Research Article

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What are the predominant parameters for Down syndrome risk estimation in first-trimester screening: a data mining study

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Abstract

Objectives: This study aimed to evaluate the effect size of each parameter used in the first trimester Down syndrome (DS) risk analyses by using multiple regression analysis techniques.

Methods: This data mining study included data of 44,260 pregnant women screened at the Acibadem Labmed laboratories from 2010 to 2019. In this study, risk was calculated using the PRISCA software on the basis of nuchal translucency (NT), crown-rump length measurement, *in vitro* fertilization application, diabetes mellitus, Down syndrome story, smoking, maternal age, and the level of maternal serum biochemistry markers including pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (hCGβ).

Results: Forty-four thousand two hundred sixty risk analysis patients result data were re-investigate, and 851 (1.93%) risk analysis results were found as positive. PAPP-A 747 (CI%, 476–1,170) times, NT value 512 (CI%, 343–764) times, DS story 21 times (CI%, 6.7–63.2) and hCGβ value 7.01 (CI%, 6.31–7.79) times affect the combined first-trimester risk analysis results.

Conclusions: We have suggested that those accurate PAPP-A levels and NT levels evaluation are the most critical point of combined risk analysis and that the risk of free hCGβ levels after PAPP-A is essential as a biochemical test.

Keywords: data mining; first trimester Down syndrome (DS) risk analyses; free beta-human chorionic gonadotropin (hCGβ); nuchal translucency (NT); pregnancy-associated plasma protein-A PAPP-A.

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Introduction

Down syndrome (DS) is a chromosomal problem caused by a random error in cell division and resulted in the presence of an extra copy of chromosome 21. It was first defined by Landon Down in 1866 and informed to be a congenital disease by Fraser and Mitchell in 1876. Down syndrome, which influences almost one in 700–800 live births, has abnormality such as a wide face, short and underdeveloped neck, flat nose, short fingers, curved little finger, thick nape, and a small mouth [1–4].

The first-trimester DS screening is performed in generally between 10 and 14 weeks of gestation. The first-trimester screening test consists of beta-human chorionic gonadotropin (beta-hCG or free beta-hCG subunit, hCGβ), pregnancy-associated plasma protein-A (PAPP-A) in

maternal serum and ultrasound measurement of nuchal translucency (NT) [5–7].

If the first trimester screening test is positive, chorionic villus sampling, might have a significant impact on the management of the pregnancy, should be included for a definitive prenatal diagnosis. At or after the 15th gestational week, a few weeks should not be waited after the screening positive combined test result for amniocentesis. In accordance with the American College of Obstetricians and Gynecologists (ACOG), we recommend that all women should be offered aneuploidy screening before 20 weeks of gestation [8, 9].

For women who early diagnosis is a priority, the combined test is the best biochemical marker-based screening test available for Down syndrome Because it does not contain measurement of maternal serum AFP, second trimester AFP or sonographic screening for open fetal neural tube defects should be performed in the second trimester if desired. desired.

Serum hCGβ levels are twice as high in pregnancies affected with DS than in euploid pregnancies. hCGβ can be assayed in its free or total form. The test for free hCGβ for DS screening is effective at 10–14 weeks, and screening performance improves as gestational age advances within this interval. There is no consensus as to whether free hCGβ performs significantly better than total hCGβ for DS screening when interpreted in conjunction with measurement of PAPP-A and NT [10, 11].

PAPP-A, a special biomarker for screening of Down syndrome in pregnant women, is a complex, high molecular weight glycoprotein. Its levels, on average, are lower in pregnancies affected with fetal DS. In contrast to hCGβ, PAPP-A achievement as a screening marker for Down syndrome declines with increasing gestational age from 9 to 13 weeks [11, 12]. In screening for DS by maternal age, hCGβ and PAPP-A, the estimated detection rate was 65% for a false-positive rate of 5% [13, 14].

NT refers to the hypoechoic space in the posterior fetal neck. Its thickness is measured by ultrasound between 10 and 14 gestational weeks. The NT measurement is, on average, increased in fetuses with DS [15, 16]. Specifically, NT provides 50–60 percent detection of DS for a five percent FPR. The performance of NT as a scanning marker may have reproducibility problems between studies, possibly due to variability in operator expertise and equipment quality [17, 18].

The objective of SURUSS was to identify the most effective and safe method of antenatal screening for DS. At a diagnostic ratio of 85%, the false (0.9%) was lowest for the first- and second-trimester fully integrated test [19].

In recent years, the diagnosis of Down syndrome has become widespread and recommended in the fetal DNA in a mother's blood analysis. However, the evaluation of DS with first-trimester screening is still widely used both in the world and our country because of its very expensive and performed in limited locations [20–22].

Materials and methods

CRL and fetal NT were measured using standard techniques by experienced sonographers. PAPP-A and free hCGβ serum biomarkers with IMMULITE_XPI_2000 (SIEMENS Healthcare Diagnostic, Germany). All of these tests were performed under internal and external suitable quality control rules. Intraassay and interassay imprecision values of PAPP-A and free hCGβ are lower than <8%. Uncertainty values are <18.2% for PAPA-A and <16.9% for hCGβ. The intra- and inter-individual biological variation for PAPA A is 12.6%, 14.0% (Fabruary 2022, https://www.westgard.com/biodatabase1.htm). There is no data for hCGβ in the biodatabase. However, Sennels et al. found that, the ranges for biological variation were 11.9–48.5% for hCGβ and 31.6–63.3% for PAPP-A, increasing with time between sampling. In the laboratory, especially in calibrator and reagent lot changes, the internal control study for PAPP-A and hCGβ and patient samples were compared to evaluate whether there was a change. In addition, median values PAPP-A and hCGβ and NT of are updated according to patient results at regular intervals [23]. The effect on Down syndrome risk analysis with combination test of biochemical tests, PAPP-A and free hCGβ, NT, CRL, maternal age, weight, *in vitro* fertilization (IVF) application, DM measurement as well as Down story and smoking with PRISCA 4 and PRISCA 5 SOFTWARE (Siemens® Typology, Germany) was retrospectively investigated.

This retrospective study of the patients' medical was approved by the Ethics Committee of Acibadem Mehmet Ali Aydınlar University (2021-09/23). The study was designed and conducted was in accordance with the principles of the Declaration of Helsinki. In this study, 851 positives and 43,409 negatives of first trimester DS screening tests were performed in a population of women attending the Acibadem Lambed-Clinlab laboratories between 2010 and 2019, and were agreed by all patients.

This study aims to examine the results of the first Trimester DS screening test in a very large group and to evaluate the risk effects of factors affecting both biochemical and combined risk analysis results with multiple logistic regression analyses.

The statistical analysis of the data was performed using IBM SPSS Statistics 18.0 software. Definitive statistical, t-test and logistic regression analysis was used for the evaluation of effects of risk analysis. A probability value of less than 0.05 ($p<0.05$) was accepted as statistically significant.

Results

For the positive limit value, the accepted value was over 1/250 [24, 25]. The positive test rate in patients who applied to our laboratory was 1.93%. Statistically significant

Table 1: Demographic data and statistical results of positive and negative groups according to screening test results.

	Down syndrome test negative n=43,409		Down syndrome test positive n=851		p-Value
	Mean	SD	Mean	SD	
NT MoM	0.846	0.208	1.162	0.620	<0.001
PAPP-A MoM	1.236	0.714	0.665	0.507	<0.001
Free hCGβ MoM	1.136	0.792	2.579	1.448	<0.001
CRL, mm	61.2	8.6	59.5	8.8	<0.001
Mother age, years	29.2	5.1	34.6	6.0	<0.001
Mother weight, kg	65.1	12.0	65.2	11.9	0.831
	Yes	No	Yes	No	
Smoking	3,361	40,048	92	759	0.010
IVF	1,195	42,214	64	787	<0.001
DM	205	43,204	9	842	0.015
Tri 21 story	42	43,367	10	841	<0.001

differences in all parameters studied except the weight of the mother were observed between the groups (Table 1). According to this result, all parameters except the weight of the mother were observed to be significantly different between the groups. Multiple regression analysis results for both Tr21 combined risk and biochemical risk are presented in Table 2.

We have suggested that accurate NT evaluation and PAPP-A measurements are the most critical point of combined risk analysis and that the risk of free hCGβ values after PAPP-A is essential as a biochemical test (Table 1 and Figure 1). In biochemical DS risk assessment, the most important parameters were observed to be PAPP-A, and there was much less hCGβ and DS story (Table 1).

Discussion

So far, the many biochemical markers have been studied to use first trimester screening risk analysis to detect DS. These studies concluded that screening tests double biochemical marker combination of PAPP-A and free β-hCG significantly overperformed more than other [26–29].

Sørensen et al. shown, center-specific own medians for NT, hCGβ, and PAPP-A should be used in risk calculation programs to ensure high diagnostic risk and low false-positive ratio [30]. Consequently, using different software, kits, and laboratory analytical performances for DS scanning evaluation can affect the results [31, 32].

Durkovic et al. in a population of including 340 pregnancies with positive results of prenatal screening for Down syndrome, they investigated the specificity, sensitivity, positive and negative expected values of biomarkers for each marker using PRISCA 5 and suggested that the sensitivity of biochemical markers is much higher than that the sensitivity of NT [24]. NT has no noticeable effect on the final risk of DS. The sensitivity and specificity of PAPP-A and free hCGβ are higher than the other serum biomarkers for DS screening in the first trimer compared with the other maternal serum markers evaluated [24, 27, 33]. However, in this study, it was not specified which parameters affect how much. Our study is especially first with this aspect.

Table 2: Multiple regression analysis results of factors affecting combined and biochemical risk analysis. All levels were expressed in multiples of the normal median (MOM) for NT, PAPP-A, free β-hCG.

	Combined Down syndrome risk multinominal regeresyon					Biochemical Down syndrome risk multinominal regeresyon				
	B	Sig.	Odd ratio	Odd ratio 95% CI		B	Sig.	Odd ratio	Odd ratio 95% CI	
				Lower	Upper				Lower	Upper
NT MoM	6.24	<0.001	512	343	764	−0.16	0.24	0.85	0.65	1.11
PAP-A MoM	−6.62	<0.001	1.34^{10-3} (−747)	0.85^{10-3} (−1,170)	2.09^{10-3} (−476)	−8.98	<0.001 <0.001	0.12^{10-3} (−7,956)	0.09^{10-3} (−11275)	0.18^{10-8} (−5,614)
hCGβ MoM	1.95	<0.001	7.01	6.31	7.79	4.07	<0.001	58.7	50.9	67.8
CRL, mm	−0.01	0.11	0.99	0.98	1.00	−0.02	<0.001	0.98	0.97	0.99
Age, years	0.36	<0.001	1.43	1.40	1.47	0.47	<0.001	1.61	1.58	1.64
Weight, kg	−0.06	<0.001	0.94	0.93	0.95	−0.08	<0.001	0.92	0.92	0.93
Smoking	−0.43	0.01	0.65	0.47	0.90	−0.94	<0.001	0.39	0.31	0.49
IVF pregnancy	0.24	0.22	1.27	0.87	1.86	0.11	0.44	1.12	0.84	1.50
Diabetes	0.53	0.25	1.70	0.69	4.16	0.66	0.033	1.93	1.05	3.54
DS history	3.02	0.00	20.55	6.68	63.24	4.09	<0.001	59.68	18.3	195.0
Constant	−13.64	0.000	0.000			−8.17	0.000	0.00		

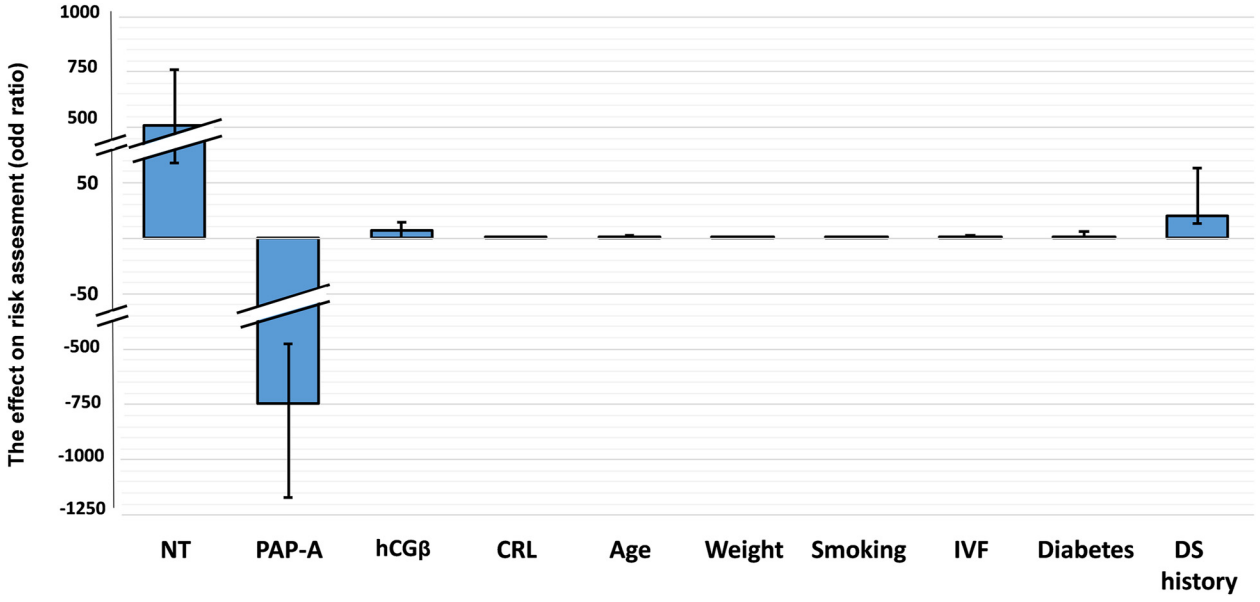

Figure 1: The odd ratios of all parameters of first trimester Down syndrom risk assessment.

Advanced maternal age is a well-reported risk factor associated with DS. On the contrary environmental factors such as smoking, alcohol intake, fertility drugs, and birth control pill have been reported not to be risk factors associated with DS [33]. Interestingly, in our study, we found that there is a connection between maternal age and smoking with Down syndrome, as well as advanced maternal age and smoking are risk factors associated with DS, Among Factors affecting the risk of Down syndrome, maternal age.

Our study is the first study related with understanding of which factors impact on the success of the first-trimester detection and how much these factors affect. Therefore, future studies should contribute to carry out similar studies with other commercial software and kits in addition to do Second Trimester test.

In particular, NT measurement is essential for the high quality of the DS screening program. He has made an important contribution to Fetal Medicine Foundation certified proficiency studies for NT measurements. However, despite appropriate training, experience, accredited certification and optimal quality standards achieved, continued monitoring of individual operators is likely to result in better performance of NT measurements. According to our results, it was considered to be the most influencing parameter after PAP-A. Therefore, we think it is important to repeatedly emphasize the standardization of NT measurements for the effectiveness of DS scans [34, 35].

There are some critical limitations in this study. The most important of these was not compared with amniocentesis results and abnormality data at birth. However, the effectiveness of the first trimester study has already been established with previous studies. The main purpose of this study is to define how much it affects the positive risk analysis. Because it is important to know which parameters are more critical when doing the test.

There are different software for Down syndrome risk analysis and Prisca is also one of the commonly used software. In this data mining study, we showed which parameters affect the risk analysis result in this software. According to the results of this study, it is to understand which parameters are more concentrated.

In our study, we especially focused on the first timester test. In fact, it has been shown that by combining (integrated, contingent and stepwise strategy), the first and second trimesters (AFP, uE3, total hCG tests) the sensitivity can be increased up to 91–94% and the specificity up to 89–95%. As a result, it should not be forgotten that nowadays they can be used in combination [36–38].

In our study, the effect of biochemical tests, PAPP-A, and free hCGβ on combined risk are significantly high as compared to others. For a whole risk assessment combining maternal age, biochemical and ultrasound markers, Combined risk respectively biochemical markers of PAPP-A and free hCGβ, ultrasound measurement of NT and CRL, maternal age, smoking significantly affect. Consequently, according to the results of this study, PAPP-A, NT measurements are more important than other parameters and their measurements are critical. It is important for both

biochemists and obstetricians to consider this information when evaluating the first trimester test results.

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