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CLINICAL STUDY

Fetal anatomy scan with integrated nuchal translucency and combination of PAPP-A and fβhCG for prediction of aneuploidy

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ABSTRACT

BACKGROUND: Nuchal translucency (NT) is an important finding of early fetal anatomy scan because of the association with genetic and structural anomalies. Enlarged nuchal translucency can be easily detected even without measurement on fetal anatomy scan as a neck pathology. Because of demanding criteria for measurning NT in established prenatal aneuploidy screening we came with an idea of improvement and simplification with availabe methods. The aim of this study is to compare established screening methods with new model of screening composed of fetal anatomy scan with integrated nuchal translucency and combination of PAPP-A and fβhCG.

METHODS: A prospective one center study analyzed a total of 351 pregnancies between January 2017 and December 2020. Sonographic measurement of NT and fetal anatomy scan (FAS) were performend with biochemical testing from blood sample in the first trimester. Combined screening and fetal anatomy scan was performed. Patients with a pathological screening or with structural defects underwent an invasive procedure. In patient with positive screenining who missed the first trimester invasive procedure, amniocentesis was performed. Fetuses were divided into two groups according to positive or negative karyotype and to calculate sensitivity and specificity of screening methods. From statistical methods regression analysis, significance p of individual predictor, sensitivity and specificity with graphic drawing of ROC charts were used. Data were analyzed using statistical tools of Microsoft Excel 365 and BESH stat.

RESULTS: Four models for aneuploidy screening were tested. 1) Model of „Age at the time of diagnosis" was slightly significant predictor with insignificant odds ratio (P=0.04, OR=1). 2) Model of„ First trimester biochemical screening" (age, free beta human chorionic gonadotropine – fβhCG and pregnancy associated plasmatic protein A – PAPP-A) were significant (P=0.0001; LR=21) with sensitivity of 87.5 % and specificity of 65.7 %. 3) Model of „First trimester combined test" (age of patients at the time of diagnosis, fβhCG, PAPP-A, NT) was significant ($P=7.9 \times 10^{-14}$, LR=67, sensitivity 87 %, specificity 80 %). 4) Model of „Fetal anatomy scan with biochemistry" (structural abnormality finding with combination including age, fβhCG and PAPP-A) was significant ($P=4.9 \times 10^{-18}$, LR=87, sensitivity 95 %, specificity 80 %).

CONCLUSION: Fetal anatomy scan combined with age, fβhCG and PAPP-A has the highest sensitivity and specificity for both, the detection of fetal aneuploidies and structural abnormalities. Our study shows that fetal anatomy scan is the best possible option for first trimester diagnostics *(Tab. 4, Fig. 5, Ref. 16)*. Text in PDF *www.elis.sk*

KEY WORDS: nuchal translucency, first trimester, fetal anatomy scan, PAPP-A, prenatal ultrasound.

Introduction

Prenatal diagnosis has shifted into the first trimester over the last decades. From the ultrasound point of view nuchal translucency (NT) scan for aneuploidies and fetal anatomy scan for detection of structural abnormalities were two tools developed with two different goals (1, 2). First trimester prenatal diagnostic options are mentioned in Table 1.

The measurement of the nuchal translucency thickness is a well-established component of the first trimester screening for fetal aneuploidy. Fetuses with enlarged NT are at an increased risk of aneuploidy as well as triploidy or monosomy X (3). The evaluation of the nuchal translucency requires the certificate of competence in measurement of nuchal translucency from Fetal

Tab. 1. First trimester prenatal diagnostic options.

Screening method	markers	Sensitivity (5% FPR)
MA	MA	30%
NT + MA	MA + NT	75–80
First trimester biochemistry	age, fβhCG, PAPP-A	60–75 %
Combined screening	fβhCG, PAPP-A, NT	85–95%

MA – maternal age, NT – nuchal transclucency, fβhCG – free beta human chorionic gonadotropine, PAPP-A – pregnancy associated plasmatic protein, FPR – false positivity rate according to Nicolaides (13)

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Tab. 2. Descriptive statistics.

	Affected group with pathological karyotype n=23			Control group n=328		
	mean	minimum	maximum	mean	minimum	maximum
Age (years)	34.6	25	40	32.4	16	45
Gravidity	2.4	1	6	1.75	1	7
Parity	1.3	0	5	0.6	0	5
Week of gestation	14	12	20	13.6	11	23
Nuchal translucency (mm)	3.9	1	11	1.67	0.14	6.97

Tab. 3. Results of screening methods according to karyotype.

	Affected group with pathological karyotype n=23		Control group n=328	
	n	%	n	%
NT more than 99centile	12	52	10	3
Abnormal fetal scan	20	86.9	28	8.5
Abnormal biochemical screening	20	86.9	56	17

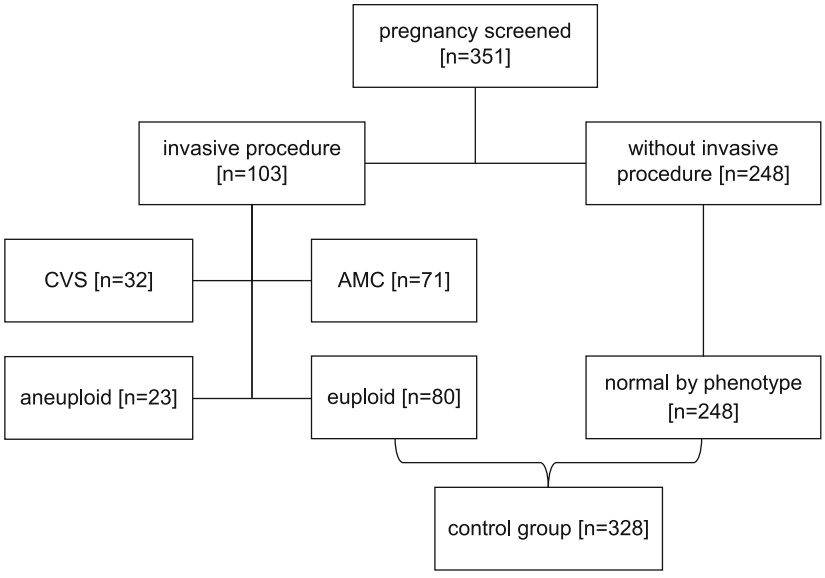

Fig. 1. Data flow chart.

Medicine Foundation with the use of strictly specific methodology. Although enlarged nuchal translucency can be easily detected even without measurement on fetal anatomy scan as a neck pathology, either nuchal edema or cystic hygroma (4).

With the improvement in ultrasound equipment and the accrual of the knowledge on sonographic appearance of normal and anomalous anatomy, the timing of the fetal anatomy scan was shifted earlier in pregnancy (5). The fetal anatomy is not furthermore routinely assessed until the morphology screening at week 20 (6). Besides that, aneuploid fetuses are susceptible to carry structural defects what can often be detected by a thorough fetal scan during NT scan. Moreover, in euploid fetuses an increased NT is also associated with a wide range of structural anomalies (7, 8, 9).

Detection of aneuploidies increased by the improvement of NIPT (non-invasive prenatal testing) with very good sensitivity and specificity (10). Besides that, positive screening result (positive NIPT result, combined test risk higher than 1 : 100) needs to be confirmed by an invasive procedure. Chorionic villi sampling (CVS) in the first trimester and by amniocentesis in the second trimester (11).

Eventhough the combined test has very good sensitivity and specifilicy, its realisation is not possible without certification of examiner. This subsequently leads to high false positivity of lower sensitivity screening methods and more invasive procedures. Because of demanding criteria for measurning NT in established prenatal aneuploidy screening we came with an idea of improvement and simplification of available methods. The aim of this study is to compare established screening methods with new model of screening composed of fetal anatomy scan with integrated nuchal translucency and combination of PAPP-A and fβhCG.

Material and methods

One-center prospective study was performed between January 2017 and December 2020 after gaining the ethical approval from the Institutional Ethical Review Committee. Informed consents from all patients were obtained.

All patients underwent detailed examinations. These examinations included a sonographic measurement of NT between 11+0–13+6 weeks of pregnancy, biochemical testing from blood sample at weeks 10+0–11+6 and sonographic scan for anatomical defects.

Ultrasound scans were realized by certified obstetricians at GE Voluson S6, S8. In all patients gestational age, age, gravidity and parity were obtained. Cut off for positive screening was 1 : 100 for the combined test.

Patients with a pathological combined screening or with structural defects underwent an invasive procedure according to the time of their diagnosis in our center. Chorionic villi sampling was performed during the diagnostics in the first trimester and amniocentesis in the second trimester when the patient missed the first trimester invasive procedure.

Karyotypes were detected from the samples of amniotic fluid or chorionic villi. Women were divided according to karyotypes into 2 groups. There were women, who had fetuses with pathological karyotypes in the first group. Patients with normal fetuses were included in the second group. We have defined normal fetuses to be euploid fetuses from CVS or AMC results or fetus without need of karyotyping because of negative screening and who were

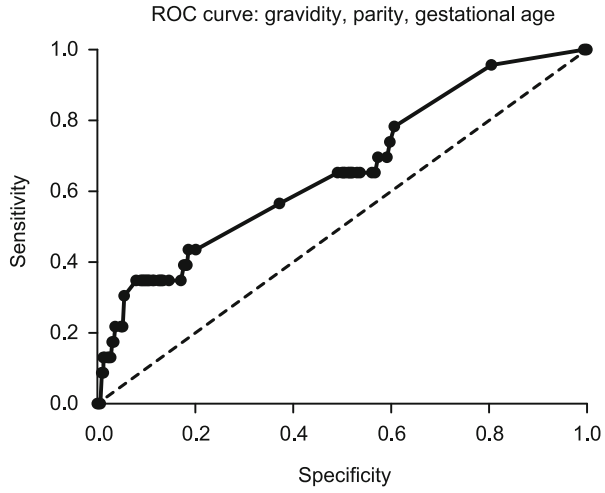

Fig. 2. ROC curve of gravidity, parity and gestational age.

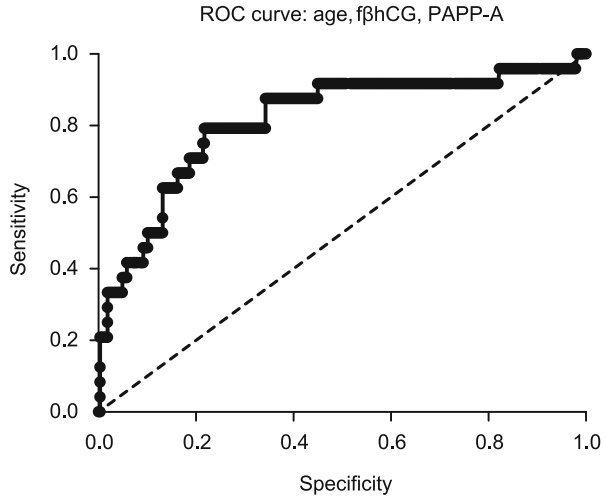

Fig. 3. ROC curve for age, fβhCG, PAPP-A.

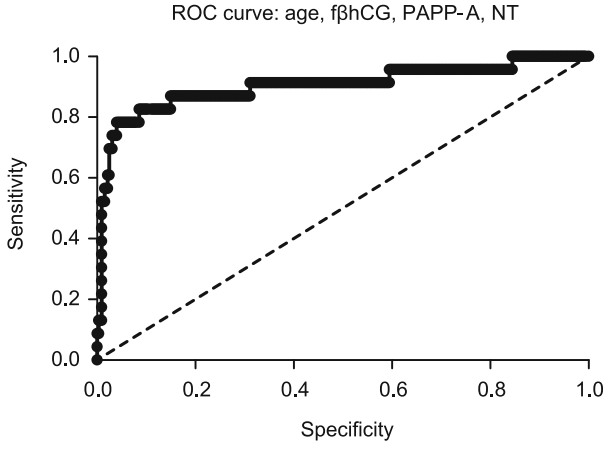

Fig. 4. ROC chart for age, fβhCG, PAPP-A, NT.

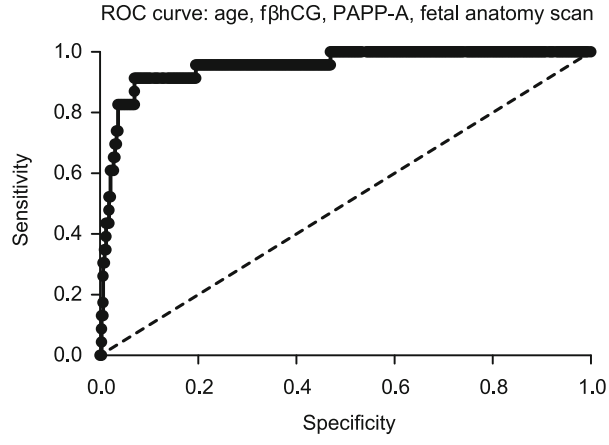

Fig. 5. ROC chart for age, fβhCG, PAPP-A, fetal anatomy scan.

subsequently delivered fenotypically normal. Second group was denoted as control group. Finally, all the delivered babies from control group were healthy.

The results were analyzed by regression analysis. Individual morphological structures were analyzed in each group. Data are presented as means or numbers (as percentages). Regression analysis was used to examine two study groups and significance p of individual predictor, sensitivity and specificity with graphic drawing of ROC charts.

Data were analyzed using statistical tools of Microsoft Excel 365 and BESH stat.

Results

A total of 351 pregnancy examinations were screened. From all over of patients 103 underwent invasive procedure (32 – CVS and 71 – amniocentesis). Fetuses with pathological karyotypes were 23. Euploid fetuses were 80 and 248 babies were normal by phenotype. There were 2 groups gained. Affected group, that included fetuses with abnormal karyotypes. Control group included fetuses with normal karyotypes and healthy babies by phenotype (Fig. 1). Descriptive statistic is presented in Table 2. Results of the screening are shown in Table 3.

Neither gravidity (p=0.86, OR=1.07), nor parity (P=0.29, OR=1.64), nor gestational week at the time of diagnosis (P=0.82, OR=1.02) are significant predictors. They show low sensitivity and specificity (Fig. 2).

1) Model of „Age at the time of diagnosis“ was slightly significant predictor with insignificant odds ratio (P=0.04, OR=1).

2) Model of „First trimester biochemical screening“ (age, fβhCG, PAPP-A) was tested by regression analysis. Isolated examination of fβhCG was statistically insignificant (P=0.64). Isolated examination of PAPP-A was statistically significant (P=0.0012). Combination of predictors (age, fβhCG a PAPP-A) were significant (P=0.0001; LR=21). Sensitivity of this model is 87.5 % and specificity 65.7 % (Fig. 3).

Tab. 4. Fetal anatomy scan – results. Data from 46 patients with finding on FAS.

Area of scanning	Pathologic finding	n	%
Fetal head and neck	Nuchal edema	17	36.9
	Hydrops	6	13
	Hygroma coli cysticum	3	6.5
	Ventriculomegaly	2	4.3
	Spina bifida	2	4.3
	Low-set ears	1	2.1
	Cystis plexus choroideales	2	4.3
	Fossa posterior abnormality	1	2.1
	microcephaly	1	2.1
Abnormality of fetal profile	Facial clefting	1	2.1
	hypoplastic nasal bone	1	2.1
Heart	Hypoplastic left heart syndrome	1	2.1
	TOF	2	4.3
	Hypoplastic right heart syndromes	3	6.5
	AVSD	1	2.1
Chest		0	0
Abdominal wall	Omphalocele	3	6.5
	gastroschisis	5	10.8
Abdomen cavity	Megavesica	6	13.0
	ascites	1	2.1
Spine and limbs	Sandal gap	1	2.1
	Polydactyly	1	2.1
	Abnormal deviation of spinal cord	1	2.1
	Talipes equinovarus	1	2.1
Umbilical cord	Single umbilical artery	3	6.5
Placenta	Thin placenta	1	2.1
Amnionitic fluid	anhydramnion	1	2.1

TOF – tetralogy of Fallot, AVSD – atrioventricular septal defect

3) Model of „First trimester combined test“ (age of patients at the time of diagnosis, fβhCG, PAPP-A, NT). Age of patients was insignificant (P=0.07, OR=1.1). fβhCG was also insignificant (P=0.76, OR=1.08) as well as in the first model. NT measurements were highly significant ($P=9.8x10^{-6}$, OR=2). PAPP-A was a significant predictor (P=0.0009, OR=0.04) and it seems to be a protective factor. Combined test had significance ($P=7.9x10^{-14}$, LR=67) with sensitivity of 87 % and specificity of 80 %. It is presented in Figure 4.

4) Model of „Fetal anatomy scan with biochemistry“ was focused on the anatomy scan in 12th week of gestation. We make an assumption that any finding of structural abnormality (Tab. 4) on fetal anatomy scan is considered to be pathologic FAS. This predictor is highly significant ($P=1.2x10^{-16}$, OR=71.4) Significance was proved also by Fisher´s exact test. Patients with abnormal fetal scan had also 71-fold chance to have child with pathological karyotype. Model of „Fetal anatomy scan with biochemistry“ (structural abnormality finding with combination including age, fβhCG and PAPP-A) had sensitivity of 95% and specificity of 80 %. It is shown in Figure 5. In this model, age of patient at the time of diagnosis was an insignificant predictor (P=0.07, OR=1.1) and fβhCG was an insignificant predictor as well (P=0.95, OR=0.98). PAPP-A protein was a significant predictor in this model (P=0.007, OR=0.1). This model had significance of $P=4.9x10^{-18}$ and LR=87.

From all 23 patients with fetuses with abnormal karyotypes, 20 patients underwent termination of pregnancy and 3 patients had spontaneous abortion.

Discussion

Eventhough nuchal tranlucency is well described, there are only few papers about fetal anatomy scan integrating nuchal translucency in the first trimester. It is commonly known that the most frequent aneuplodies carry structural defects found on fetal anatomy scan with increased nuchal translucency. These papers bring conclusion that incorporation of a detailed FAS into first-trimester screening algorithms can improve the detection rates for the most common aneuploidies. There is no evidence that they bring integration and simplification to the first trimester screening methods (14, 15).

Tekesin assessed the diagnostic value of an early anomaly scan in fetuses with increased nuchal translucency (NT) in the prediction of aneuploidy. In his work with 115 fetuses, the presence of major sonographic finding was significantly predictive (79.1 %) for aneuploidy. He underlines the importance of a detailed anatomical ultrasound in fetuses with increased NT, as major sonografic finding occurred frequently (5). In our work we did not make difference between major and minor sonographic findings and the prediction for aneuploidy was 71.4 %. Smaller number is considered to be because of smaller patient group.

Wiechecz‘s results showed good screening performance of ultrasound-based risk calculation models in trisomy 18. Following study pointed out the first trimester ultrasound pattern of trisomy 18 (increased NT, tricuspid regurgitation, single umbilical artery, omphalocele and right dominant heart). Biochemistry markers were not integrated into the ultrasound-based risk calculation (16). In our patient group we had 4 fetuses with trisomy 18, all of them had findings of multiple structural abnormalities on FAS.

Although nuchal translucency and combined screening is well established for decades (13) and fetal anatomy scan for detection of structural abnormalities, they aree two tools developed with two different goals. Yagel wrote his opinion about integration nuchal translucency measurment and fetal anatomy scan. He points out that this approach has the potential to rationalize the number and length of clinic visits for most patients and maximize detection of structural abnormalities at the earliest feasible gestational age (1). His opinion is missing data which we bring in our research. Fetal anatomy scan is most effective screening method for aneuploidy with sensitivity 95 % and specificity 80 %.

Conclusion

Nuchal translucency is the first-choice option for detection of aneuploidies in Europe. The benefits are relative. Related measurements require specific methodology which takes time. During the fetal anatomy scan the nuchal area is well visualized and pathology is easily detected as nuchal edema or cystic hygoma. Morphological changes of nuchal pathology can be usually distinguished as various NTs (7). If NT is increased above 99 percentiles, it is usually obvious without specific measurement and the NT type can be distinguished as well. By choosing the best strategy in the prediction of fetal abnormalities we are able to decrease the amounts of visitations in the hospital (12). It also leads to early detection of fetal abnormalities (2). It was found in this study that the model where predictors were age, fβhCG, PAPP-A, fetal anatomy scan is most effective with sensitivity 95 % and specificity 80 %. This could lead to new screening strategies favoring fetal anatomy scan.

Because of the association with genetic and structural anomalies, nuchal translucency will remain an important finding of early fetal anatomy scan. The time has come to rethink the paradigm of prenatal anomaly screening. Besides that first trimester combined test is the most used test in the first trimester, in our study we confirmed that fetal anatomy scan combined with age, fβhCG and PAPP-A has the highest sensitivity and specificity. Nuchal translucency measurement could be integrated into an early fetal anatomy scan with simply evaluation as neck pathology. We acknowledged that simplification of nuchal translucency evaluation integrated into fetal anatomy scan with first trimester biochemistry is the best possible option for both, fetal aneuploidy and fetal abnormality screening.

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