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Professional Paper

COMBINED FIRST TRIMESTER SCREENING FOR FETAL DOWN SYNDROME AT THE SPLIT UNIVERSITY HOSPITAL CENTER: A SEVEN-YEAR EXPERIENCE

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SUMMARY – The aim of this study was to present the results and to explore the success of combined screening at the Split University Hospital Center. A cross-sectional retrospective study was performed, including all pregnant women who underwent combined screening at the Split University Hospital Center from 2011 to 2017. Data were collected from the hospital archives. During the research period, a total of 6898 pregnant women underwent combined screening. With the high risk cut-off value set at 1:250, the sensitivity of combined screening was 81.0% and specificity 96.8% (AUC 0.929, 95% CI 0.859-1.000; p<0.001). The mean value of *a priori* risk of Down syndrome based on age was higher than the one calculated by combined screening (1:487.57 vs. 1:13216.9; p<0.001). The number of women who were *a priori* at a high risk of Down syndrome was significantly higher than the number of those at a high risk based on combined screening results (1457 *vs.* 239; p<0.001). With the increase in women's age, a statistically significant increase was detected in the mean value of *a priori* risk of Down syndrome, as well as in the risk based on combined screening results (p<0.001). Combined screening detected a high risk in 8.09% (118/1457) of pregnant women *a priori* at a high risk of Down syndrome, as well as in 2.22% (121/5441) of pregnant women *a priori* at a low risk of it. Thus, combined screening placed 121 pregnant women *a priori* at a low risk in the high-risk group. Down syndrome was subsequently confirmed in 17 (14.05%) women. Analysis of the combined screening results confirmed the validity of using the said fetal Down syndrome screening method in the study population of pregnant women.

Key words: *Combined first trimester screening; Prenatal diagnostics; Down syndrome*

Introduction

Down syndrome is the most common trisomy, occurring in about 1:650 live births[1]. It is caused by an extra chromosome 21, and most commonly occurs as a consequence of fertilization of a disomic gamete, which is the result of the failure of homologous chromosomes to separate. This failure can occur both in meiosis during gametogenesis, and in the early mitotic divisions of the zygote[2]. The syndrome is often associated with various inherited anomalies, mental retardation, and susceptibility to various diseases[3]. The probability of Down syndrome increases with an increase in mother's age (*a priori* risk), and especially after 36 years of age[4].

Prenatal detection of fetal chromosome abnormalities begins with screening procedures, which always are

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noninvasive and suitable for all pregnant women. The aim is to select the high-risk group whenever the application of further invasive prenatal diagnostics (such as early amniocentesis) is justified[5]. The gold standard among screening methods for fetal chromosome abnormalities in contemporary perinatology is combined first trimester screening[6,7]. Risk calculation is based on the *a priori* risk of the pregnant woman, with regard to her age, as well as ultrasound (nuchal translucency, nasal bone and ductus venosus flow) and biochemical factors from the pregnant woman's blood serum (pregnancy associated plasma protein A [PAPP-A] and beta subunit of human chorionic gonadotropin [β-hCG]). Down syndrome detection by combined first trimester screening amounts to up to 90%, with false-positive findings amounting to 5%[8]. Alternative biochemical screening methods during the second trimester yield less reliable results, and are routinely used as methods of the second order[9]. Combined first trimester screening detects Down syndrome earlier than biochemical tests in the second trimester, which opens the possibility for an earlier, safer and less traumatic termination of pregnancy. A disadvantage is the fact that combined first trimester screening also detects a part of pregnancies with Down syndrome that would end in a miscarriage by the second trimester. Therefore, in cases when a combined first trimester screening is performed, the incidence of abortions for eugenic or medical reasons is slightly higher than when biochemical tests in the second trimester are performed[5,9]. Contemporary screening methods based on the determination and analysis of cell-free DNA fetal fraction in the serum of pregnant women are superior relative to other methods, but have not taken precedence over combined first trimester screening anywhere in the world due to their price[10].

This paper presents the results of the application of combined first trimester screening to the population of pregnant women at the Split University Hospital Center, Split, Croatia.

Subjects and Methods

A retrospective cross-sectional study was carried out. The study involved all pregnant women who underwent combined first trimester screening for fetal chromosome abnormalities at the Split University Hospital Center from January 1, 2011 to December 31, 2017. Relevant data were collected from digital archives of the Department of Medical Laboratory Diagnostics, as well as from the archives of the Department of Gynecology and Obstetrics. The following data were taken into account: (a) age of participants, (b) gestational age, (c) values of *a priori* risk of fetal chromosome abnormalities based on the pregnant women's age, (d) values of risk of fetal chromosome abnormalities calculated by combined first trimester screening, (e) previous implementation of combined first trimester screening in women to whom abortion was approved for eugenic or medical reasons, and (f) previous implementation of combined first trimester screening in women who bore a child with chromosomal abnormalities.

The ultrasound part of the screening was performed by means of an Aloka SSD 3500 SX ultrasound device. Biochemical analysis was performed by ElectroChemiLuminiscence (Elecsys)® Roche method for free ß-hCG and PAPP-A. Combined first trimester screening was performed by the Roche SsdwLab V5.0 software that was granted by Fetal Medicine Foundation accreditation.

The calculated probability of having a child with trisomy 21 higher than 1:250 was considered to be high-risk, while the probability lower than this value was considered as low-risk. *A priori* high risk of fetal Down syndrome based on the age of pregnant women implies the age of 36 years and above, while *a priori* low risk implies the age under 36 years.

The study was approved by the Research Ethics Committee of the Split University Hospital Center (Class: 500-03/18-01/19; Ref. No.: 2181-147-01/06/M.S.-18-2) as of April 10, 2018.

Statistical analysis

The Kolmogorov-Smirnov test was performed in order to assess the normality of the variables. Quantitative variables were described as mean ± standard deviation (M ± SD). Qualitative variables were analyzed by means of the χ^2-test, while quantitative variables were analyzed by means of the ANOVA. Pearson's correlation coefficient was applied in order to determine the association between variables. Sensitivity, specificity and diagnostic accuracy were calculated by means of the Receiver Operating Characteristics (ROC) analysis, indicating the area under the curve (AUC) value, relevant 95% confidence intervals (CI) and p-value. The level of statistical significance was set at $p \leq 0.05$. Statistical analysis was performed by means of SPSS for Windows® (version 25.0, IBM Corp., Armonk, NY, USA) and Microsoft Excel for Windows 11.0 (Microsoft Corporation).

Results

During the observed seven-year period, a total of 8423 screenings for fetal chromosome abnormalities was performed at the Department of Gynecology and Obstetrics, Split University Hospital Center, which amounted to 27.28% of all births. Combined first trimester screening was performed in 6898 (81.89%) pregnant women and biochemical tests in the second trimester in 1525 (18.11%) pregnant women. The share of combined first trimester screening gradually increased over time, from 55.66% at the beginning to 91.13% in the last study year. At the time of screening, the highest number of pregnant women (n=2758, 39.99%) were 30-35 years old. In addition, 70 (1.01%) women were younger than 20, and 652 (9.45%) of them were between 20 and 25 years old. Also, 1891 (27.41%) women were between 25 and 30 years old, while 1391 (20.17%) women were between 35 and 40 years old, and only 136 (1.97%) of them were older than 40.

Combined first trimester screening was performed between the 10th and 14th week of pregnancy. The highest number of pregnant women underwent screening in the 12th (n=3375, 48.93%) and 13th (n=2611, 37.85%) week of pregnancy. However, 12 (0.17%) women underwent screening in the 10th week, 586 (8.50%) women in the 11th week, and 314 (4.55%) women in the 14th week of pregnancy.

The low-risk combined first trimester screening result was calculated for 6659 (96.5%) pregnant women, with 4 (0.06%) results turning out to be false-negative. Out of 239 high risk results, Down syndrome was confirmed in 17 (7.1%) cases. Out of the total of 21 pregnancies with Down syndrome, combined first trimester screening successfully detected 17 (80.1%) of them.

The combined first trimester screening found 239 pregnant women at a high risk of Down syndrome. In the same period, 94 early amniocentesis procedures were indicated based on the results of combined first trimester screening, meaning that the approximate acceptance of early amniocentesis amounted to 40%.

The AUC shows diagnostic accuracy, and amounted to AUC 0.929, 95% CI 0.859-1.000, p<0.001, for the combined first trimester screening for Down syndrome of the study population (Fig. 1). With the specificity fixed at 95%, the sensitivity of the combined first trimester screening was 81% for the study population. With the cut-off value fixed at 1:250, the sensitivity of the combined first trimester screening was 81% and specificity 96.8%.

As for the total sample, the mean value of *a priori* risk of Down syndrome based on the age of pregnant women was 1:487.57, and was statistically significantly higher than the mean risk value calculated by means of combined first trimester screening, which was 1:13216.9 (ANOVA, p<0.001). With the increase in the age of pregnant women, the mean value of *a priori* risk of fetal Down syndrome based on age increased, and so did the risk calculated by means of combined first trimester screening. The difference in the mean value of *a priori* risk based on age, as well as on the results of combined first trimester screening between age groups was statistically significant (ANOVA, p<0.001). Both risks increased with the age of pregnant women. *A priori* risk based on age was higher than the risk calculated by means of combined first trimester screening in all age groups (Table 1).

Analysis of the study group showed that there was a positive correlation between *a priori* risk of fetal Down syndrome based on age and the risk calculated by means of combined first trimester screening (r=0.377, p<0.001). With the increase of *a priori* risk based on age, the value of the risk based on combined first trimester screening increased as well, and *vice versa*.

Table 2 shows comparison of the number of pregnant women *a priori* at risk of fetal Down syndrome and number of pregnant women at risk based on the

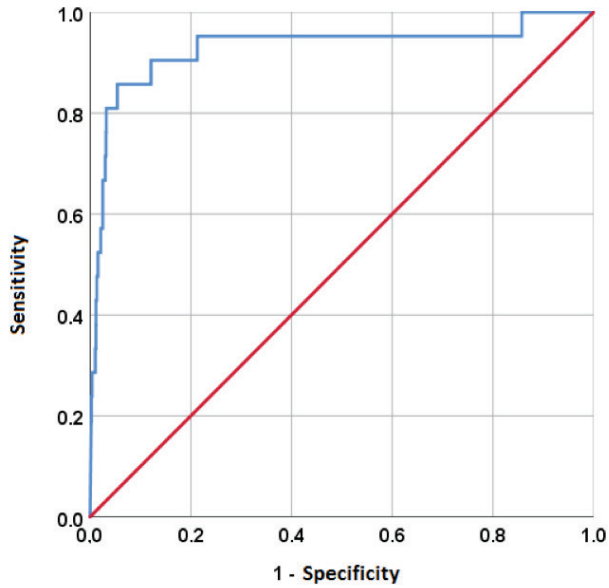

Fig. 1. Receiver Operating Characteristic (ROC) curve for combined first trimester screening of the study population.

Table 1. Mean values of a priori risk of fetal Down syndrome based on age and risk calculated by means of combined first trimester screening in different age groups

	Age group (years)					
	<20	20-25	25-30	30-35	35-40	>40
A priori risk based on age (mean)	1:928.48	1:872.04	1:702.1	1:415.24	1:179.53	1:51.84
Risk based on combined screening (mean)	1:24583.71	1:22420.54	1:19529.69	1:11223.23	1:4859.9	1:1372.82

Table 2. Comparison of the number of pregnant women a priori at risk of fetal Down syndrome based on age and number of those at risk based on the results of combined first trimester screening, with the cut-off value set at 1:250

Risk group	Risk >1:250	Risk <1:250	p
A priori risk based on age, n (%)	1457 (21.1)	5441 (78.9)	<0.001*
Risk based on combined screening, n (%)	239 (3.5)	6659 (96.5)	

*χ^2-test

results of combined first trimester screening, with the cut-off value set at 1:250. There were 1457 (21.1%) pregnant women *a priori* at a high risk based on age, while 239 (3.5%) women were at a high risk based on the combined first trimester screening results. The difference between the number of pregnant women at a high risk based on age and number of women at a high risk based on combined first trimester screening was statistically significant (χ^2=997.3242, p<0.001).

Out of 1457 pregnant women *a priori* at a high risk of fetal Down syndrome based on age, high risk was detected by means of combined first trimester screening in 118 (8.09%) women, with trisomy 21 being confirmed in 10 cases. Out of 5441 pregnant women *a priori* at a low risk of fetal Down syndrome, combined first trimester screening detected 121 (2.22%) women at a high risk, with trisomy 21 being subsequently confirmed in 17 (14.05%) cases.

Discussion

Nowadays, combined first trimester screening represents the gold standard among fetal chromosome abnormality detection techniques[6,7]. The fact that it is performed in the first trimester constitutes its great advantage. All of its characteristics show that it is more successful than previously widely used biochemical tests and ultrasound screening in the second trimester[9]. Successful detection of up to 90% of Down syndrome cases with false-positive results amounting to 5% is expected[11,12]. As for the population, this means that 5% of all screening subjects will be characterized as high-risk. By carrying out invasive prenatal diagnostic methods, by means of which chromosome abnormalities can be proven, 90% of all Down syndrome cases will ultimately be detected. The remaining 10% will remain 'unidentified' within the group of 95% of women at a low risk based on screening results.

In 2006, systematic application of combined first trimester screening was initiated in Croatia (Zagreb), at the Sestre milosrdnice University Hospital Center[13]. At the Department of Gynecology and Obstetrics, Split University Hospital Center, combined first trimester screening was initiated in 2011, and it makes up about 90% of all screenings. Prenatal screening at the Split University Hospital Center is applied to more than a quarter of all pregnancies (27.28%). Acceptance of prenatal screening for fetal chromosome abnormalities by pregnant women in developed countries varies from 20% to more than 90%[14]. The most significant factors are adequate awareness and the possibility of

performing the test during a routine pregnancy check-up. However, one should not ignore the level of education, as well as religious views of women, and many other factors[14-17]. The evidence for the foregoing is a very small share of pregnant women who undergo screening in countries where prenatal care is not part of the primary health care[15]. In countries where the OSCAR program is accepted as a standardized model for informing pregnant women, performing combined first trimester screening and obtaining the results on the same day, the acceptance of combined first trimester screening reaches 98%[18].

Our results show that the acceptance of combined first trimester screening gradually increased over time, as during the first few years after it had been introduced, a large proportion of prenatal screening methods for fetal Down syndrome still consisted of biochemical tests in the second trimester. Over time, more and more pregnant women started accepting the newly introduced combined first trimester screening, which had been unknown to them until then. That may also partly be because gynecologists started dedicating more time to introducing pregnant women to the combined first trimester screening. Combined first trimester screening is undoubtedly better and more reliable and has therefore replaced second trimester biochemical tests, as well as started being used more often[9].

At the time of carrying out the combined first trimester screening, 77.86% of pregnant women were younger than 35. Most women were aged between 30 and 35 years (39.99%), while the lowest number of them were aged under 20 (1.01%) and over 40 (1.97%). These results are in harmony with the report compiled by the Croatian Institute of Public Health regarding the age of new mothers in Croatia[19]. In 2015, 73.6% of pregnant women who underwent combined first trimester screening in California were younger than 35[20]. The results from Korea were almost identical, as 78.4% of pregnant women were younger than 35, with 49% being aged from 30 to 35[21]. The combined first trimester screening at the Split University Hospital Center is performed between the 10th week and the end of the 14th week of pregnancy, in accordance with the international standards and evidence-based medical recommendations[5,8]. In Split, the highest number of pregnant women underwent screening in the 12th (48.93%) and 13th (37.85%) week of pregnancy, while only 8.50% of them underwent it in the 11th week, when the detection level is highest. Due to difference in concentration between trisomy and euploid pregnancies, PAPP-A as an isolated marker has the highest sensitivity between the 9th and 11th week. ß-hCG follows a different pattern and its significance is highest after the 13th week. The mathematical significance of PAPP-A in final calculation was estimated to be higher. Thus, according to reference works, combined first trimester screening should optimally be carried out in the 11th week of pregnancy[18,22].

A number of studies confirm that, due to the aging of primary oocytes, the risk of bearing a child with chromosome abnormalities increases with the increase in age[4]. Therefore, older pregnant women have a higher mean value of *a priori* risk of fetal Down syndrome based on age, as well as a higher mean value of risk based on the results of combined first trimester screening, which was proven by our results too. This connection was expected given the fact that the starting point for the calculation of risk in combined first trimester screening is *a priori* risk based on age.

The share of pregnant women at a high risk of fetal Down syndrome based on age was six times higher than the one based on combined first trimester screening (21.1% *vs*. 3.5%) for the examined population. It is evident that the use of combined first trimester screening is a medically cost-effective procedure that can significantly increase the rate of chromosome abnormality detection, with less invasive prenatal diagnostic procedures. In that way, the risk of complications and miscarriages is reduced (with early amniocentesis, they occur in 0.5% to 1% of the procedures)[23].

In developed countries, 50% to 80% of pregnant women opt for early amniocentesis or some other confirmatory method after a high-risk combined first trimester screening result[18-21]. The acceptance rate of early amniocentesis in the Split University Hospital Center was lower than the above and amounted to 40%. Studies show that more pregnant women agree to invasive confirmatory methods if they are properly informed about the importance of prenatal screening for fetal chromosome abnormalities, as well as about the procedure itself[24].

In the examined population, ROC analysis showed that the sensitivity of combined first trimester screening pertaining to the detection of Down syndrome amounted to 81%, with 96.8% specificity and cut-off value set at 1:250. Reference works describe the sensitivity of combined first trimester screening in Down

syndrome detection to range from 80% to 90%, with 5% of false-positive findings[5,8]. Our results fit into the expected sensitivity range, with fewer false-positive findings, or slightly higher specificity. It should be pointed out that the calculation of sensitivity and specificity in our population was indicative only and it did not fully reflect the real situation, which was one of the limitations of our research. We were not able to follow the outcome of each tested pregnancy, but only the ones pertaining to the pregnant women who requested abortion for eugenic reasons, who underwent the procedure of early amniocentesis, or who delivered a child with chromosome abnormalities at the Split University Hospital Center. As for others, we assumed that they gave birth to children with a normal karyotype. Another limit was a relatively small sample considering the low incidence of Down syndrome in the population (0.29% of pregnancies and 0.15% of newborns)[1].

In the Republic of Croatia, screening for chromosome abnormalities is not organized at the national level. In 2010, the Croatian Society for Perinatal Medicine suggested that early amniocentesis be recommended to every pregnant woman aged 36 or older at the time of conception, as well as that biochemical screening of the second trimester or the combined first trimester test be recommended to younger women[25].

In recent years, the techniques of cell-free fetal DNA analysis of maternal blood for the purpose of detecting chromosome abnormalities (noninvasive prenatal testing, NIPT) are being increasingly applied. Their advantage is 99% sensitivity, with false-positive findings amounting to only 1%. With a slightly higher level of detection, the number of invasive procedures decreases five times (1% *vs.* 5% of false-positive results)[10,26]. Financial savings resulting from a decrease in the number of early amniocentesis and other similar procedures is not yet nearly enough to compensate for the extremely high cost of NIPT. For this reason alone, combined first trimester screening remains the fundamental screening procedure for fetal chromosome anomalies in contemporary perinatology[27,28].

References

1. Irving C, Basu A, Richmond S, Burn J, Wren C. Twenty-year trends in prevalence and survival of Down syndrome. Eur J Hum Genet. 2008;16(11):1336-40. doi: 10.1038/ejhg.2008.122.
2. Turnpenny P, Ellard S. Chromosomes and cell division. In: Turnpenny P, Ellard S. Emery's Elements of Medical Genetics, Edition 15. Philadelphia: Elsevier/Churchill Livingstone, 2017; p. 24-41. ISBN: 9780702066856.
3. Korenberg JR, Chen XN, Schipper R, Sun Z, Gonsky R, Gerweher S, *et al.* Down syndrome phenotypes: the consequences of chromosomal imbalance. Proc Natl Acad Sci USA. 1994;91(11):4997-5001. doi: 10.1073/pnas.91.11.4997.
4. Hook EB. Rates of chromosome abnormalities at different maternal ages. Obstet Gynecol. 1981;58(3):282-5. PMID: 6455611
5. American College of Obstetricians and Gynecologists. Practice Bulletin No. 163: Screening for fetal aneuploidy. Obstet Gynecol. 2016;127(5):e123-37. doi: 10.1097/AOG.0000000000001406.
6. Ekelund CK, Petersen OB, Jørgensen FS, Kjaergaard S, Larsen T, Olesen AW, *et al.* The Danish Fetal Medicine Database: establishment, organization and quality assessment of the first trimester screening program for trisomy 21 in Denmark 2008-2012. Acta Obstet Gynecol Scand. 2015;94:577-83. doi: 10.1111/aogs.12581.
7. Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol. 2017;49(6):714-20. doi: 10.1002/uog.17283.
8. Alldred SK, Takwoingi Y, Guo B, Pennant M, Deeks JJ, Neilson JP, Alfirevic Z. First trimester serum tests for Down's syndrome screening. Cochrane Database Syst Rev. 2015;(11):CD011975. doi: 10.1002/14651858.CD011975.
9. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, *et al.* First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med. 2005;353(19):2001-11. doi: 10.1056/NEJMoa043693.
10. Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2015;45:249-66. doi: 10.1002/uog.14791.
11. Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first-trimester screening for Down's syndrome. Prenat Diagn. 1997;17:821-9. PMID: 9316126
12. Spencer K, Spencer CE, Power M, Moakes A, Nicolaides KH. One stop clinic for assessment of risk for fetal anomalies: a report of the first year of prospective screening for chromosomal anomalies in the first trimester. Br J Obstet Gynecol. 2000;107:1271-5. doi: 10.1111/j.1471-0528.2000.tb11619.x.
13. Tišlarić-Medenjak D, Košec V, Kos M, Latin V, Harni V, Lovrić B, *et al.* Kombinirani ultrazvučno-biokemijski probir fetalnih aneuploidija od 10.-14. tjedna trudnoće: Prvi rezultati primjene testa u Hrvatskoj. Gynaecol Perinatol. 2008;17(4):195-200. (in Croatian)
14. Dormandy E, Michie S, Weinman J, Marteau TM. Variation in uptake of serum screening: the role of service delivery. Prenat Diagn. 2002;22(1):67-9. doi: 10.1002/pd.245.
15. Van den Berg M, Timmermans DR, Kleinveld JH, Garcia E, Van Vugt JM, Van der Wal G. Accepting or declining the offer of prenatal screening for congenital defects: test uptake and women's reasons. Prenat Diagn. 2005;25(1):84-90. doi: 10.1002/pd.1090.
16. Stefansdottir V, Skirton H, Jonasson K, Hardardottir H,

Jonsson JJ. Effects of knowledge, education, and experience on acceptance of first trimester screening for chromosomal anomalies. Acta Obstet Gynecol Scand. 2010;89(7):931-8. doi: 10.3109/00016341003686073.

17. Sorta-Bilajac Turina I, Šupak Smolčić V. Informed consent in Croatian clinical laboratory practice – current issues and future perspectives. Acta Clin Croat. 2019;58(3):497-507. doi: 10.20471/acc.2019.58.03.14.
18. Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three year prospective experience. Br J Obstet Gynecol. 2003;110:281-6. PMID: 12628268
19. Stevanović R, Capak K. Hrvatski zdravstveno-statistički ljetopis za 2016. godinu. Zagreb: Hrvatski zavod za javno zdravstvo; 2017;265-84. (in Croatian)
20. Baer RJ, Flessel MC, Jelliffe-Pawlowski LL, Goldman S, Hudgins L, Hull AD, *et al*. Detection rates for aneuploidy by first-trimester and sequential screening. Obstet Gynecol. 2015;126(4):753-9. doi: 10.1097/AOG.0000000000001040.
21. Park SY, Jang IA, Lee MA, Kim YJ, Chun SH, Park MH. Screening for chromosomal abnormalities using combined test in the first trimester of pregnancy. Obstet Gynecol Sci. 2016;59(5):357-66. doi: 10.5468/ogs.2016.59.5.357.
22. Shiefa S, Amargandhi M, Bhupendra J, Moulali S, Kristine T. First trimester maternal serum screening using biochemical markers PAPP-A and free β-hCG for Down syndrome, Patau syndrome and Edward syndrome. Indian J Clin Biochem. 2013;28(1):3-12. doi: 10.1007/s12291-012-0269-9.
23. Tara F, Lotfalizadeh M, Moeindarbari S. The effect of diagnostic amniocentesis and its complications on early spontaneous abortion. Electron Physician. 2016;8(8):2787-92. doi: 10.19082/2787.
24. Brajenović-Milić B, Babić I, Ristić S, Vraneković J, Brumini G, Kapović M. Pregnant women's attitudes toward amniocentesis before receiving Down syndrome screening results. Womens Health Issues. 2008;18(2):79-84. doi: 10.1016/j.whi.2007.10.003.
25. Hrvatsko društvo za perinatalnu medicinu Hrvatskog liječničkog zbora. Nacionalna stručna preporuka za prenatalni probir i dijagnostiku kromosomopatija. Gynaecol Perinatol. 2010;19(2):119-26. (in Croatian)
26. Robson SJ, Hui L. National decline in invasive prenatal diagnostic procedures in association with uptake of combined first trimester and cell-free DNA aneuploidy screening. Aust N Z J Obstet Gynaecol. 2015;55:507-10. doi: 10.1111/ajo.12380.
27. Morris S, Karlsen S, Chung N, Hill M, Chitty LS. Model-based analysis of costs and outcomes of noninvasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK national health service. PLoS One. 2014;9(4):e93559. doi: 10.1371/journal.pone.0093559.
28. O'Leary P, Maxwell S, Murch A, Hendrie D. Prenatal screening for Down syndrome in Australia: costs and benefits of current and novel screening strategies. Aust N Z J Obstet Gynaecol. 2013;53(5):425-33. doi: 10.1111/ajo.12136.

Sažetak

KOMBINIRANI TEST PROBIRA NA FETALNI DOWNOV SINDROM U KLINIČKOM BOLNIČKOM CENTRU SPLIT: SEDMOGODIŠNJE ISKUSTVO

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Cilj ovog istraživanja bio je prikazati rezultate i istražiti uspješnost kombiniranog testa probira u Kliničkom bolničkom centru Split. Provedeno je presječno retrospektivno istraživanje. Uključene su sve trudnice u kojih je proveden kombinirani test probira u Kliničkom bolničkom centru Split od 2011. do 2017. godine. Podatci su prikupljeni iz bolničke arhive. Kombiniranom testu u istraživanom razdoblju je pristupilo 6898 trudnica. Uz graničnu vrijednost rizika od 1:250 osjetljivost kombiniranog testa bila je 81,0% uz specifičnost od 96,8% (AUC=0,929, 95% CI 0,859-1,000, p<0,001). Srednja vrijednost *a priori* rizika od Downova sindroma prema životnoj dobi bila je veća od rizika izračunatog kombiniranim testom (1:487,57 naspram 1:13216,9, p<0,001). Broj *a priori* visokorizičnih trudnica za Downov sindrom bio je značajno veći od broja visokorizičnih trudnica prema rezultatima kombiniranog testa (1457 naspram 239; p<0,001). Porastom životne dobi trudnica statistički se značajno povećava prosječna vrijednost *a priori* rizika za Downov sindrom i rizika prema rezultatima kombiniranog testa (p<0,001). Kombiniranim testom je visoki rizik izračunat u 8,09% (118/457) *a priori* visokorizičnih i 2,22% (121/5441) *a priori* niskorizičnih trudnica. Na taj je način kombinirani test od *a priori* niskorizičnih izdvojio 121 trudnicu u visokorizičnu skupinu. Downov sindrom je naknadno protvrđen u njih 17 (14,05%). Analizom rezultata kombiniranog testa je potvrđena opravdanost primjene ovog načina probira na Downov sindrom ploda na istraživanoj populaciji trudnica.

Ključne riječi: *Kombinirani test; Prenatalni probir; Downov sindrom*