT result for trisomy 18 and 13

Li Zhen ^a, Yu-Juan Li ^b, Yan-Dong Yang ^c, Dong-Zhi Li ^{a,*}^a Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center affiliated to Guangzhou Medical University, Guangzhou, Guangdong, China^b Department of Ultrasound, Dongguan Women and Children Healthcare Hospital, Dongguan, Guangdong, China^c Department of Ultrasound, The Sixth Affiliated Hospital of Sun Yat-san University, Guangzhou, Guangdong, China

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ABSTRACT

Objective: The aim of this study was to evaluate the usefulness of ultrasound in pregnancies with a positive non-invasive prenatal testing (NIPT) result for trisomy 18/13.**Materials and methods:** During a four-year period, the pregnant women who were referred for invasive genetic testing because of positive NIPT results for trisomy 18/13 were included in this study. An in-depth ultrasound was done for these patients before invasive procedures. The data of fetal ultrasound and cytogenetic results were collected.**Results:** There were 81 patients with a positive NIPT result for trisomy 18/13, including 39 (30 positive for trisomy 18; 9 positive for trisomy 13) within 12–14 weeks of gestation, and 42 (31 positive for trisomy 18; 11 positive for trisomy 13) within 15–22 weeks. The PPV of NIPT was 60.7% for trisomy 18, and 30% for trisomy 13, respectively. When adding ultrasound to NIPT, the new PPV for trisomy 18 was 100%, and the negative predictive value (NPV) was 92.3%, with a NPV of 85.7% in the first trimester and a NPV of 100% in the second trimester, respectively. The new PPV and NPV for trisomy 13 were 100% and 100%, respectively.**Conclusion:** By adding ultrasound to the NIPT, we achieved much higher PPVs and NPVs for trisomy 18/13. A normal scan can help to alleviate stress in parents caused by false positive NIPT results.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The main purpose of prenatal screening programs is to identify fetuses with common trisomies since they are the most frequent aneuploidies in newborns. Non-invasive prenatal testing (NIPT) using cell-free fetal DNA in maternal plasma is a method of testing for the three common fetal trisomies. It is currently available across countries around the world. NIPT is capable of identifying nearly all trisomy 21/18/13 pregnancies with very low false-positive rates [1]. However, the positive predictive values (PPVs) of NIPT for trisomy 18/13 are lower than that for trisomy 21 because of their much lower prevalence. For example, the PPVs for trisomy 13, 18, and 21 are 45%, 76%, and 84%, respectively, from data of a large referral genetic diagnostic laboratory [2]. Thus, it is not surprising that a positive NIPT result should be always confirmed with invasive diagnostic testing. On the other hand, although most of fetuses

affected with trisomy 21 may lack major congenital abnormalities, almost all pregnancies affected by trisomy 18/13 have demonstrated anomalies via ultrasound [3,4]. In this study, we report the usefulness of ultrasound in pregnancies with positive NIPT results for trisomy 18/13.

Methods

From January 2015 to June 2018, there were 81 pregnant women referred to three referral centers for invasive testing due to indications of a positive NIPT result for trisomy 18/13. A detailed sonographic examination was conducted in all these pregnancies before invasive procedures. Performance of a comprehensive review of fetal anatomy was completed by specially trained physicians according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines. Sonographic images were captured using Voluson E8, 730 Expert or 730 Pro units (GE Healthcare, Waukesha, WI, USA). Ultrasound examinations were considered positive if a congenital anomaly were detected. Major malformations were defined as fetal structural anomalies that

* Corresponding author. Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, 510623, China.

E-mail address: drliidongzhi2014@sina.com (D.-Z. Li).

would either require surgery after birth or cause major morbidity and/or mortality. A fetal biometric evaluation was done, and if biometric values were <10th percentile for that period of gestation, it was considered abnormal and the fetus was predicted to have intrauterine growth restriction (IUGR). Approval for the study was obtained from the ethics committee of Guangzhou Women and Children's Medical Center.

Results

During the study period, 61 pregnancies with positive NIPT results for trisomy 18 and 20 pregnancies with positive NIPT results for trisomy 13 were referred to our centers for invasive genetic testing. Among the 81 cases, 39 (30 positive for trisomy 18; 9 positive for trisomy 13) were within 12–14 weeks of gestation, and 42 (31 positive for trisomy 18; 11 positive for trisomy 13) were within 15–22 weeks. All of the pregnant women had a normal nuchal translucency (NT) measurement during 11–13 weeks, and they opted for NIPT because of either a positive serum screening result or advanced maternal age. Invasive testing was offered to these high risk women, with CVS performed in 39 cases and amniocentesis performed in 42 cases. An in-depth ultrasound was carried out in all cases before invasive procedures.

The results of sonographic examinations and karyotyping are showed in Table 1 and Fig. 1. Of the cases within 12–14 weeks, 18 out of 30 cases positive for trisomy 18 were confirmed by karyotyping, and fetal anomalies were found in 16 out of these 18 affected fetuses. The remaining 12 cases had a normal karyotype and a normal scan. Three out of 9 cases positive for trisomy 13 were confirmed by karyotyping, and were found to have fetal anomalies; the remaining 6 cases had a normal karyotype and a normal scan. Of the cases within 15–22 weeks, 19 out of 31 cases positive for trisomy 18 were confirmed by karyotyping and were found to have fetal anomalies; the remaining 12 cases had a normal karyotype and a normal scan. Three out of 11 cases positive for trisomy 13 were confirmed by karyotyping and were found to have fetal anomalies; the remaining 8 cases had a normal karyotype and a normal scan. The PPV of NIPT was 60.7% for trisomy 18, and 30% for trisomy 13, respectively. For women with a positive NIPT result, the total sensitivity and specificity of ultrasound were 94.6% and 100% for trisomy 18, and 100% and 100% for trisomy 13, respectively. Therefore, when adding ultrasound to NIPT, the new PPV for trisomy 18 was 100%, and the negative predictive value (NPV) was 92.3%, with 85.7% in the first trimester and 100% in the second trimester, respectively. The new PPV and NPV for trisomy 13 were 100% and 100%, respectively.

Table 1
Abnormal ultrasound findings noted in 43 fetuses with trisomy 18/13.

| Abnormalities | n (%) |
|----------------------|-----------|
| Trisomy 18 (n = 37) | |
| Cardiac anomalies | 29 (78.4) |
| Limb anomalies | 30 (81.1) |
| CNS anomalies | 15 (40.5) |
| Facial clefts | 7 (18.9) |
| Omphalocele | 3 (8.1%) |
| Choroid plexus cysts | 15 (40.5) |
| IUGR | 9 (24.3) |
| Trisomy 13 (n = 6) | |
| Cardiac anomalies | 6 (100) |
| Limb anomalies | 6 (100) |
| CNS anomalies | 4 (66.7) |
| Facial clefts | 5 (83.3) |
| Echogenic kidneys | 2 (30) |
| IUGR | 3 (50) |

Discussion

Trisomy 18 and 13 are the second and third common autosomal aneuploidies with a prevalence of 1/3500–8000 births and 1/5000–20,000 births, respectively. The targeted chromosomal abnormalities of NIPT include these two aneuploidies, but with lower PPVs for trisomy 18/13 than that for trisomy 21. For example, even in high-risk populations with the relatively high prevalences of trisomy 21 (1:185), 18 (1:470) and 13 (1:1500), a NIPT test with 99.9% specificity (false-positive rate of 0.1%) would yield PPVs of 90% for trisomy 21, 67% for trisomy 18, and 53% for trisomy 13 [5]. In this study, we only obtained a PPV of 60.7% for trisomy 18 and of 30% for trisomy 13 respectively. PPV is dependent not only on the sensitivity and specificity of the test, but it is highly dependent on the prevalence of the condition. Currently in mainland China, a NT scan prior to NIPT testing is mandatory, and if there is a major anomaly or increased NT, invasive diagnostic testing instead of NIPT was the next step. Therefore, most of fetuses with trisomy 18/13 would have been identified by the first-trimester ultrasound. The remaining population with a low a priori risk would yield decreased PPVs for trisomy 18/13.

The finding of low PPVs for trisomy 18/13 has important implications for counseling after NIPT testing. Since ultrasound plays a major role in the detection of trisomy 18/13, we had performed detailed sonographic scans in women with a positive NIPT result before invasive procedures. As expected, we successfully distinguished 94.6% (35/37) of true affected cases from false positive cases in those with a positive NIPT for trisomy 18, and distinguished 100% of true affected cases in those with a positive NIPT for trisomy 13. Only two cases of trisomy 18 were missed by first-trimester ultrasound. Although these cases had undergone a NT scan in early pregnancy, and the first-trimester scan is fast becoming a pillar in obstetric care [6,7], an in-depth first-trimester examination protocol is not currently practiced at most centers which provide first-trimester screening in mainland China. The detailed first-trimester examinations involve supplementary resources: additional examination time, specialized personnel for the abnormal suspected/detected cases and high-resolution machines. Therefore, in real clinical practice, we only perform an in-depth anatomy scan during the first trimester in selective cases, such as those with an increased NT, an extremely higher risk for trisomies, or any unexpected findings. As evidenced by this study, most of the trisomy 18 fetuses and all of the trisomy 13 fetuses were detected by ultrasound at first trimester. The contribution of prenatal sonographic findings to the detection of trisomy 18/13 increases significantly with the fetal growth. In this study, all of the affected fetuses were identified by our second-trimester anatomic scans. Fetuses with complex heart defects, limb defects, brain anomalies, gastrointestinal anomalies, midline facial defects, abdominal wall defects and others (such as IUGR) are strongly suggestive of trisomy 18 and 13 [8,9]. Our results indicate that the prenatal identification of sonographic markers poses the fetus a high risk of aneuploidy, and a negative finding would be indicative of a high possibility of normal fetuses.

Performing an ultrasound scan among women already screen positive for trisomy 18/13 is routine in many referral centers. The stated aim of the scan is to 'refining the assigned risk'. In modern prenatal care practice with continuing improvements in sonographic imaging, normal sonographic findings in experienced hands essentially rule out the presence of trisomy 18/13. However, there are different conditions such as maternal obesity and fibroids casting shadow which may limit such evaluation in some cases. Additionally, a first-trimester detailed scan is still challenging for some centers. Also mosaic trisomy 18/13 fetuses, occasionally, may present with no abnormal sonographic features [10,11]. Therefore,

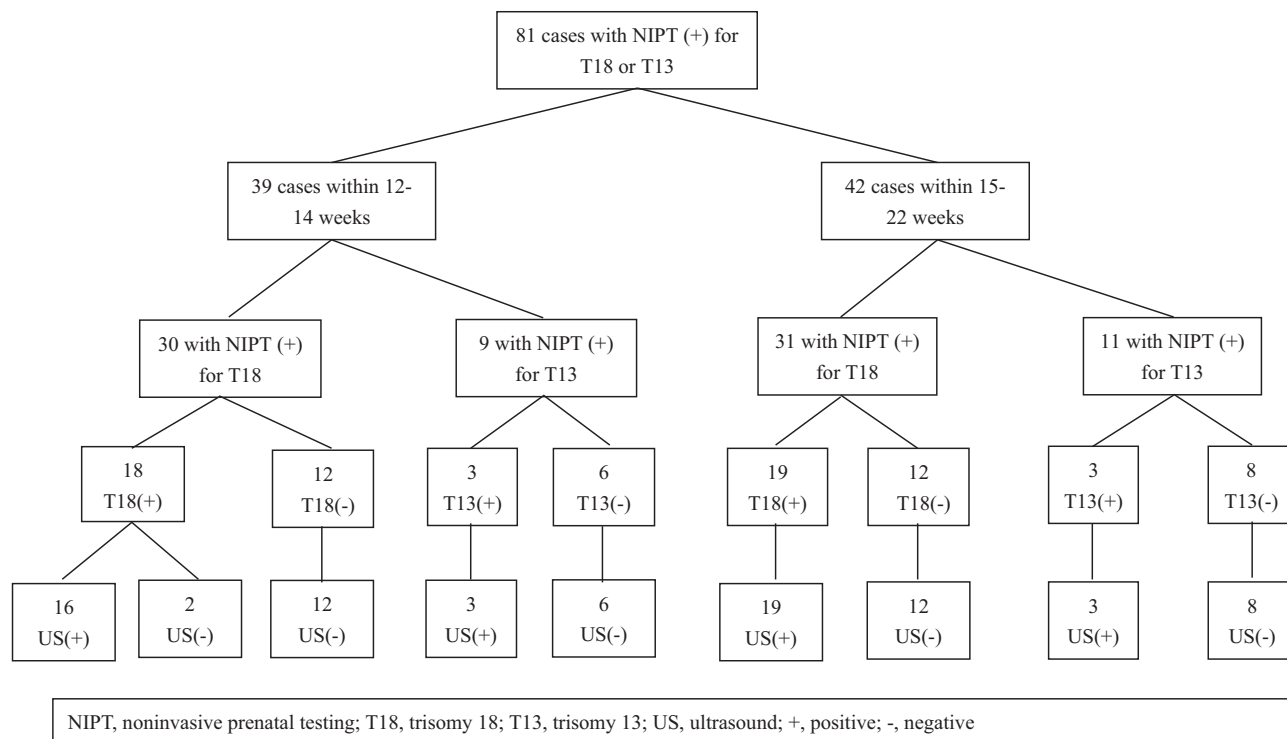


Fig. 1. Flowchart of cytogenetic and sonographic findings from 81 pregnancies with positive NIPT results for trisomy 18/13.

we currently still recommend invasive testing for those with no remarkable findings, but provide significant reassurance to them. For those who are reluctant to undertake a diagnostic procedure after a normal scan, follow-up scans are offered with a thorough counseling.

In conclusion, we first present the sonographic and cytogenetic results of positive NIPT for trisomy 18/13 in a selected population. We found much lower PPVs of NIPT for these two aneuploidies in our patients. However, by adding ultrasound to the NIPT, we achieved much higher PPVs and NPVs for trisomy 18/13. Based on our preliminary results, ultrasound may be useful in NIPT post-test counseling. We emphasize that the sonographic examination should be done by maternal-fetal medicine specialists in tertiary centers, and the scans should focus not only on a careful anatomic survey but also on fetal biometric measurements. Early IUGR is common in affected fetuses at mid-trimester gestation or even in the first trimester [12]. As NIPT testing becomes more widely used in clinical practice, clinicians should ensure with current updated data that women in a low-risk population are more likely to be unaffected even with positive NIPT results for trisomy 18/13. We hope that a normal scan can help to alleviate stress in parents caused by false positive NIPT results.

Conflicts of interest statement and funding/support statement

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