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Original Article

Trisomy 21 screening based on first and second trimester in a Taiwanese population

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ABSTRACT

Objective: This study investigates the performance of first- and second-trimester screening tests for detecting fetal trisomy 21 in a Taiwanese population.
Materials and methods: This multicenter study 29,137 cases enrolled the chromosomal abnormality screening between 2013 and 2014 two years period from Taipei city. There were 23,990 was done the first trimester screening using a combination of fetal nuchal translucency, maternal serum β-human chorionic gonadotropin, and pregnancy-associated plasma protein-A between 11^{+0} and 13^{+6} weeks of gestation age. Second-trimester screening was done for 5149 cases using a double test (β-human chorionic gonadotropin and serum alpha fetoprotein) between 15 and 20 weeks of gestation. The cut-off risk for both is 1:270 or higher.
Results: This multicenter study 29,137 cases that completed first- and second-trimester screening, and the outcome was available in 28,726 cases. The mean maternal age of the screen-positive group was 34.6 ± 4.2 years. The first-trimester had 891 cases screening positive with a detection rate of 97.5% for fetal trisomy 21, and false positive rate of 3.5%. In the second-trimester had 334 cases screening positive, the detection rate and false positive rate were 33.3% and 6.4% for trisomy 21, respectively.
Conclusion: The first-trimester screening had higher performance with a lower false positive rate than the second-trimester screening. First-trimester screening could reduce the rate of unnecessary invasive testing for all pregnant women.

Introduction

Trisomy 21 is the most common prenatal chromosomal abnormality, with prevalence of about 1/600–800 pregnancies [1]. This genetic disorder is caused by the presence of a complete or partial third copy of chromosome 21. The incidence of trisomy 21 increases with maternal age. Infants with trisomy 21 could have multiple defects, including mental retardation, congenital heart disease, and facial defects. Hence, prenatal screening and diagnosis of trisomy 21 for a fetus are an important issue for pregnant women aged 35 years or older.

At 11^{+0} to 13^{+6} gestational weeks, first-trimester screening using ultrasound is done to scan the fetal neck for enlarged nuchal translucency (NT). Increased NT is associated with not only trisomy 21 but also other chromosomal abnormalities [2–7]. First-trimester aneuploidy screening considers a combination of maternal age, NT, and maternal serum (i.e., pregnancy associated plasma protein A (PAPP-A) and free β-human chorionic gonadotropin (free β-hCG)). This method can identify about 90% of fetuses with Down

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syndrome with a false positive rate of 5% [8–10]. The second trimester maternal serum double test considers a combination maternal age and maternal serum markers such as β-hCG and serum alpha fetoprotein (AFP), and it has an estimated detection rate of 56% for fetal trisomy 21 with a false positive rate of 5% [11,12].

Chorionic villus sampling (CVS) or amniocentesis is the most accurate method for prenatal diagnosis of fetal trisomy 21 and other chromosomal abnormalities. However, it may result in miscarriage at a rate of 1–3% [13,14], which leads to psychological stress, especially for older pregnant women. Therefore, the American College of Obstetricians and Gynecologists (ACOG) recommends that all pregnant women be screened first to determine the individual risk. Women who have high risk can further receive genetic counseling or invasive tests [15,16]. In this study, we compared the performance of screening for fetal trisomy 21 and other chromosomal abnormalities using first- and second-trimester screening in an unselected pregnant population in Taipei.

Methods

This multicenter study was done in Taipei to screen for trisomy 21 using first- and second-trimester screening between 2013 and 2014. The first-trimester combined screening test examined a combination of fetal NT, maternal age, and maternal serum markers (free β-hCG and PAPP-A) at 11 + 0 to 13 + 6 weeks of gestation age. For fetal NT measurements, fetal crown-rump length should be 45–84 mm, and a true sagittal view was obtained. The fetus posture was a neutral position that is not hyperextended or hyperflexion, and the fetal head, neck, and upper chest should be obtained. The fetal NT thickness was measured from the inner to inner borders of the two echogenic lines at the widest part of the NT [17,18]. All sonographers were certified by The Fetal Medicine Foundation (FMF) or the Taiwan Maternal Fetal Medicine Society (TMFMS). The Institutional Review Board of the institution approved this study.

After the fetal dating was determined, first-trimester serum markers of PAPP-A and free β-hCG were measured at 9 to 13^{+6} weeks of gestation at an outpatient clinic. Maternal blood serum was isolated for analysis at less than 20 °C within 24 h after collection using a Kryptor analyzer (Brahms Diagnostics GmbH, Berlin, and Germany). The laboratory that performed the testing is a part of the quality control program of the United Kingdom National External Quality Assessment Service. Maternal age, weight, height, method used for conception, and smoking status were recorded at the time of blood sampling. The ultrasound measurements and biochemical results were recorded, and the risk for trisomy 21 was calculated using the FMF or the first trimester screening of TMFMS algorithm [19].

The second-trimester serum test was done using maternal serum markers including β-hCG and AFP. The test was carried out between 15 and 20 weeks of pregnancy. The risk of trisomy 21 was calculated using a combination of maternal age and maternal serum markers. A risk above 1:270 was considered screen-positive, and an invasive test such as CVS or amniocentesis was offered. Karyotypes and outcomes of the pregnancy were added to the database. Statistical analysis was done using Microsoft Excel (2007) and SPSS v. 19.0. Both of the detection rate and the false-positive rate were calculated.

Results

The characteristics of the high-risk population of the first- and second-trimester screening test shows in Table 1. In the screen-positive group, there were mostly singleton and spontaneous conceptions. The mean times of performing the screening test in the first- and second-trimester screening tests were 12 ± 0.7 and 16 ± 1.08 weeks of gestation age. The mean maternal age of the screen-positive group was 34.6 ± 4.16 years, and 48.1% of the study sample had advanced maternal age (35 years or older).

Table 1
Characteristics of the screen-positive population.

	Value (n (%))			
	First-trimester screening		Second-trimester test	
Number of fetuses				
Singleton	871 (97.8)		331 (99.1)	
Twins	20 (2.2)		3 (0.9)	
Method of conception				
Spontaneous conception	853 (95.7)		324 (97.0)	
Ovulation induction drugs	11 (1.2)		6 (1.8)	
In vitro fertilization	27 (3.0)		4 (1.2)	
Maternal age				
≥35 years	462 (51.9)		136 (40.7)	
<35 years	429 (48.1)		198 (59.3)	
Gestation age				
	11 weeks	194 (21.8)	15 weeks	115 (34.4)
	12 weeks	460 (51.6)	16 weeks	151 (45.2)
	13 weeks	237 (26.6)	17 weeks	43 (12.9)
			18 weeks	11 (3.3)
			19 weeks	8 (2.4)
			20 weeks	6 (1.8)
Total	891 (100)		334 (100)	

Among the first trimester screening group, 778 pregnant women (87.3%, 778/891) were screen-positive and underwent an invasive diagnosis, of which 93.8% (730/778) underwent amniocentesis and 6.2% (48/778) underwent CVS. Maternal age distribution of the screen-positive group in two screening group and general population of Taipei shows in Fig. 1. There were 92 women (10.3%, 92/891) accepted non-invasive prenatal testing (NIPT) as a second option. Of the 21 screen-positive cases that did not accept advanced diagnosis, three spontaneous abortions occurred before the diagnostic test (14.3%, 3/21). In the second-trimester screening group, 89.8% screen-positive pregnant women underwent amniocentesis to confirm the fetal karyotype, and 5.7% screen-positive pregnant women accepted NIPT as a second option. There were 17 pregnant women who did not receive any invasive diagnosis, and one of them had a spontaneous miscarriage before amniocentesis.

Screening was carried out in 29,137 cases (23,990 first trimester and 5147 s trimester). Outcomes were obtained in 28,726 cases

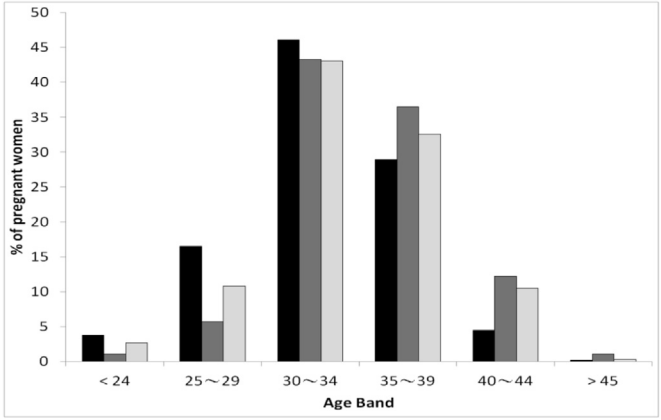

Fig. 1. Maternal age distribution of the screen-positive group in first-trimester screening group (□), second-trimester screening group (▒), and general population of Taipei (■).

(98.6%). In first-trimester screening, 891 pregnant women had a risk above 1:270, while 334 women had such risk in second-trimester screening. The screen-positive rates (SPRs) were 3.5% and 6.4%, respectively. There were 43 trisomy 21 cases among all pregnancies, including 40 from the screen-positive group and three from the screen-negative group. The detection rate in the first-trimester combined test and second-trimester serum test were 97.5% and 33.3%, and the false-positive rates were 3.5% and 6.4%, respectively. In addition, there were 23 other chromosomal abnormalities in the first-trimester screen-positive group, including trisomy 18, trisomy 13, monosomy X and others in 8, 3, 5 and 8 cases respectively. In the second-trimester group, there were two cases of trisomy 21 and one case of trisomy 18. The overall outcome of the screen-positive cases shows in Fig. 2.

Of the 1161 cases that were screen-positive and had normal chromosomal karyotype, 13 cases were spontaneous miscarriages. There were 11 cases of terminated pregnancy with fetal structure malformation, including central neural system defect, congenital heart disease, and renal disease. There were 1137 false positives and normal live births with normal chromosome karyotype.

The detection rate and false positive rate for different cut-offs of trisomy 21 according to first- and second-trimester screening shows in Table 2. Using a risk cut-off of 1:100, the detection rates were 90% and 33.3% with false positive rates of 1.4% and 2.4% in first- and second-trimester screening, respectively. However, under a risk cut-off of 1:270, the detection rates were 97.5% and 33.3% with false positive rates of 3.5% and 6.4%, respectively. The overall detection rates for all chromosomal abnormalities in first- and second-trimester screening tests were 98.4% and 50% with false-positive rates of 3.5% and 6.6%, respectively.

Discussion

Our results showed detection rates of 100% and 33.3% with false-positive rates of 3.5% and 6.4% for first- and second-trimester screening for fetal trisomy 21 in an unselected population, respectively. Our detection rate for trisomy 21 in first-trimester screening is higher than in previous studies [20–23]. However, the false-positive rate is similar to other studies [22,24,25]. In the first-trimester screening, our study has shown a prevalence of 16.85/10,000 for trisomy 21. However, a previous study suggested that approximately 30% of cases of trisomy 21 will be spontaneously lost before 16 weeks. Hence, the adjusted prevalence of live-born fetuses with trisomy 21 in the studied population would be 11.80/10,000 (1/847), which is similar to previous reports [26–28].

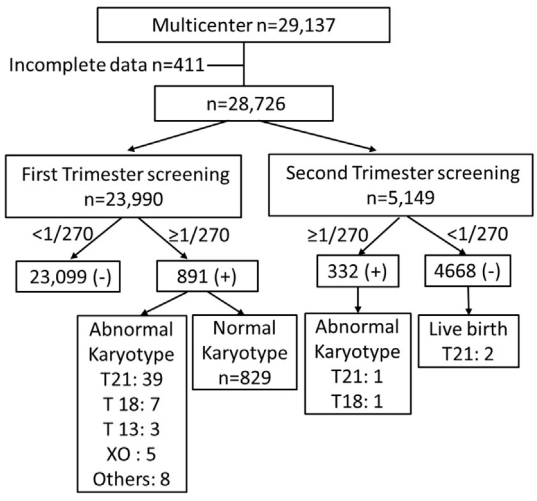

Fig. 2. Flow chart showing the overall outcome of all screening cases.

Table 2
Detection rate and false positive rate of trisomy 21 for given risk cut-offs.

Risk cut-off	First-trimester screening		Second-trimester screening	
	DR (%)	FPR (%)	DR (%)	FPR (%)
1:50	80	0.8	33.3	1.0
1:100	90	1.4	33.3	2.4
1:270	97.5	3.5	33.3	6.4

In the first-trimester NT scan, we believe that the high detection rate and low false-positive rate of the screening are mainly based on the well-trained and experienced sonographers, who obey standard imaging methods proposed by the Fetal Medicine Foundation [18,29]. Therefore, high-standard quality control of fetal NT measurements may play an important role in reducing the variation of risk assessment for fetal chromosome.

According to previous studies, in addition to ultrasound markers of fetuses, examining fetal nasal bone, tricuspid flow and ductus venosus flow in the first-trimester combined screening can improve the detection rate up to 100% [19,30,31,32]. This shows that ultrasound plays an important role in prenatal screening. Furthermore, we could expect a better detection rate if we add one or two additional ultrasound makers.

Another prenatal screening method for fetal chromosomal abnormalities is using maternal age and a combination of serum markers in the second trimester. Our detection rate for trisomy 21 in the second-trimester double test was 33.3%, which is lower than the detection rate of 61% shown in a Caucasian population, with a false positive rate of 5% [33]. A Chinese population had a detection rate of 56% and false-positive rate of 4.9% [11]. The bias may cause of small screening amount. However, the false-positive rate is similar to other studies. Furthermore, taking a blood test from the mother in the second trimester is easier than first-trimester screening, but the higher false-positive rate in second-trimester screening could lead to unnecessary invasive tests.

The advantages of earlier diagnosis is that we can decrease the physiological and the psychological stress of pregnant women and their families [34]. Besides, fetal ultrasound examination is included in first-trimester screening, and many major anatomical abnormalities of the fetus can be found during scanning [8]. First-trimester screening can also afford patients more time to make decisions about their pregnancy. Moreover, we believe that most pregnant women desire to know the result of as soon as possible in their pregnancy period.

Among the screen-positive pregnant women, 87.3% and 89.7% underwent an invasive test in the first- and second-trimester screening, respectively. This is different from other studies, which reported rates of 62% in Caucasian women and 98% in Hong Kong [35,36]. Our invasive test rate is lower than these two previous Chinese studies. A potential explanation for this could be that in our study had, 9.06% (111/1225) of women overall underwent NIPT as an option to an invasive test.

In this study, the false-positive rate for major chromosomal abnormality in the first-trimester screening was 3.5%. This shows that we can reduce the need for unnecessary invasive tests for younger pregnant women and pregnant women aged 35 years or older. This is important for all pregnant women, but especially for pregnant women with advanced age. In addition, first-trimester screening has a lower false-positive rate than second-trimester screening. It is notable that when the first-trimester screening used a cut-off value of 1:100, 90% (34/40) of trisomy 21 cases were detected with a false positive rate of 1.4%. This means a

lower false-positive rate with an acceptable detection rate can be implemented.

In conclusion, first-trimester screening for fetal trisomy 21 has a higher detection rate but also a lower false-positive rate, which can reduce the amount of unnecessary invasive diagnostic tests performed, which are associated with collateral damage to the fetuses. In addition, results can be obtained as early as possible and let pregnant women know if the fetus is healthy. For these reasons, the first-trimester combined screening test is the better option for all pregnant women.

Conflict of interest

There are no conflict of interest for this article.

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