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CREDIBILITY OF THE COMBINED TEST IN PRENATAL DIAGNOSTICS

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Congenital anomalies are the cause of perinatal death in 20-25% of the cases, while 3% of children are born with malformation of varying size. The objective of this study was to examine the predictive value and define the credibility ratio of the combined test results. Of 317 examined pregnant women, we had sixteen (5.05%) with the result of pathological karyotype after amniocentesis including: nine (2.84%) with fetal numerical aberrations and seven (2.21%) with fetal structural aberrations. While determining the ultrasonographic parameters of the combined test we used the standards of the Fetal Medicine Foundation. We carried out the quantitative settings of free β-HCG and PAPP-A from vein blood of patients by applying commercial tests of firm DPC-USA. Tests were based on the analytical *immunochemiluminescence* assay and were realized by using the automated analyzer IMMULITE 2000. Manufacturer of the analyzer is also the firm DPC-USA. Sensitivity of the test is 94%, and specificity is 99%. Positive likelihood ratio [likelihood ratio test (LR

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+)] is 94.00, a negative likelihood ratio is [likelihood ratio test (LR-)] 12:06. Pretest probability that pregnant women carries fetus with chromosomal abnormality is 1:250 or 0004. Posttest odds after the combined test to discover this abnormality is 0.3760, and probability of the same case is 0.2732 if it happens that the test result is positive. The result of our study confirms the justification of combined test usage in routine clinical practice, since the posttest odds rate in the case of a positive screening increases several times over (almost 90 times), the probability of detecting a chromosomal abnormality was about 70 times. Combined screening test if used methodologically correct, has a high predictive value in detecting fetal congenital anomalies.

Key words: family, migraine, recurrent headache.

INTRODUCTION

Congenital anomalies are the cause of perinatal death in 20-25% of the cases, while 3% of children are born with malformation of varying size. Usable value of the screening test is estimated on the basis of its sensitivity, specificity and possibility of the disease in case the result is positive. By combining the values of pregnancy-associated plasma protein A (PAPP-A) and free beta-subunit of choriogonadotropin (Free β-HCG) in serum with nuchal translucency (NT) diameter (Combined test), the possibility of detecting DS is rising up to considerable 90% with 5% of false positive findings, SPENCER (2001). The testing is being done between 11 and 13+6 weeks of gestation. If the result happens to be positive, some invasive methods of prenatal diagnosis are suggested to the pregnant woman. A limit value of the combined test is 1: 250. Special problem is the test result interpretation. According to the literature data, even 32% of pregnant women answered that after getting the results and talking to the doctor, WALD *et al*. (1999), they didn't know what the term "high risk" really meant.

Research objective was:

1. To examine the sensitivity and specificity of ultrasonographic (nuchal translucency - NT) and biochemical (Free β-HCG and PAPP-A) markers as parameters of the combined test and amniocentesis in diagnostics of congenital fetal anomalies.
2. To set the credibility ratio of the combined test results.

MATERIALS AND METHODS

Prospective, observational study was conducted at the Gynecology and Obstetrics Clinic at Clinical Center Kragujevac (GOC, CC Kragujevac) in the period 2008-2009 on singleton intrauterine pregnancies in the first trimester of pregnancy. Clinical and experimental model of study was used throughout the research. Ethics Committee at the CC Kragujevac confirmed the rightness of this study and authorized its conduct. 317 pregnant women were included in the examination and observed by Board of Genetic Counseling at GOC CC Kragujevac. All ultrasound

examinations were conducted on the "Aloka Prosound 3500" apparatus at GOC CC Kragujevac. Pregnancy was 11-13+6 weeks of gestation. Crown-rump length (CRL) of the fetus was between 45 and 84 mm. While measuring fetal NT we used the ultrasound apparatus of high resolution with the option"cine loop" so that image could be returned by calipers that allow measurement of one decimal. Screen image on which NT was measured, encompassed only the head and the upper part of fetal rib cage. We used the maximum enlargement, so that little movement of the caliper altered the diameter for only 0,1mm. The nuchal translucency was measured by transvaginal approach of color Doppler technique with fetus in neutral position. We measured the maximal thickness of subcutaneous illumination between the skin and soft tissue located above cervical part of the fetal spine. We set the calipers on lines that define the fold, so that they were barely visible on the white limit line of the accumulation behind the neck. During the examinations we conducted more measurements and took into consideration only the highest thickness of the nuchal translucency. We carried out the quantitative settings of free β-HCG and PAPP-A from vein blood of patients by applying commercial tests of firm DPC-USA. Tests were based on the analytical *immunochemiluminescence* assay and were realized by using the automated analyzer IMMULITE 2000. Manufacturer of the analyzer is also the firm DPC-USA.

On all pregnant women included in the research we carried out the amniocentesis by standard transabdominal procedure with the ultrasound control, using "free hand" technique, in gestational age of 16 to 17+6 weeks of gestation. We did the puncture by needles with mandrene of 20-22G thickness and aspirated 15-20 ml of amniotic fluid into a syringe without rubber seal. The amniotic fluid sample we received, we were delivering to the Cytogenetics laboratory at GOC CC Kragujevac. All received results were deposited into the unique data base with required logistic control.

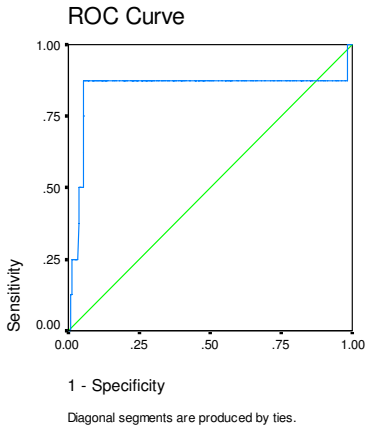
RESULTS

After conducted combined test in total sample of pregnant women, we find the following individual values of the examined parameters (Table 1).

Table 1 Difference between values of free beta-subunit of HCG, PAPPA and NT in the examined groups of pregnant women (total sample); n=317

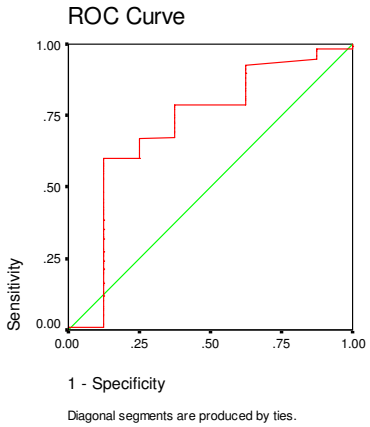
Parameters	Free-β HCG In ml/ml	PAPP-A In ml/ml	NT mm
Pathological karyotype	114.00	1.36	2.55
Physiological karyotype	19.20	1.84	1.90
Mann Whitney (U)	704.5	2191	621.5
p	0.000	0.543	0.000

We notice the statistically significant difference in values of free β HCG and NT in examined groups of pregnant women ($p< 0.05$). Parameter PAPP-A doesn't show statistically significant difference in examined groups of pregnant women. We also find the same characteristics of the examined parameters in the ROC curves analysis in the examination of predictive characteristics of specified parameters. (Figure 1 and 2).



Field below ROC curve 0.846 (95% Confidence interval 0.628-1.064)

Figure 1. Probability of the predictive value of free fraction beta HCG



Field below ROC curve 0.715 (95% Confidence interval 0.508 – 0.921)

Figure 2. Probability of the predictive value of PAPP-A

The distribution of parameter values necessary for the methodologically regular measurement of the fetal NT according to the instruction of the Fetal Medicine Foundation - FMF, is on the table 2.

Table 2. Review of the middle values (MV) and standard deviations (SD) of the ultrasonographic parametres and gestational age in total sample of pregnant women

Parameters	Pathological karyotype =16	Control group=301	P
Nuchal translucency (mm)	2.49±0.37	1.92±0.39	<0.05
Crown-rump length (mm)	60.12±8.48	64.83±8.23	p>0,05
Gestational age (days)	85.69±3.98	87.40±7.10	p>0.05

Analysis of the value distribution of the NT thickness measurement showed that the distribution was regular and that measurements were being set regularly around the median (44% below and 56% above median), which was in accordance with the criteria for quality control established by

Fetal Medicine Foundation (FMF) and was supposed to be 40- 60% above median. Distribution of fetal NT for given CRL in examination is no different from the established distribution of FMF used as a standard. On the basis of that, our measurements of NT thickness can be considered regularly conducted and usable in further examination.

Diameter of nuchal translucency did significantly statistically differ in the examined groups of pregnant women ($p<0.05$). Crown-rump length and gestational age were not different statistically ($p>0.05$). Using the contingency table, we set the predictive value of the combination of ultrasonographic and biochemical markers after taking over the results of amniocentesis (Table 3).

Table 3 Contingency table formed on the basis of data processing in the total sample of pregnant women after amniocentesis

Test result	Disease present	Disease absent	Total
Positive	SP =15	LP= 1	SP+LP =16
Negative	LN= 3	SN=298	LN+SN = 301
Total	SP+LN =18	LP+SN =299	N = 317

Table 4. Calculation of the probabilities and predictive values of the parameters of the combined test in relation to the result of the early amniocentesis

Parameter	Value	Confidence interval 95% CI
Sensitivity	0.9375	0.6977 -0.9984
Specificity	0.9900	0.9712 - 0.9979
Positive predictive value	0.8333	0.5858 - 0.9642
Negative predictive value	0.9967	0.9815 - 0.9999
Prevalence	0.0505	0.0291 - 0.0807
False positive rate	0.0100	0.0046- 0.0245
False negative rate	0.0625	0.0145- 0.0998
Positive likelihood ratio LR+	94.0000	30.2937 - 292.0653
Negative likelihood ratio LR-	0.0631	0.01746 - 1.2712
Overall test accuracy	***0.9873***	0.07215- 0.9981

Estimation of probability that some disease is present before testing is called pretest probability ("a priori probability"). Pretest probability is received on the basis of available information about the patient, also including the testing previous to the actual one. Estimation of the probability of disease after the testing is called posttest probability ("a posteriori probability"). Posttest probability is less or higher than pretest probability depending on the test results. Measures of diagnostic accuracy (sensitivity, specificity) can not directly answer the important clinical questions:

1. If the disease pretest probability is known, and the examinee is positive on the test, what is the probability that he/she really has the disease?
2. If the disease pretest probability is known, and the examinee is negative on the test, what is the probability that he/she really doesn't have the disease?

These questions can be answered by application of the pretest odds of the disease and the credibility ratio. Disease odds ratio is the ratio of probability that the disease is present (p) and probability that is not present (1–p):

Odds=p/1-p

According to that, pretest disease odds are:

Pretest odds=pretest probability /1- pretest probability

Likelihood ratio (LR) is the probability ratio of the certain test result (+ or -) of the examinee who has the disease divided with the probability of the same result of the person who doesn't have the disease. Two types of likelihood can be calculated:

1. Likelihood ratio of the positive test (LR+) is the ratio of sensitivity and false positive ratio (1–specificity):

LR+ = sensitivity / 1- specificity

2 Likelihood ratio of the negative test (LR-) the ratio of sensitivity and false negative ratio (1–sensitivity) and specificity:
LR- = 1- sensitivity / specificity

Likelihood ratio shows how the test result can alter the pretest disease probability. LR+ shows how much the test result increases disease probability, LR- shows how much the test result decreases disease probability.
Likelihood ratios are not under the influence of the disease prevalence.

Likelihood ratio can help measuring the posttest probability. How big the change from pretest to posttest probability is, depends considerably on the values of the likelihood ratio. It is desirable for (LR+) to have the highest values and (LR–) to have values close to 0. For calculating the posttest disease probability, posttest odds are first to be calculated:
1. For positive test result:
Posttest odds = pretest odds × LR+
2. For negative test result:
Posttest odds = pretest odds × LR–
Posttest probability is obtained by the formula:
Posttest probability= posttest odds/1+ posttest odds
According to the literature data, the diagnostic accuracy of the combined test, in relation to the result of the early amniocentesis (referral standard) is: sensitivity 0.88, specificity 0.90. In our sample sensitivity is 0.94 and specificity 0.99.
Likelihood ratios:
LR+ =0.94/1-0.99=94.00
LR– =1-0.94/0.99=0.06
Pretest probability that the pregnant woman carries the fetus with the chromosomal abnormality is 1:250=0.004
Pretest odds =0.004/0.996=0.004
If the test is positive:
Posttest odds = pretest odds x LR+ = 0.004 x 94 = 0.3760
Posttest probability=posttest odds/1+ posttest odds=0.3760/1+0.3760=0.2732
If the test is negative:
Posttest odds = pretest odds × LR– = 0.004 × 0.06 = 0.00024
Posttest probability=posttest odds/ 1+posttest odds= 0.00024/1+0.00024=0.00024.

Table 5. Review of the influence of the combined test on the pretest odds and probability of the outcome in relation to the likelihood ratio in case of positive and negative outcome

Pretest odds/ probability	Posttest odds/ Positive test	Posttest odds/ Negative test	Likelihood ratio/LR+	Likelihood ratio /LR-	Posttest probability/ Positive test	Posttest probability/ Negative test
0.0040	**0.37600**	**0.00024**	**94.00000**	**0.06000**	**0.27320**	**0.00024**

DISCUSSION

In our research, we had nine (2.84%) pregnant women with numeric aberrations in total and seven (2,21%) pregnant women with structural aberrations in fetuses which could be explained by the fact that the sample was preselected, because all pregnant women were sent to the Genetic Counseling at GOC CC Kragujevac (Table 3), for some suspicious reason (positive personal and/or family case history, age of the pregnant woman, giving birth to child with chromosomal aberrations and/or fetal anomalies in previous pregnancies etc.). Similar results were reported in the study conducted in Great Britain in 2000, stating that the total incidence of Down syndrome 2, 1 on 1000 deliveries, which was 50% more than in the national reports, WALD *et al*. (2003). The importance of the nuchal translucency (NT) measurement in screening DS during the first trimester of the pregnancy was recognized back in 1990. With the limit value of 3mm nuchal translucency thickness, the detection rate DR is 64%, STOJILJKOVIĆ- MIKIĆ and RODECK (2003); HADDOW *et al.* (1998). Screening sensitivity of *chromosomopathies in comparison to NT was 75% with the value of false positive ratio of* 2.1%, WALD (1996); PIDOUX *et al*. (2007). In our sample 11 pregnant women in total from the group of 16 had measured value of NT above the median for the given CRL in the group of pathological karyotypes that was 68, 75%. By the analysis of the total sample we find that with 26 pregnant women we measure NT of 2.55mm above median for the given CRL and by invasive diagnostics we confirm 16 cases of chromosomal fetal aberrations or 61.54% (Table 2). Methodology of the combined test (Table 1) indicates that the ultrasound screening is done first and after that to set the level of Free ß HCG-a and PAPP-A, whereas risks are calculated as the combination of these two information, WALD *et al*. (1996). For a certain gestation, level of Free β-HCG and PAPP-A represents the factor of probability which is multiplied with the initial risk in order to calculate the new one, SNIJDERS *et al.* (1996). Difference in the concentration of free β-HCG between normal pregnancies and those with trisomy 21 is increasing, and difference in the level of PAPP-A is decreasing with the age of the pregnancy. There is no significant connection between thicknesses of the fetal NT, level of free β-HCG or PAPP-A in maternal serum in pregnancies with trisomy 21 in relation to the normal pregnancies, so ultrasound and biochemical markers can be combined in order to get more efficient screening. Numerous studies have confirmed the connection between the low level of PAPP-A and trisomy 21 during the first trimester, SPENCER (2001); WALD *et al*. (2003a); MALONE *et al*. (2003). In normal pregnancies level of PAPP-A in maternal blood is increasing with gestation, and in pregnancies with trisomy 21 is decreasing (MoM<0.5). By setting the value of PAPP-A, it is possible to detect 52% of DS cases with 5% false positive results, SPENCER (2001). In pregnancies with trisomy 21, the level of free beta-subunit of choriogonadotropin (Free β-HCG) is increased between 8 and 14 week of gestation, LONČAR *et al.* (2010); PIDOUX *et al*. (2007). The level of free β HCG in maternal blood decreases normally with the gestation, and in pregnancies with trisomy 21 level of free β HCG increases (MoM>2.0), CUNNINGHAM *et al*. (2005); WELLESLEY *et al.* (2002). On the basis of free β-HCG level, detection rate DR amounts to 42%

with 5% false positive findings, LONČAR *et al*. (2010). Frequency of false positive results, according to the available literature, is estimated at 5%, HALLAHAN *et al*. (2000); BRIGATTI, MALONE (2004); NICOLAIDES (2004); SPENCER *et al.* (2004). Our research has shown that the rate of the false positive findings is 1%, and that free β HCG is more sensitive predictor than PAPP-A. Other authors have reported the identical conclusion, NICOLAIDES (2004). Predictive value of the individual biochemical markers is represented at the charts 1 and 2 by setting the area below ROC curve. In final result review of the combined test predictive value of our sample of pregnant women, we find the following facts: sensitivity of the test is 94%, specificity is 99%. Positive predictive value of the test is 0.83, and negative predictive value of the test is 0.99 (99%). Positive likelihood ratio (LR +) is 94.00 and negative likelihood ratio (LR -) is 0.06 (Tables No. 4 and 5). We have confirmed already published positive qualifications of this screening method, LONČAR *et al.* (2010); KRANTZ (2000); CROSSLEY *et al.* (2002) and pointed out to its justification in every day clinical practice, SPENCER *et al.* (2000) regarding that posttest odds rate in case of positive screening increases several times over (almost 90 times). In the available literature we don't find the reports that have the calculation of the credibility of the combined test and prediction of posttest odds of this screening method. It is very important to mention to the patients that it is the process of screening and not the final diagnosis, CROSSLEY *et al*. (2002). It can be given only on the basis of invasive intervention and defining of the fetal karyotype.

CONCLUSION

A. By examining the sensitivity and specificity of the combined screening test in the period of 11.-13+6 weeks of gestation, we find that sensitivity of the test is 0.94 (94%), and its specificity 0.99 (99%).

B. Pretest probability that the pregnant woman carries the fetus with the chromosomal abnormality is 1:250 or 0.004. Posttest odds after the combined test to discover this abnormality is 0.3760, and probability of the same case is 0.2732 if it happens that the test result is positive.

C. Posttest odds after the combined test and the probability of the same case is identical if it happens that the test result is negative and amounts to 0,0002.

List of Abbreviations
CRL - embryonic crown-rump length
NT - fetal nuchal translucency
Free βHCG - free beta-subunit of choriogonadotropin
PAPP-A - pregnancy-associated plasma protein A
MoM - Multiple of the Median

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VERODOSTOJNOST KOMBINOVANOG TESTA U PRENATALNOJ DIJAGNOSTICI

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I z v o d

Kongenitalne anomalije su uzrok perinatalne smrti u 20-25% slučajeva, dok se 3% dece rodi sa većom ili manjom malformacijom. Cilj rada je bio da se ispita prediktivna vrednost i odredi odnos verodostojnosti rezultata kombinovanog testa. Od 317 ispitanih trudnica imali smo šesnaest (5.05%) trudnica sa patološkim rezultatom kariotipa nakon amniocenteze i to: devet (2.84%) trudnica sa numeričkim aberacijama fetusa i sedam (2.21%) trudnica sa strukturnim aberacijama kod fetusa. Pri određivanju ultrasonografskih parametara kombinovanog testa koristili smo standarde Fondacije za fetalnu medicinu. Kvantitativna određivanja Free β HCG i PAPP-A vršili smo iz venske krvi pacijentkinja primenom komercijalnih testova firme DPS-USA. Testovi se zasnivaju na analitičkom principu imunohemiluminiscencije i realizovani su upotrebom automatskog analizatora IMMULITE 2000. Proizvođač analizatora je takođe firma DPC-USA. Senzitivnost testa je 94%, specifičnost 99%. Pozitivni faktor verovatnoće [likelihood ratio test (LR +)] iznosi 94.00, a negativni faktor verovatnoće [likelihood ratio test (LR-)] 0.06. Pretest verovatnoća da trudnica nosi plod sa hromozomskom abnormalnošću je 1:250 ili 0.004. Posttest šansa nakon kombinovanog testa da se ova abnormalnost otkrije je 0.3760, a verovatnoća istog dešavanja je 0.2732 pod uslovom da je rezultat testa pozitivan. Rezultat našeg istraživanja potvrđuje opravdanost upotrebe kombinovanog testa u svakodnevnoj kliničkoj praksi obzirom da se odds rate posttesta (posttest šansa) u slučaju pozitivnog skrininga povećava višestruko (skoro 90 puta), a verovatnoća otkrivanja hromozomske abnormalnosti oko 70 puta. Kombinovani skrining test ako se metodološki ispravno upotrebljava ima visoku prediktivnu vrednost u otkrivanju urođenih fetalnih anomalija.

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