Medical Science

25(118), December, 2021

Double test positive predictive value assessment for fetal defect screening in the first trimester of pregnancy at suburban district hospitals of Ho Chi Minh City

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To Cite:
Vo T, Pham B, Vu H, Ho N, Vo B. Double test positive predictive value assessment for fetal defect screening in the first trimester of pregnancy at suburban district hospitals of Ho Chi Minh City. Medical Science, 2021, 25(118), 3078-3084

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Peer-Review History
Received: 15 October 2021
Reviewed & Revised: 18/October/2021 to 14/November/2021
Accepted: 16 November 2021
Published: December 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Objectives: To determine positive predictive value of Double test for fetal defect screening during the first trimester of pregnancy among high-risk cases by Double test at suburban hospitals of Ho Chi Minh City. *Methods:* Retrospective cohort study conducted in the period of December 2019 – April 2020. By total population sampling, study objects were 149 pregnant women who had gestational ages of 11-13^{+6} weeks, participated into prenatal screening with Double test in the first three months of pregnancy, and obtained a high-risk test result for at least one of the three trisomy disorders 21, 18 and 13 at 7 suburban hospitals of Ho Chi Minh City. *Results:* During 5 months of study conduction, 149 pregnant women had Double test results as high risk, it is recorded that predictive value of Double test in fetal defect screening during the first trimester of pregnancy was 5.3%. All high-risk Double test cases had a chromosomal anomaly of trisomy 21 via amniocentesis. *Conclusion:* Although positive predictive value is very low (5.3%) and false positive rate is high (94.7%), Double test still plays a role in antenatal screening in the first three months of pregnancy. However, when positive, counseling for pregnant women is needed to assure them that there are about 5 true deformities per every 100 high-risk cases. It is necessary to conduct more specialized tests for confirmed diagnosis.

Keywords: Free β-hCG, PAPP-A, NT, prenatal diagnosis, high risk.

1. INTRODUCTION

The quality of population is a current huge challenge for the world of which disable people are increasing due to various causes, and congenital deformity accounts for 34.15% (Bui, 2014). To early detect chromosomal anomalies, especially in cases with Down (T21), Edwards (T18) and Patau (T13) syndromes, Double test is conducted at gestational ages of 11-13^{+6} weeks. The

test is based on bio-chemical indicators including Pregnancy-Associated Plasma Protein A (PAPP-A) and free β-human Chorionic Gonadotrophin (free β-hCG) in maternal blood, maternal weight, fetal Nuchal Translucency (NT) on sonography, and gestational age. Screening effectiveness is dependent on the reliability and precision of NT ultrasound measurement and mean of medians (MoM) of PAPP-A and free β-hCG. For high-risk Double test cases, amniocentesis is recommended to assess chromosomal map for positive diagnosis.

In Ho Chi Minh, suburban district hospitals have had a prenatal screening project in place under the program of "Medically specialized staff rotation from higher level hospitals to lower ones in order to improve medical care service quality" since 2017 (MOH Vietnam, 2008). However, the implementation is not synchronized among hospitals. Most of screening cases have been referred to such higher level as Tu Du hospital and Hung Vuong hospital.

Double test result as high risk makes pregnant women be anxious. Physicians must explain with specific data to calm pregnant women down; and amniocentesis results with chromosomal mapping should be the gold standard in congenital defect diagnosis. However, there have been no studies or reports to assess Double test positive predictive values produced at district hospitals. Therefore, we conduct a study to evaluate double test positive predictive value collected from fetal defect screening at suburban district hospitals of Ho Chi Minh City, and research question is "What is true fetal chromosomal defect rate in pregnancies that have high-risk Double test results at suburban district hospitals in Ho Chi Minh City?" Our Study objectives are to determine positive predictive value of Double test in fetal defect screening during the first trimester at suburban district hospitals of Ho Chi Minh City, and to describe pregnancy outcomes of high-risk Double test cases.

2. SUBJECTS AND METHODS OF THE STUDY

Study design

Retrospective cohort study conducted in the period of December 2019 – April 2020

Study subjects

All pregnant women who have Double test screening at gestational ages of 11-13^{+6} weeks produce a high-risk result for at least one of the trisomy disorders 21, 18 and 13 at 7 district hospitals – District 2, Thu Duc District, Thu Duc Township, District 9, District 12, Binh Tan District and Tan Phu District.

Admission criteria

Pregnant women from target population had a high-risk Double test result in the period of 01/01/2019 – 31/12/2019. A high-risk Double test result based on bio-indicators of free β-hCG and PAPP-A in maternal blood, maternal weight, number of children, ethnic group, smoking, type I diabetes, number of fetuses, IVF, NT, and fetal age. Parameters of free β-hCG and PAPP-A were adjusted with maternal weight, number of children and ethnic group; NT was adjusted with fetal age (other variables used for reference). Next, a software program calculated a risk level for each fetal defect case including risk by maternal age (base risk), risk by test, mixed risk. Mixed risk was the ultimate one to determine high or low risk. The hospitals in our study used programs LifeCycle 6.0 and Mozzie with cut-off level of 1/250. Double test result was concluded as high risk if the risk was linked to one of the three disorders – trisomy 21, 18, 13 – above the cut-off level of 1/250.

Exclusion criteria

Pregnancy by assisted reproduction; mental disorders, dumb and deaf; unable to understand Vietnamese; uncompleted questionnaires; disagreed to have amniocentesis for confirmed diagnosis.

Sample size

Below is sample size formula to determine positive predictive value of a test:

$$N = \frac{Z^2_{1-\alpha/2} P(1-P)}{d^2}$$

Z= 1.96; P = 0.13 by Lang (2010); d = 0.6; N = 145

Sampling method and data collection

Retrospective cohort study conducted in the period of December 2019 – April 2020. Sampling was based on total population sampling approach. We recruited all pregnant women who had been screened fetal defects with Double test during the period between 01/01/2019 and 31/12/2019 had a high-risk result, and then obtained an amniocentesis for chromosomal mapping.

Data collection steps

Step 1: Listing pregnant women who visited hospital from 1/1/2019 to 31/12/2019 and had high-risk Double test results at 7 study hospitals.

Step 2: Calling study objects to explain study objectives, benefits, and risks. If a pregnant woman agreed to join the study, she would be scheduled for a home interview.

Step 3: Collecting data by two sections: (Section 1) Taking information from medical records to prepare background on a study subject. (Section 2) Interviewing the subject at her residence after consent form signed.

Step 4: Information from completed questionnaires was entered with Epidata 3.1 and data analysis was conducted with Stata 13.0.

Data analysis

Distributions of variables were examined using descriptive analyses. Mean and standard deviation were reported for continuous variables and frequency and proportion were reported for categorical variables, and 95% confidence intervals were reported.

3. RESULTS AND DISCUSSION

After reviewing cases in the period of 1/1/2019 – 31/12/2019, 210 pregnant women had a high-risk Double test result. However, there were 149 pregnant women only with agreement on amniocentesis for chromosomal mapping. All those 149 pregnant met inclusion criteria for sampling.

Characteristics of study subjects

The results are presented as follows: Pregnant women aged ≥ 35 and < 35 years in the study accounted for 51.9% and 48.1%, respectively. Most of them (67.7%) had secondary education or higher, junior secondary 31.0% and the rest 1.3%. Moderate BMI took place in more than half of pregnant women (54.3%) whereas high BMI group accounted for 33.8%, and low BMI was the smallest one (11.9%) (Table 1).

Table 1 Epidemiologic characteristics

Description	Frequency (N=149)	Percent
Age group		
< 35	71	48.1
35+	78	51.9
Educational level		
Primary and lower	2	1.3
Junior secondary	46	31.0
Secondary	65	43.8
Higher	36	23.9
Occupation		
Workers	68	45.7
Public staff	49	33.3
Housework	32	21.0
BMI (kg/m^2)		
Low	18	11.9
Moderate	80	54.3
High	51	33.8

More than half of pregnant women were more than 35 years old, and fetal defect risk increases with this maternal age group. The average maternal age in the study was 34.3 ± 5.23 years, and still within women's reproductive age; it is logically worth

screening fetal defects for those pregnant women. The maternal mean age in our study is higher than that of Le Thi My Trinh's 32.3 ± 4.2 years (Le, 2014). Our study was conducted in suburban districts where factory workers are living for easy access to their workplace. They have economically restricted conditions, and therefore, there is a marital delay trend among them.

Secondary education was common in 43.8% of pregnant women. The majority was workers (45.7%), then public staff (33.3%), and housework and other (21.0%). This is easy to understand because the study was conducted in suburban area of Ho Chi Minh City where the residence has a certain level of education, and they are aware of the importance of antenatal care services. Nulliparous women took the most part in the study at 59.0%, next was uniparous (22.9%), and multiparous (18.1%). It is disclosed that a child with a chromosomal disorder is recognized as a burden to an individual family and the society (Table 2).

Table 2 Medical history features of study objects

Description	Total (N=149)	Percent
Spontaneous abortion/ still birth		
0	128	86.2
1	16	11.4
2+	5	2.4
Fetal defect birth		
0	148	99.5
1	1	0.5
2+	0	0
Diabetes mellitus		
No	143	96.2
Yes	6	3.8
Fetal defect family relations		
No	147	99.0
Yes	2	1.0

No previous spontaneous abortion or still birth was reported by most of pregnant women (86.2%) whereas less than 12% of cases reported to have a previous still birth. The result is higher than that of Nguyen Nhi study (2015) in which 77.18% of pregnant women reported no previous still birth or abortion at Hung Vuong hospital, but it is lower than that of Le Trinh (2014) where 93.2% of pregnant women had no history of still birth or abortion. The difference may be due to our larger sample size.

A history of congenital defect birth and having a direct family relation of congenital defects were reported by very few pregnant women at 0.5% and 1.0%, respectively. The study results are higher than those of Le Trinh study (2014) where all 59 pregnant women had no antecedent congenital defect birth or direct relationship of congenital defect family. Similarly, in the study by Nguyen Nhi, (2015) there were 390 pregnant women reporting no antecedent congenital defect births. This is rational since congenital defects are rare in the population. There were 8 cases only with diabetes mellitus (3.8%) before pregnancy. The occurrence was recorded in pregnant women aged more than 35 years. The number of diabetic pregnant women was a favorable factor to control confounders for pregnancy outcomes since diabetes in pregnancy is considered a risk of fetal defects and other adverse pregnancy outcomes like still birth, preterm labor, and etc.

Amniocentesis results

There were 149/210 pregnant women with high-risk Double test results (70.9%) agreeing amniocentesis. Post-amniocentesis chromosome mapping revealed that 8 cases (5.3%) were having trisomy 21 and the remaining 141 pregnant women (94.7%) having normal chromosomes, no cases with chromosomal anomalies like trisomy 13 or 18, abnormal sex chromosomes and others (Table 3). The study results are different from those of Ha Thi et al., (2018) conducted at Hue University of Medicine and Pharmacy in 2018. In that study, chromosomal disorders included trisomy 21 (68.8%), trisomy 18 (31.2%) and no trisomy 13 was found.

Table 3 Results of chromosome set in 149 pregnant women who experienced amniocentesis for chromosome mapping

Description	Total (N=149)	Percent
Results of amniocentesis		
Normal	141	94.7

Description	Total (N=149)	Percent
Trisomy 13	0	0.0
Trisomy 18	0	0.0
Trisomy 21	8	5.3

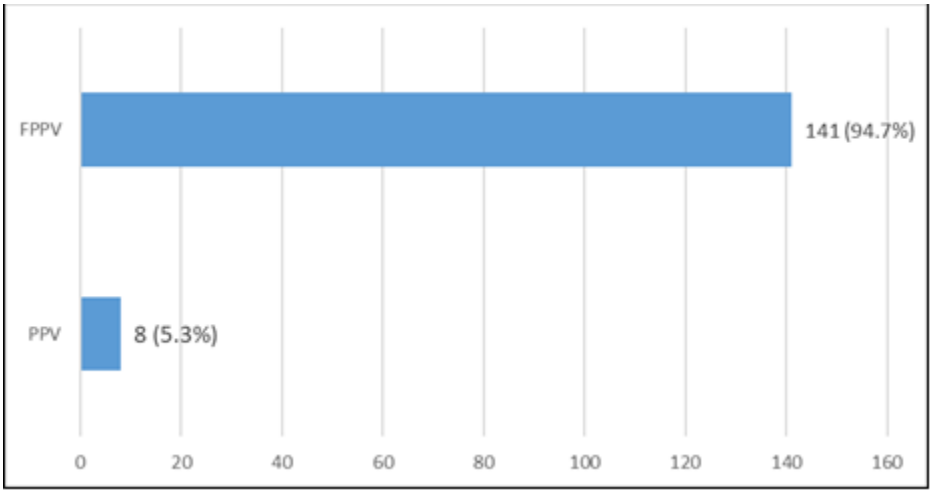
Pregnancy outcomes

In 149 pregnant women with amniocentesis, 8 cases (5.3%) had a chromosomal disorder result of trisomy 21, and all decided to terminate their pregnancy. The rest of 141 cases (94.7%) had normal chromosomal maps and were monitored to labor date (Table 4). Among 141 pregnant women on follow-up to labor date, most of fetal ages (85.1%) on birth delivery ranged between 37 and 40 weeks, next was more than 40 weeks (6.5%). The fetal ages of 28-36^{+6} weeks occurred at 4.9% and less than 28 weeks 3.5%. About 59% of newborn weights ranged 3000-3500g, the groups of 2500-2900g and >3500g shared nearly equivalent rates at 18.4% and 17.8%, respectively. The weight of less than 2500g took the smallest rate of 4.9%. Assisted delivery occurred in 2.1% of labor cases while normal delivery took a little higher rate than cesarean section at 50.4% and 47.5%, respectively.

Table 4 Pregnancy outcomes from high-risk Double test cases

Description	N=149 (%)
Healthy child	141 (94.7)
Deformed child	0 (0)
Pregnancy termination	8 (5.3)
Abortion/ still birth	0 (0)
< 28 weeks	5 (3.5)
28 – 36^{+6}	7 (4.9)
37– 40	120 (85.1)
> 40	9 (6.5)
< 2500g	7 (4.9)
2500–2900	26 (18.4)
3000–3500	83 (58.9)
> 3500	25 (17.8)
Normal delivery	71 (50.4)
Assisted delivery	3 (2.1)
Cesarean section	67 (47.5)

Positive predictive value of Double test



Graph 1 Positive predictive value of Double test

In 149 cases with amniocentesis, there were 8 cases having abnormal chromosomes, and therefore, double test positive predictive value for fetal defect screening in the first trimester is 5.3% and false positive is 94.7% (Graph 1). The results are much higher than those by Phan Xuan Diep et al., (2012) in 758 pregnant women with high-risk Double test results, among them 17 pregnant women (2.24%) had a chromosomal disorder. In the study by Nguyen Minh Hung (2012), 31 high-risk cases agreed to have amniocentesis, and 2 cases (6.4%) were found to have Down syndrome. Prenatal screening with Double test obviously has a humble positive predictive value. However, screening test should be recommended to find chromosomal anomalies in the first trimester for pregnant women, hinting further inspection for confirmation (Chou, 2008; Dubravka, 2010).

Pregnancy outcomes from high-risk cases by Double test

There were 8 cases having chromosomal anomalies among 149 pregnant women with amniocentesis. All eight selected pregnancy termination. All 141 cases with normal results after amniocentesis delivered normal newborns. Most of them (85.1%) had birth delivery at 37-to-40-week pregnancy. Pre-term birth at less-than-28-week pregnancy occurred at 3.5%. This evidenced that invasive assessment like amniocentesis was not so dangerous, and did not become a pre-term birth factor. Mean newborn weight was 3050 ± 836g, lower than that in Sylvie study – 3483.95 ±376.3g (Sylvie, 2012). Sylvie study was conducted in Brazil where newborns have bigger stature than Vietnamese newborns.

As compared with Sylvie's results, our study had a higher cesarean section rate, 47.5% vs 33%. The increased c-section rate in our study is on the common trend of c-section increase in Vietnamese pregnant women, not due to high-risk Double test results. In our study, a high rate of normal newborn delivery (94.7%) over high-risk test pregnant women was recorded.

4. CONCLUSION

During 5 months, the study over 149 pregnant women with high-risk Double test results discloses: (1) Double test positive predictive value for fetal defect screening in the first trimester is 5.3%; (2) Pregnancy outcomes of high-risk Double test cases are 5.3% for pregnancy termination due to chromosomal anomalies, and 94.7% with healthy childbirth. Double test prenatal screening should be a routine procedure for pregnant women at primary health care level, especially district level, to improve the performance of Double test on site. It should be assured to pregnant women with high-risk Double test results that the test is used for screening only with a very low positive predictive value (5.3%), and further specialized assessment needs to be conducted.

Acknowledgement

We are indebted to the participants for making this research possible and to all physicians and staff of District 2, Thu Duc District, Thu Duc Township, District 9, District 12, Binh Tan District and Tan Phu District at Ho Chi Minh City.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval for the study was obtained from the University of Medicine and Pharmacy at Ho Chi Minh City (Approval number: 510/DHYD-HD/2019). Data were kept anonymous and confidential during all stages of the study.

Funding

This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are presented in the paper.

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