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Review

Biochemical Screening of Fetal Aneuploidies and Neural Tube Defects by »Double-Test« in Croatia: A 10 Years' Experience

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A B S T R A C T

The aim of the study is to investigate the efficiency of the second-trimester biochemical screening, with maternal serum alpha-fetoprotein (MS-AFP) and free β-subunit of human chorionic gonadotropin (free β-hCG), during the ten-year period. The study included 11,292 of pregnant women between the 15th and 18th gestational week, who underwent screening from November 1996 to December 2006. The risk for trisomy 21 and trisomy 18 were calculated by computer software, based on a model which generated the final risk for fetal aneuploidies from the pregnant woman's a priori age risk and the likelihood ratio of the distribution of the biochemical markers, according to the second-trimester gestation. With the cut-off value of the final risk ≥1:250, the detection rate for trisomy 21 was 75% (21/28). In women less than or equal to 35, the detection was 57.1% (8/14) and 92.9% (13/14) in those over 35 years, respectively. The detection rate of trisomy 18 was 50% (2/4). The results confirmed that the implementation of double-test, as non-invasive screening for fetal aneuploidies, should be accepted as a complementary method of antenatal care.

Key words: *Down syndrome screening, second-trimester, alpha-fetoprotein, hCG free β-subunit, fetal aneuplodies, neural tube defects*

Introduction

The second-trimester biochemical screening of trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), as well as neural tube defects (NTD) and ventral wall anomalies in fetal development is an established part of the mother and child antenatal care. The biochemical screening with two maternal-serum markers: alpha-fetoprotein (MS-AFP) and free β-subunit of human chorionic gonadotropin (free β-hCG) has been conducted in Croatia since 1996[1,2]. Use of the test is available to pregnant women of all ages, between the 15th and 18th week of gestation. It includes the ultrasound estimate of gestational age by fetal biometry, following the peripheral blood analysis of serum marker concentrations. Individual risk of fetal trisomies is derived from maternal age and the likelihood ratio of the distribution of the biochemical markers, according to the second-trimester gestation. The risk of fetal open NTD is computed on the basis of the measured MS-AFP in relation to the

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median value of the relevant gestational week. The testing costs have been completely covered by The National Institute of Health Insurance for all pregnant women. Although a conclusive national policy on organized implementation has not yet been achieved, this approach ensures a standard of care comparable to other European countries with distinguished and modern concepts of antenatal care[3].

Previous studies have displayed the efficiency of double-test screening of fetal aneuploidies and morphological anomalies, which is determined by the sensitivity and specificity of the selected biochemical markers[4–6]. Since 1996, double-test screening has been performed in the Laboratory of Endocrinology, University Hospital »Sestre milosrdnice«, in addition to a select few of other centres in our country executing biochemical screening with a varied combination of serum markers[7–9].

In this study we present the first long-term retrospective study of the ten-year period of applying second-trimester biochemical screening in Croatia, using the same clinical protocol and standardized analytical methods for serum marker determination.

Materials and Methods

The program of the biochemical screening using maternal age and serum markers MS-AFP and free β-hCG was started in Laboratory of Endocrinology, »Sestre milosrdnice« University Hospital Centre (Zagreb) in November 1996.

At the very beginning, written brochures about the Down syndrome, non-invasive methods of the detection and the characteristics of the biochemical screening were sent to primary and secondary centres of obstetric care all over the country. Pregnant women were informed about the features of the screening, its purpose and limitations, by obstetricians and specially trained midwives and were sent to our Laboratory when decided for the option.

The blood was taken by venipuncture between the 15th and 18th gestational week and serum was separated by means of centrifuge. The samples were frozen at –20°C until analysis or put to procedure on the same day. Each patient submitted a form, which was filled out by a well-versed obstetrician. The form included woman's personal data, parameters referring the course of the pregnancy and fetal biometry defining gestational age (biparietal diameter, femur length, and abdominal circumference). When gestational age estimated by ultrasound examination was found to differ for more than 10 days in relation to amenorrhoea, we recommended revising the assessment of gestational age and recalculated the accurate risk values.

In the period between 1996 and 2000, we measured the concentrations of MS-AFP and free β-hCG with immunoradiometric assay (CIS Biointernational, B.P.GIF--SUR-YVETTE, Cedex, France), and from 2001. until the end of the study, with immunoflorometric assay (»Dual--assay«, Perkin Elmer Live and Analytical Sciences, Wallac Oy, Turku, Finland). Both kits contained monoclonal antibodies for the markers; high-specific antibodies FBT11 were used for the quantitative detection of free β-hCG.

The measured concentrations of the serum markers were expressed as multiples of the median values (MoM) for each marker in correlation of the gestational week of unaffected pregnancies, previously established for the Croatian pregnant women population[1]. The MoM values were corrected for maternal weight and for twin-pregnancy or insulin-dependent diabetes of the mother (IDDM), respectively[10]. Median values were estimated monthly, according to our database.

The calculation of the individual term-risk for trisomy 21, trisomy 18 and NTD, respectively, was enabled by use of the »CIS Prenat' Screen« software[11].

Pregnant woman with the final risk of ≥1:250 was considered to belong to a group with elevated risk for trisomy 21. The cut-off values of MoM MS-AFP <0.7 and MoM free β-hCG <0.3 were taken for the risk of trisomy 18. The value of MoM MS-AFP ≥2.5 was considered as elevated risk for open NTD[1].

In cases of high risk for trisomies, genetic counselling was recommended to the pregnant women in question or, if necessary, an additional ultrasound examination was advised with the aim of revising gestational age and/or the presence of ultrasonographic markers of aneuploidies. When the presence of an anomaly was suspected, or upon a specific personal request on behalf of the patient, amniocentesis and fetal cell karyotyping was performed. The data pertaining to the remainder of the pregnancy period and the results of the diagnostic procedures were collected from the two Laboratories of Cytogenetic analysis in Zagreb, as well as from medical staff from the centres where the pregnant women were first enrolled.

Statistical analyses were performed using MedCalc® statistical software (MedCalc 9.3.9.0, Frank Schoonjans, Mariakerke, Belgium) and descriptive statistics using Excel 7.0, respectively. The level of $p<0.05$ was considered statistically significant.

Results

During the study period, from November the 15th 1996 to December the 31st 2006, a total of 11,292 pregnant women underwent the screening program in our hospital. The majority of the screened population originated from Zagreb and its vicinity, while 5% of pregnant women came from other, more distant parts of the country.

Demographic characteristics of the studied pregnant women are presented in Table1. There were only seven pregnant women of Asian descent, with whom standardized race-specific median values were used for the correct MoM values of the serum markers[11]. The remaining 11,285 women were Caucasian. In twelve pregnant women with IDDM the correction of MoM MS-AFP was performed according to current recommendations[10]. Although the MoM value of the markers and the computed risk were not corrected for the smoking habits of the pa-

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF THE STUDIED PREGNANT WOMEN

Total (N)	11,292
– Singleton pregnancies	11,154 (98.8%)
– Twin pregnancies	138 (1.2%)
Maternal age* (mean±SD)	31.6±4.8
– Range	16–49
<35 yr., N (%)	7,849 (69.5%)
≥35 to <37 yr.	1,850 (16.4%)
≥37 yr.	1,593 (14.1 %)
First delivery	5,255 (46.5%)
Second delivery	3,819 (33.8%)
Third delivery	1,356 (12.0%)
>3 previous births	862 (7.6%)

SD – Standard deviation
* Age at time of the delivery

tients, smoking status was noted at the time of the sampling. In the studied population, there were 1,865 (16.5%) pregnant women who smoked. In 144 (1.3%) of studied women, pregnancy was achieved by the method of assisted reproduction (*in-vitro* fertilization).

The mean gestational age at sampling was 15+5/7 weeks; the majority of tests were performed between 15+0/7 and 16+6/7 weeks (N=5053, 44.7%). Between the week 14+0/7 and 17+6/7, a total of 10,194 (90.2%) of pregnant women underwent testing. Gestational age based on the last menstrual period was used in less than 3% of subjects.

The distribution of tested pregnant women during the study period, the number of women at risk for trisomies and the number of amniocenteses performed per year are illustrated on Figure 1. Linear regression analysis found a statistically significant trend in the number of participants over the study period ($p<0.001$). In the period from 1997 to 2000, the number of amniocenteses exceeded the number of pregnancies at high risk

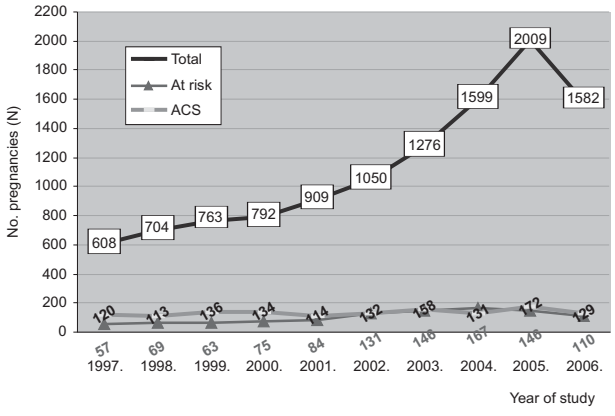

Fig. 1. Number of screened, number at high-risk and amniocenteses (ACS) in pregnant women during the study period.

after biochemical screening. In addition, until the year 2000, the proportion of pregnant women at age of 37 or older was on average 19.0% with respect to 10.5% in the period from 2001–2006. Accordingly, the majority of amniocenteses before the year 2000 were performed mostly due to concern over advanced maternal age rather than on the basis of the elevated risk estimates after screening alone.

Of the studied pregnant women, we found a total number of 1,062 (9.4%) with the final risk for trisomy 21 of ≥1:250. Out of 28 pregnancies with trisomy 21 in our study population, 21 affected cases were detected through biochemical screening; the average detection rate was 75% (65.2 to 86.7, with a 95% confidence interval). In pregnant women ≤35 years of age, the detection rate was 8/14 (57.1%) and in those older than 35 the detection rate was 13/14 (92.9%), respectively. The difference in the proportions was not statistically significant ($p=0.07$; Fisher's exact test). Only one pregnant woman declined the termination of pregnancy after being informed of the diagnosis. The number of cases with trisomy 21, according to mothers' term-age, the detection rates and false-positive rates are presented in Table 2.

Table 3 summarizes the incidence of Down syndrome in relation to risk bands, the number of detected pregnancies in biochemical screening (sensitivity) and the corresponding false-positive rates. The majority of affected pregnancies were categorized at risk ≥50 after bio-

TABLE 2
RESULTS OF DOWN SYNDROME SCREENING BY MATERNAL AGE BAND

Age (yr.)	Total DS	Detected DS	No. Pregnancies	FPR (%)
<20	1	1	149	2.0
20–25	0	0	1,119	2.7
26–30	4	3	3,104	3.9
31–35	9	5	4,424	6.8
36–40	10	9	2,275	13.5
>40	4	4	221	37.1

DS – Down syndrome
FPR – false-positive rate

TABLE 3
FREQUENCY OF DOWN SYNDROME CASES BY RISK BAND

Calculated risk	DS (N)	Positive	FPR (%)	OAPR
>1:50	11	188	1.6	1:17
1:51 to 1:100	4	197	1.7	1:49
1:101 to 1:150	3	193	1.7	1:64
1:151 to 1:200	2	198	1.7	1:99
1:201 to 1:250	1	187	1.6	1:187
<1:250	7	10,329	–	–

DS – Down syndrome
FPR – false-positive rate

TABLE 4
OTHER CHROMOSOME ABNORMALITIES IN PREGNANCIES AT RISK ≥1:250

Abnormality	Karyotype	Outcome
Mosaic trisomy of autosomes	47,XX,+9/46,XX	Born alive
	47,XY,+20/46,XY	Miscarried
	47,XY,+22/46,XY	Miscarried
	47,XX,+mar/46,XX	Born alive
Turner syndrome	45,X	Born alive
Monosomy X mosaicism	45,X/46,XX (5 cases)	Born alive
	45,X/46,XY	Born alive
Klinefelter syndrome	47,XXY (2 cases)	Born alive
Balanced translocations	46,XY,t(9;19)(q21;p13)pat	Born alive
	46,XY,t(4;7)(q23;q11.2)mat	Miscarried
	46,XX,t(2;15)(q24.2;q11.2)dn	Born alive
	46,XY,t(10;17)(q26;q21)mat	Born alive
	46,XY,der(14;21)(q10;q10)	Miscarried
Non-balanced translocations	46,XX,der(4)t(3;4)(q23;q35)pat	TOP*
	46,XX,der(9)t(9;16)	Miscarried

* TOP – Termination of pregnancy

chemical screening (N=11); in addition to other 18 affected pregnancies that were found at risk ≥150.

Also, there were 59 (0.5%) pregnant women with an elevated risk for trisomy 18. In that group, two cases of trisomy 18, out of 4 in the study population, were detected on the basis of biochemical screening, giving a detection rate of 50%. The two other cases were detected by ultrasound examination. In all four cases, the diagnosis was confirmed by cytogenetic analysis. Beside the pregnancies with fetal trisomies 21 and 18, found in the pregnant women population under risk ≥1:250 after the biochemical test, there were 20 cases with other chromosomal anomalies, which are presented in Table 4.

Table 5 is a summary of neural tube and ventral wall defects in screened pregnancies, revealed on the basis of cut-off MS-AFP MoM ≥2.5. All of the fetal developmental defects were unequivocally detected during additional ultrasound examinations and the pregnancies were terminated.

TABLE 5
DETECTED FETAL MORPHOLOGICAL ANOMALIES (MS-AFP MOM ≥2.5

Anomaly	Number of cases
Neural tube defects	
– Open defects	6
– Hydrocephalus	2
Omphalocela	1
Gastroshisis	2

MS-AFP – maternal serum alpha-fetoprotein
MoM – Multiple of the Median

Discussion

Non-invasive methods of screening for fetal trisomy 21, trisomy 18 and NTD are widely accepted as complementary treatments in pregnancies primarily due to their simple use and admissibility to pregnant women of all ages. In most centres in Croatia with organized specialized units of antenatal care, diagnostic procedures (*chorionic villus* sampling, amniocentesis) are recommended to pregnant women at 35 or over years of age, and to those with inherited personal and/or family medical history[12]. On average, in four hospital's maternity units in Zagreb, around 11,500 deliveries are registered each year. These data suggest that 10% of all pregnant women that underwent yearly screening examinations were cared for in our Laboratory, most recruited from the departments of gynecology of Public Health Centres, outpatient clinics and other clinics of obstetrics. In the last ten years, since biochemical and ultrasonographic screening of aneuploidies have been implemented in Croatia, there is an increasing number of pregnant women who have decided to accept this opportunity. In this study, we have shown a statistically significant increase of pregnant women undergoing double-test biochemical screening from the year 1996 to 2006. Until now, there were no elaborated multi-centered data on prenatal screening results in our country. Still, published papers suggest that the acceptance of screening methods is to a large degree based on specific educational and socio-economic backgrounds of the female population in the studied regions of Croatia[13]. On the other hand, there is evidence of increasing numbers of women bearing their first child at a later age. It is possible to assert that under such circumstances, pregnant women accept invasive diagnostic procedures unwillingly, and the use of invasive procedures becomes limited when facing a potentially high-risk pregnancy[14,15].

In our research, the mean maternal age of 31.6 years, estimated at term of delivery, is relatively higher than in other studied populations, but corresponds to the age distribution data of Croatian pregnant women in the period coincident with our investigation[16]. In regard to the distribution of the studied pregnant women according to their age risk for trisomy 21, the theoretical number of fetuses with trisomy 21 at term would be 28.2 and this corresponded well with the 28 cases registered in pregnancies under study. On the basis of the cut-off value of biochemical screening we were able to detect 21 of fetuses with Down syndrome, which yielded the overall detection rate of 75%, congruent with the results obtained earlier on a much greater number of pregnancies[5,6]. Some authors have suggested that, when reporting detection rates of trisomy 21 from intervention trials, allowance must be made for the natural loss of affected fetuses between the second-trimester and term[17]. If a fetal loss rate of the recommended 12% was applied, the actual detection rate at term in our study would have been 71.7%. Our results confirmed that the detection of trisomic pregnancies was more successful in pregnant women over age of 35, compared to those younger than 35,

although we were not able to prove the significance of the difference, probably because of the limited number of Down syndrome pregnancies. However, the detection rate (sensitivity of the test) is a function not only of the *a priori* age risk, but is also dependent on the properly chosen cut-off likelihood ratio, which correctly estimates the high-risk pregnancy. The results presented in this report have shown that 20 out of 21 true-positive pregnancies with Down syndrome would be considered as high-risk even at the cut-off value 1:200. The outcomes of controlled, randomized studies in the world have shown that the risk of amniocentesis-related complications of pregnancy ranges between 0.5 – 0.7%, compared to the control population, which primarily encompass spontaneous fetal loss before the 24th week of gestation[18–20]. When these risks are applied to pregnant women undergoing biochemical screening, the decision of implementing an invasive procedure should be well thought through when the final risk of a test is ≥1:200. However, there are different other indications for diagnostic procedures in pregnancy (maternal age, abnormal ultrasound scan, inherited personal or family medical history, exposition to toxic and mutagenic agents). Nevertheless, competent medical services should allow the pregnant women to develop and actively voice their own personal attitude toward the tests and/or diagnostic procedures, supplying that attitude be developed through informed consent[21,22].

This implies that the primary purpose of biochemical screening is to detect those pregnancies at high-risk for trisomy 21 and 18 and NTD, but screening procedures remain less successful in discerning other fetal numeric and structural chromosomal abnormalities. In the pregnant women included in this study, 20 chromosomal aberrations different from trisomy 21 and 18 were found through cytogenetic analysis. They were identified through amniocentesis performed because of high age risk or results of the screening tests.

Aside from the indisputable contribution of second-trimester biochemical screening in pregnant women in Croatia, significant progress has been made with the implementation of systematic ultrasound examination in the early weeks of pregnancy. A statistical proof of that claim can be found in the latest published report of the Croatian National Institute of Public Health that claims that more than 75% of all pregnant women underwent an ultrasound examination before the 14th week of gestation during the year 2006[16]. This figure speaks not only in favor of a higher degree of antenatal care, but also introduces new opportunities of further planning and developing other methods of prenatal screening for fetal anomalies. Alternatively, our results show a slightly lower number of pregnant women that underwent second-trimester biochemical screening in the year 2006, compared to the preceding study period. Both of these facts could be explained with the introduction of new, first-trimester combined ultrasound-biochemical screening tests in the »Sestre milosrdnice« University Hospital Centre. In our opinion, years of practical experience in the second-trimester screening program was a suitable platform for the introduction the first-trimester combined screening for fetal aneuploidies. In addition, the second-trimester biochemical test should remain available for the pregnant women who were late for the earlier frame of screening, and for those targeted for the screening of neural tube and ventral wall defects.

Modern trisomy screening combines the first-trimester biochemical markers (free β-hCG + Pregnancy associated plasma protein-A, PAPP-A) with the fetal nuchal translucency measurement (NT). Since 1998, when Snijders and co-workers presented the large prospective intervention study of The Fetal Medicine Foundation, ultrasound screening with NT for Down syndrome has been increasingly used in the routine practice[23]. The implementation of the first-trimester screening of fetal trisomies in Croatia, using the combination of early biochemical markers and NT measurement, has been published previously[24]. We have shown that the first-trimester combined screening was superior to the second-trimester biochemical screening, because it provided a greatly reduced false-positive rate[25]. One of the main challenges to our health systems will be to insure that the ultrasound measurements of the markers of fetal trisomies are interpreted by competent and accredited sonographers[26]. On the other side, analytical laboratory that provides the first-trimester biochemical analyses should follow the recommendations of the internal and external quality control assessment[27].

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PRENATALNI PROBIR FETALNIH KROMOSOMOPATIJA I OŠTEĆENJA NEURALNE CIJEVI DVOSTRUKIM BIOKEMIJSKIM TESTOM: ISKUSTVA NAKON 10 GODINA PRIMJENE TESTA U HRVATSKOJ

S A Ž E T A K

Cilj ovog preglednog istraživanja je prikaz rezultata desetogodišnje primjene biokemijskog testa probira fetalnih kromosomopatija, pomoću alfa-fetoproteina (AFP) i slobodne podjedinice β-hCG (sl. β-hCG) u serumu trudnica tijekom drugog tromjesečja. Istraživanje je obuhvatilo 11,292 trudnice između 15. i 18. tjedna trudnoće koje su pristupile probiru od studenog 1996. do prosinca 2006. godine. Individualni rizik za fetalne trisomije 21 i 18 u trudnica na termin poroda izračunavali smo pomoću računalnog programa (PRENAT' SCREEN™). Konačni rizik fetalnih aneuploidija izračunava se množenjem dobnog rizika trudnice (*a priori*) s omjerom vjerojatnosti, a koji ovisi o odstupanju MoM vrijednosti biokemijskih biljega u odnosu na normalnu trudnoću. Na osnovi granične vrijednosti rizika trisomije 21 (≥1:250) stopa detekcije bila je 75% (21/28). U žena od 35 godina i mlađih, stopa detekcije bila je 57,1% (8/14), a u starijih od 35 godina bila je 92,9% (13/14). Stopa detekcije trisomije 18 bila je 50% (2/4). Rezultati istraživanja potvrdili su vrijednost dvostrukog biokemijskog testa, kao neinvazivne metode probira, u okviru antenatalne zaštite.

ABREVIATIONS

free β-hCG – Free β-subunit of human chorionic gonadotropin
MS-AFP – Maternal serum alpha-fetoprotein
PAPP-A – Pregnancy associated plasma protein-A
NT – Nuchal translucency
NTD – Neural tube defects
MoM – Multiple of the median
ACS – Amniocentesis
TOP – Termination of pregnancy
IDDM – Insulin-dependent diabetes mellitus
FPR – False-positive rate
OAPR – Odds of being affected given a positive result