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Original Research

IMPACT OF NON - INVASIVE PRENATAL TESTING ON PRENATAL DIAGNOSIS AT DA NANG HOSPITAL FOR WOMEN AND CHILDREN

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ABSTRACT

Background: *Non-invasive prenatal testing (NIPT) is being applied more widely in Vietnam. However, the effects of NIPT on prenatal diagnosis have not been studied much in our country. This study aims to analyze the impact of NIPT on the changes in the number of routine screening tests for chromosomal abnormalities 21, 18, and 13 and the impact of NIPT on invasive prenatal diagnostic procedures and propose strategies to screen for fetal aneuploidy.*

Results: *NIPT did not change the number of routine screening tests for chromosomal abnormalities 21, 18, and 13. The rate of amniocentesis used to confirm the diagnosis of aneuploidy was decreased by 6,32 (p < 0,0001, 95% CI: 3,99 – 10,45). Among the strategies to detect aneuploidy 21, 18, and 13 suitable for socio-economic conditions in Vietnam, a 2-step screening method can be applied.*

Conclusions: *NIPT did not change the number of routine screening tests. NIPT reduced the number of invasive prenatal procedures. The screening strategy for fetal aneuploidy should follow a two-step approach.*

Keywords: *NIPT, double test, triple test*

I. INTRODUCTION

Prenatal screening for trisomies 21, 18, and 13 is regularly advised and indicated for pregnancies in countries with developed health systems. The most common method is to perform the Combined or Triple test if the pregnant woman has not been screened in the first trimester [1]. Conventional screening methods have significant limitations, leading to the omission of common fetal aneuploidies and an increase in invasive prenatal procedures. Tests that screen for chromosome abnormalities 21, 18, and 13 show variable values with a sensitivity ranging from 70% to 90%, with a false positive rate of 5% [2].

Currently, noninvasive prenatal testing (NIPT), which provides high sensitivity and specificity, has become a more popular screening tool. Recent studies have also provided clinical evidence to reinforce the indications of NIPT for pregnant women [3]. At the same time, many reputable medical associations have published guidelines for using NIPT as a first-line test for all pregnancies at risk [1, 2]. Technology-based assessments done by the healthcare sector and government agencies have shown that NIPT has a sensitivity and specificity significantly superior to conventional screening methods. Therefore, screening with NIPT for the entire pregnancy will generally provide more accurate detection of high-risk pregnancies with trisomies than conventional tests. Some countries have offered NIPT as a first-line tool to screen for trisomies (chromosomal abnormalities) 21,18, and 13 [4]. Vietnam is a developing country with resource constraints, which remain a significant barrier to assigning screening tests to all pregnancies. However, thanks to technological development, people's access to information through health staff or the internet has become widespread and very up-to-date. Pregnant women can now pay for many tests not covered by health insurance, including the

NIPT. It has led to a change in the approach and treatment of obstetricians, especially in prenatal diagnosis.

Invasive prenatal diagnosis has been performed at Da Nang Hospital for Women and Children (DHWC) since September 2016, and NIPT has been offered there since September 2019. Therefore, assessing the impacts of NIPT on prenatal diagnosis is a matter of importance. We carry out this project with the aims to: (1) analyze the impact of NIPT on the change in the number of routine screening tests for chromosomal abnormalities 21, 18, and 13 and (2) analyze the impact of NIPT on the prenatal invasive diagnostic procedures and propose a strategy to screen for fetal aneuploidy.

II. MATERIALS AND METHODS

2.1. Study population

The study was conducted on 5678 pregnant women who came for prenatal care and delivery at Da Nang Hospital for Women and Children from September (DHWC) 2018 to August 2020.

Patient selection criteria:

During the period from September 2018 to August 2019 (NIPT had not been offered at the hospital): (1) Pregnant women performed routine screening tests (Combined test, Triple test) at DHWC. (2) Pregnant women who omitted diagnostic testing by amniocentesis during routine screening had a high risk of fetal aneuploidy. (3) Pregnant women who underwent diagnostic testing by amniocentesis during routine screening had a high risk of fetal aneuploidy.

During the period from August 2019 to August 2020 (NIPT test has been implemented at the hospital): (1) Pregnant women performed routine screening tests (Combined test, Triple test) or NIPT at DHWC. (2) Pregnant women who skipped further testing (NIPT screening and/or definitive diagnosis by amniocentesis) during routine screening had a high risk of fetal aneuploidy. (3) Pregnant women who underwent follow-up testing (NIPT and/or amniocentesis) during routine screening had a high risk of fetal aneuploidy. (4) Pregnant women who had a diagnostic test by amniocentesis when the NIPT result is positive. (5) Pregnant women who did not have amniocentesis when the NIPT was positive.

Exclusion criteria: (1) No routine screening test (Combined test, Triple test) or NIPT. (2) There are no data on pregnancy outcomes (specifically, a fetus with chromosomal abnormalities 21, 18, 13 through assessment of the child's external morphological features) for the period from September 2019 to August 2020.

2.2 Research methods

The study was designed as a cross-sectional descriptive retrospective (September 2018 to August 2019) and a descriptive, longitudinal prospective follow-up (September 2019 to August 2020).

Sampling method: Select a convenience sample that meets the criteria of each research group.

Study period: Patient records were collected from DHWC's archival data system from September 2018 to August 2019. New cases that came to the hospital from September 2019 to August 2020 were collected through the examination process.

2.3. Statiscal Analysis

We analyzed the data on Medcalc 16.0 software with the following algorithms: percentage, statistical estimation, hypothesis testing with statistical significance with $P < 0.05$. The Chi-square test is used when the expected frequency in each cell is above 5. If the expected frequency of each cell does not exceed 2, Fisher's exact test is applied. Finally, if the above two conditions are not met, the Yate correction test is used.

To analyze sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and positive predictive value, we enter the data into a 2 x 2 table in Medcalc 16.0 software so that the computer performs the calculation automatically and gives the final result.

2.4. Ethics in research

The research protocol was approved by the Ethics Committee in Biomedical Research of the DHWC and was subsequently submitted to the Appraisal Council of the Da Nang Department of Health.

III. RESULTS

Table 1: Characteristics of the number of cases of screening for the risk of aneuploidy of chromosomes 21, 18, and 13 by routine testing

Period	9/2018 - 8/2019		9/2019 - 8/2020		P
	N	%	N	%	
Total screening	2660	100	3018	100	

Period	9/2018 - 8/2019		9/2019 - 8/2020		P
	N	%	N	%	
Combined test low risk	2169	81,5	2427	80,4	0,29
Combined test high	135	5,1	161	5,3	0,73
Triple test low risk	286	10,8	361	12,0	0,15
Triple test high risk	70	2,6	69	2,3	0,85

The difference in the number and rate of screening tests for fetal aneuploidy was not statistically significant between the 2 study periods, with p > 0.05.

Table 2: Characteristics of routine aneuploidy screening group with high - risk results.

Period	Total screening (cases)	High risk of aneuploidy 21, 18, 13		
		Number (cases)	%	Age maternal (years)
9/2018 - 8/2019	2660	205	7,8	32,3 ± 6,3
9/2019 - 8/2020	3018	230	7,6	31,9 ± 5,8
P		0,46		0,49

The difference in gestational age between the two periods was not statistically significant for the group of fetuses at high risk of aneuploidy, with p = 0.49.

Table 3: Characteristics of using the following test when screening results reveal a high risk of aneuploidy 21, 18, 13

Period		9/2018 - 8/2019	9/2019 - 8/2020	p	Rate ratio	95% CI
Number of pregnancies at high risk		205	230			
No further testing	ca	81	0	<0,0001	39,5	0- 0,16
	%	39,6	0			
Amnio-centesis	ca	124	22	<0,0001	6,32	3,99 - 10,45
	%	60,4	9,6			
NIPT	ca	0	208	<0,0001	90,4	0,77 - 1,03
	%	0	90,4			

NIPT reduced the number of amniocentesis procedures to diagnose aneuploidy in the fetus at risk by 6,32 times (p < 0.001; 95% CI: 3,99 – 10,45) when comparing the two periods.

NIPT focuses mainly on the group of fetuses at high risk of aneuploidy through routine screening tests.

Table 4: Distribution characteristics of pregnancies with amniocentesis due to results of screening tests at high-risk

Period	9/2018 - 8/2019	9/2019- 8/2020	P
High-risk routine screening test (cases)	124	22	< 0,0001
High-risk NIPT (cases)	0	9	
Total (cases)	124	31	

There was a statistically significant difference in the number of amniocentesis between the two stages, with p < 0.0001.

Table 5: Distribution characteristics of amniocentesis results

Period	Chromosomal abnormality		p	Chromosomal normality		P
	High-risk routine screening test (cases)	High-risk NIPT (cases)		High-risk routine screening test (cases)	High-risk NIPT (cases)	
9/2018 - 8/2019	9	0	0,004	115	0	0,14
9/2019 -8/2020	4	8		18	1	

There was a statistically significant difference in amniocentesis for high-risk fetuses based on routine screening between the two stages, with p = 0,004.

Table 6: Distribution characteristics of chromosomes 21, 18, and 13 according to the NIPT classification in a routine screening population with high-risk results for chromosomal abnormalities 21, 18, 13

	Chromosomal abnormality (cases)	**Chromosomal normality (cases)**	**Total (cases)**
High-risk NIPT (cases)	8	1	9
Low-risk NIPT (cases)	0	199	199
Total (cases)	8	200	208

Given the prevalence of chromosome 21 abnormalities in the general population about 0,14%, the results for NIPT values in a population of high-risk routine screening pregnancies are as follows: sensitivity: 100% (95% CI: 63 - 100); specificity: 99,5% (95% CI: 97,2 - 99,9); positive odds: 200 (95% CI: 28,3 -141,2); Positive predictive value: 21,9% (95% CI: 3,8% - 66,4%).

Table 7: Features associated with amniocentesis

Period	**9/2018 - 8/2019**		**9/2019 - 8/2020**		**p**	**Rate ratio**	**95% CI**
	ca	**%**	**ca**	**%**			
High-risk routine screening test (cases)	124	61,4	22	1,6	< 0,01	4,52	2,85 - 7,47
High-risk NIPT (cases)	0	0	9	5,6	< 0,01		
Fetal abnormalities (cases)	78	38,6	131	80,9	< 0,01	0,47	0,35 - 0,63
Total number of amniocentesis (cases)	202	100	162	100			
Complications due to amniocentesis (cases)	0	0	0	0			

When comparing the two stages, amniocentesis was reduced by 4.52 times ($p < 0.01$; 95% CI: 2.85 -7.47) due to routine screening of fetuses at high risk of aneuploidy. However, there were more amniocentesis procedures performed because of fetal abnormalities.

Table 8: Estimated cost to detect a chromosomal abnormality based on screening in the general population.

Period	**9/2018 - 8/2019**	**9/2019 -8/2020**	**9/2019 - 8/2020 (*)**	**9/2019 - 8/2020 (**)**
Total number of routine screening test	2660	3018	3018	3018
Total number of NIPT	0	302	208	3018
Total number of amniocentesis	124	31	31	13
Total number of chromosomal abnormalities	9	12	12	12
Number of amniocenteses to detect 1 case of aneuploidy	13.8	2.58	2.58	12
Total number of missed high-risk cases	81	0	0	0
The total amount for screening and diagnosis (x 100.000 VND)	12,162	23,356	19,596	121,059
Estimated cost to detect a chromosomal abnormality in a population (VND)	135,133,333	194,633,333	163,300,000	1,008,825,000

(*): estimated data in the absence of 94 NIPT cases due to routine screening at average risk

(**): estimated data in case of performing NIPT test at the beginning to screen for aneuploidy.

IV. DISCUSSION

Currently, two types of aneuploidy serology tests are performed routinely in Vietnam: the Double test and the Triple test. There was no statistically significant difference in the number of routine screening tests for aneuploidy, the high risk of aneuploidy based on routine screening tests (combined test, triple test), and pregnant women's age when comparing between the two periods 9/2018-8/2019 and 9/2019-8/2020 (Table 1, Table 2). It proves the stability and superiority of the aneuploidy screening strategies being implemented in the current period.

The age of pregnant women with fetuses at high risk of aneuploidy in our study was about 31.9 to 32.3 (Table 2). For other countries in Asia, this is also the age group with the highest number of pregnant women [5]. It is different from developed countries; for example, in the US, the number of pregnant women over 35 years old accounts for more than 20% of the total number of pregnant women, so in this country, the number of pregnant women at high risk of having an aneuploidy account for 50% of all aneuploidy screenings with high-risk results [6]. In this study, amniocentesis accounted for only 60.4% of all high-risk cases for aneuploidies, and the rest were rejected (Table 3). Compared with the study of Kostenko et al. on 8788 pregnant women with a high risk of aneuploidies [4], the amniocentesis rate in our study sample was lower (60.4% compared to 87.5%), and the difference is statistically significant. This difference can be traced back to different cultures and supportive policies for congenital disabilities in different countries.

NIPT is a non-invasive screening test to investigate abnormalities of free DNA circulating in maternal blood, implemented DHWC in August 2019. In our study, the number of pregnant women selecting NIPT in the sample population at high risk of aneuploidy was up to 90.4%, and only 9.6% chose to perform amniocentesis without NIPT testing (Table 3). This resulted in no cases of fetuses at risk of aneuploidy being omitted. Thus, the rate of amniocentesis procedure used to confirm aneuploidy was reduced by 6.32 times, and this difference is statistically significant ($p < 0.0001$, 95% CI: 3.99 - 10.45) (Table 3). The study by JN Joseph et al. showed that up to 43.5% of pregnancies in the total high-risk cases of fetal aneuploidy were avoided by amniocentesis thanks to the NIPT [5]. Thus, the number of amniocentesis procedures has been reduced by 5.65 times. From September 2019 to August 2020, 302 cases were selected for NIPT, of which 94 cases (31.1%) were due to mid-range risk results from routine screening (Figure 3.1). NIPT was their second serological screening of choice, even though it costs ten times more than routine screening tests. This rate is similar to previous studies, which reported from 20 to 30% [7-10]. However, overall, NIPT was chosen by pregnant women at a higher level (90.4 %) with high-risk screening results (Table 3). This could be explained by the fact that DHWC is a tertiary referral hospital receiving high-risk pregnancies transferred from hospitals in Da Nang city, Quang Nam, and Quang Ngai provinces.

For routine screening with results of fetuses with high aneuploidy risks, the number of amniocenteses decreased significantly between September 2019 and August 2020, which is statistically significant (Table 4). The reduction in the number of procedures is that pregnant women have chosen NIPT to avoid the risk of amniocentesis complications. There was a statistically significant difference in the number of chromosomal abnormalities detected by the NIPT test compared to the routine screening test ($p = 0.004$) (Table 5). Therefore, the efficacy and effectiveness of NIPT in screening for aneuploidy (21, 18, 13) is undeniable. ACOG's 2012 guidelines stated that NIPT should not be offered to low-risk pregnancies [1]. On the other hand, the Korean Society of Maternal and Fetal Medicine recently conducted a multicenter cohort study to analyze in detail the efficacy of the NIPT test in nearly 7000 pregnancies [11]. A published study in Korea shows a very high detection rate of Down syndrome, even for those in low-risk pregnancies, through continuous screening. [12-14].

The results of this study show that NIPT has 100% sensitivity, 99.5% specificity, and 21.9% positive predictive value for the high-risk fetal population through routine screening. Research by the Ontario Health Quality Organization (2019) shows that NIPT has high accuracy for trisomy 21 and lower specificity and sensitivity than manufacturers' reported indicators. This is explained by companies providing NIPT performed on high-risk populations [15]. Although

the specificity of NIPT is high for trisomies 21, 18, and 13, the positive predictive values vary widely across studies and range from 40% to 100% [16-19]. Our study showed that the positive predictive value of the NIPT in the high-risk population was 21.9%. Therefore, more extensive research is needed with different gene sequencing techniques to have universal data for Vietnamese people.

Compared to post-NIPT implementation, the rate of amniocentesis was 4.52 times higher ($p < 0.01$; 95% CI: 2.85 – 7.47) due to routine screening with high-risk of aneuploidy, but adverse events did not occur when comparing the two periods of September 2018 – August 2019 and September 2019 – August 2020 (Table 7). This result is similar to the study of Wax et al (OR: 0.42; 95% CI: 0.32–0.55; $P < 0.0001$) [20]. According to the results of this study, although the number of amniocentesis from routine screenings with a high risk of aneuploidy has decreased, the number of amniocentesis due to fetal abnormalities increased, and this difference is statistically significant. There were no complications due to amniocentesis at all stages (Table 7). While the American College of Obstetricians and Gynecologists and the Society of Maternal and Fetal Medicine do not make any recommendations, the Royal Society of Obstetricians and Gynecologists (UK) set an annual minimum of 30 ultrasound procedures for doctors of prenatal diagnosis [21]. Similarly, the California Department of Health's public health genomic screening program required applicants to complete 25 successful amniocentesis or chorionic villus biopsies per year to maintain their status as a health practitioner. The 2014 guidance is also downsized from the minimum of 2013 in response to significant changes in diagnostic testing trends due to the impact of NIPT [22].

Research in Belgium led to government approval to cover the cost of the NIPT test, making it the first-line indicated screening method. At the cost of EUR 260 per NIPT, the efficiency achieved and the reduction of adverse events, and the cost increase compared to routine screening is reasonable [4],[23], [24]. The study estimated the cost for routine screening to detect a case of Down syndrome at EUR 86,994 and for NIPT at EUR 236,436. Research by Emilia Kosstenko et al. shows that the cost of routine screening to detect a baby with Down syndrome is also around 90,787 EUR [4]. The results in Table 8 show that using NIPT for follow-up screening for high-risk pregnancies detected by routine screening, then find out the cases with positive NIPT for amniocentesis, the total cost to confirm the diagnosis is 194,633,333 VND (equivalent to 7,208 EUR). This strategy proved effective if we look at the differences in costs, procedural complications, and the number of aneuploidies omitted. The difference in the cost of routine screening tests, NIPT, and diagnostic tests (amniocentesis, QF PCR test for aneuploidy 13,18, 21) is the main reason for differences in the estimated costs to detect a chromosomal abnormality (21, 18, 13) in the community. The difference in the cost of routine screening tests, NIPT, and diagnostic tests (amniocentesis, QF PCR test for aneuploidy 13,18, 21) is the main reason for the differences in the estimated costs to detect a chromosomal abnormality (21, 18, 13) in the community.

V. CONCLUSION

Since implementing NIPT at Da Nang Hospital for Women and Children, we can draw some conclusions as follows:

- The change in the number of routine screening tests for chromosomal abnormalities 21, 18, and 13 were not significant. The amniocentesis rate used to confirm an aneuploidy diagnosis has decreased by 6.32 times.

- Among the strategies to detect trisomies 21, 18, and 13, which are suitable for the economic conditions in Vietnam, a 2-step screening method can be applied. Step 1: screening by routine tests to detect fetuses at high risk of aneuploidies. Step 2: perform NIPT for high-risk cases selected in step 1, select NIPT cases with positive results and then conduct amniocentesis to perform diagnostic tests for chromosomal abnormalities.

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