

National Weight Adjusted PAPP-A and free β -hCG MoM Role in the First-Trimester Pregnancy Screening Risk for Trisomy 21

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Abstract

The trisomy 21 risk calculations, based on adjusted values of national MoM weight log-linear correction for biochemical markers, free- β -hCG and PAPP-A, of maternal serum concentrations, compared to the risk calculated based on own data base of COBAS6000, plays an important role for accuracy levels. Using the log-linear method for the calculation of the national maternal weight adjusted MoM value for calculating the risk for T21, normative values will be established, the screening accuracy and reliability will be improved.

Concentration values of PAPP-A and free- β -hCG were measured with COBAS6000 and NT, CRL values with standardized techniques. Calculations for fetus T21 risk are computed with ssdlab5, the relative error (η) and standard deviation (STDEV) with Excel. Age groups of the population were selected based on gestational age.

Serum analyzed for 286 Albanian Pregnant women (singleton pregnancy). The MoMs weight adjusted were calculated from 86 to 98 days of gestational age. The STDEV values are from 0.656 to 1.57 and η from 0% to 1%.

The STDEV and the η between risks for T21 calculated on Albanian MoM weight adjusted values and those of COBAS6000 own data shows little differences. The national MoM doesn't change the detection rate of risk calculation for T21.

KEYWORDS: MoM, T21, free- β -hCG, PAPP-A.

INTRODUCTION

The calculation of chromosomal abnormalities risk during the first trimester screening is important for the overall population and pregnant women, for avoiding the invasive tests like amniocentesis or chorionic villus sampling. The screening of aneuploidies in the first trimester of pregnancy adopts as common practice the correction of the analyte concentration or Multiple of Medians (MoM) per mother's weight with one of the alternative methods (Kennedy, D. M. et al., 1999). In the first trimester the risk calculations for trisomy 21 (T21) is performed by means of the statistical program SSDLAB5. An important role in the risk assessment program for these abnormalities plays the combination of the MoMs weight adjusted values of maternal concentration serum of two biochemical markers, free beta-Chorionic Gonatropin (free β -hCG) and Pregnancy Associated Plasma Protein-A(PAPP-A), as well as the Nuchal Translucency (NT) thickness (Bindra, R. at al., 2002). The detection rate for chromosomal defect through one stop clinical stop can reach up to 90% (Spencer, K.et al., 2000). The weight corrected values nowadays, is a mandatory data item for the screening methods (Spencer

et al., 2003/a). The adjusted values of national MoM weight log-linear correction for biochemical markers, free β -hCG and PAPP-A from maternal serum concentrations, compared to the risk calculated based on own data base of serum analyzer COBAS 6000, plays an important role in the accuracy levels. By using the log-linear method for the calculation of the national maternal weight adjusted MoM value for calculating the risk for T21, may establish the normative values and increase the accuracy and reliability of screening. The quantity of the biochemical markers in maternal blood does not depend on mother's weight. The importance of weight adjusted value of biochemical markers MoM is based on the fact that the concentration of these markers in the maternal serum is disproportional with body weight, because a heavier mother has bigger blood volume and smaller concentration of the biochemical markers and conversely, the lighter the mother the more concentrated the biochemical marker. This weight adjustment reduces the population variability of the markers (Wald *et al.*, 1992). Substituting in the risk assessment statistical program ssdlab5 the national weight corrected values of MoM in the risk calculation for T21 with weight corrected MoM own data from the modulator COBAS6000, will improve the accuracy of the risk assessment. The weight corrections for the biomarkers of the first trimester for T21 are calculated on two main methods; the one that the calculations are carried out in our study is the log-linear regression method (Reynolds *et al.*, 1991; Wald *et al.*, 1981) and the second one is the reciprocal-linear method (Neveux *et al.*, 1996). Their impact on the assessment of detection rate and that of reducing the false positive is of a relative importance (Wald *et al.*, 1994). In the first trimester, screening method for T21 is based on the calculation weight adjusted MoM for free β -hCG and PAPP-A combined with the value of NT (Nuchal Translucency) leading to a positive impact on the detection rate and that of false positive (Spencer *et al.*, 1999; Spencer *et al.*, 2003/b).

MATERIALS AND METHODS

Pregnant women from different obstetrical centers of Albania were sent to our laboratory in order to complete their screening for the first trimester. All 286 blood samples were taken between week 11 and 14 and on the same day were done the measurement of NT according to standardized technique (www.fetalmedicine.com/nuchal) by experienced sonographers. The calculation of weight adjusted MoM has been carried out based on the log-linear method for both biochemical markers (free β -hCG, PAPP-A) for 286 cases of singleton pregnancies of Albanian women including the normal and those with chromosomal abnormalities (T21). All cases were certified by karyotyping or completion of the pregnancy. In compliance with local ethics requirements, each woman completed a consent form. The concentrations of the biochemical markers were measured using the COBAS6000 analyzer. The calculation of the median of both markers was followed by the calculation of MoM for each of the markers and at the end the calculation of the weight adjusted MoM of the markers for each gestational age group. The values of weight adjusted MoM of free β -hCG and PAPP-A of each gestational age group were used to assess the risk for T21 by means of the risk calculator of SSDLAB5 program. To compare the results obtained from the weight corrected MoM calculated values, we calculated the relative error for each T21 risk and in the same time, we compared their standard deviations by means of EXCEL. In the calculation of the relative error, the value of own data modulator has been considered as the real value. The age groups include

pregnant women of 84, 86, 88, 89, 90, 91, 92, 94, 95 and 98 days of gestation. The selection has been done based on the number per each age group which represent 77% of the entire sample of 286 pregnant women. Both methods, the log-linear and the log-reciprocal, have the respective formulas (Spencer *et al.*, 2003/a):

MoM log-linear weight correction formula for free β -hCG and PAPP-A:

$$\text{MoM weight corrected (free } \beta\text{-hCG)} = \text{free } \beta\text{-hCG MoM}/10^{(0.276-0.0040 * \text{weight})}$$

$$\text{MoM weight corrected (PAPP-A)} = \text{PAPP-A MoM}/10^{(0.4416-0.0066 * \text{weight})}$$

MoM log-reciprocal weight corrected formula for free β -hCG and PAPP-A:

$$\text{MoM weight corrected (free } \beta\text{-hCG)} = \text{free } \beta\text{-hCG MoM}/[(46.875 * 1/\text{weight}) + 0.271]$$

$$\text{MoM weight corrected (PAPP-A)} = \text{PAPP-A MoM}/[(79.858 * 1/\text{weight}) - 0.230]$$

Cut off for risk T21 was set at 1:250.

It is hard to choose between the above methods as they both fit the data reasonably well, but the log-linear one shows a more significant reduction in variance (Watt, H. C. *et al.*, 1998). The log-linear method has been used in the SSDLAB5 statistical program for the risk assessments.

RESULTS AND DISCUSSIONS

The selected population is made up of 286 Albanian pregnant women (singleton pregnancy). The population is divided in 15 age groups with more than 6 cases per each group with a total of 220 cases or 77% of the entire sample. The age groups with less than 6 cases were of no statistical significance. Each age-group maternal blood, was tested for biochemical markers concentrations (Table 1). The performance for the risk assessment with risk calculator has been done by using the necessary data of MoMs free β -hCG, PAPP-A and NT, mother's age, NT value and CRL (Crown-Rump Length). All scans were performed transabdominally. Calculations for weight corrected MoMs were done with log-linear formula. The risk assessments were done by substituting the MoMs of own data modulator with that of Albanian MoMs. In order to compare the risk assessments for T21 calculated based on modulator's MoM and that of Albanian MoM, was used the risk calculator where the values of MoM for NT, CRL mother's age were the same. The value for standard deviations based on own data of the modulator COBAS6000 has a value equal from 0.683 to 1.507 and the standard deviation value of the Albanian women is equal from 0.656 to 1.57. Both values of STDEV overlap, while the calculation of the relative error (η) for each case varies between 0.0000026% up to 1% (Tables 2 to 11). The use of the Albanian weight corrected MoM in the T21 risk calculation reclassified only one case, in the age group of 92 days of gestation, from a high risk zone to a low risk zone (1: 341 table), all the other risk calculated cases remained at the same level of risk as calculated with weight corrected MoM of the modulator. This represents only 0.45% of the entire sample. Also the trend of both weights corrected MoM are similar (Figure 1).

CONCLUSIONS

Based on the above results as for e.g. the low relative error, overlapping of STDEV, very low changes in detection rate brings to the conclusion that the substitution of the COBAS6000 weight corrected MoM with that of Albanian weight corrected MoM doesn't lead to important changes in the risk calculation for T21 in the first trimester

screening. With exception of one case (one out of 220 cases equal to 0.45%) all other cases didn't change their risk status, so the detection rate remains the same. The weight corrected MoM of the COBAS6000 analyzer as well as that of Albanian weight corrected MoM makes this screening a suitable tool for the Albanian population. According to these results obtained from the above sample the first trimester screening for T21 risk assessment is effective also in avoiding the invasive tests.

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Table 1. Age-group frequency distribution

Age-group (gestational age)	Number of pregnant women (frequency, f)
84	16
85	9
86	16
87	11
88	13
89	21
90	15
91	21
92	20
93	11
94	26
95	17
96	8
97	6
98	10
all	220

Table 2. Calculation results for 84 days for risk T21 (confirmed abnormalities are marked in red)

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:3047	1:5153	0,00000260
1:5123	1:9862	0,00000095
1:593	1:1684	0,00006488
1:5065	1:8180	0,00000092
1:3463	1:6940	0,00000208
1:10000	1:49371	0,00000016
1:59	1:85	0,00609935
1:10000	1:39465	0,00000019
1:4818	1:9348	0,00000108
1:1662	1:2364	0,00000756
1:10000	1:27358	0,00000023
1:10000	1:100000	0,00000009
1:10000	1:66493	0,00000013
1:10000	1:30449	0,00000022
1:10000	1:49379	0,00000016
1:9854	1:4094	0,00000349

Table 3. Calculation results for 86 days for risk T21 (confirmed abnormalities are marked in red)

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:10000	1:15319	0,00000023
1:5000	1:6846	0,00000079
1:10000	1:10839	0,00000007
1:9140	1:14392	0,00000028
1:8745	1:21680	0,00000031
1:3640	1:6501	0,00001236
1:10000	1:28131	0,00000023
1:4483	1:45051	0,00000045
1:3542	1:8431	0,00000194
1:71	1:203	0,00451153
1:2865	1:5500	0,00000304
1:10000	1:35820	0,00000020
1:368	1:587	0,00017271
1:10000	1:2660	0,00001037
1:9854	1:9829	0,00000000
1:5857	1:18844	0,00000070

Table 4. Calculation results for 89 days for risk T21 (confirmed abnormalities are marked in red)

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:10000	1:100000	0,00000009
1:6699	1:5608	0,00000251
1:527	1:294	0,00051151
1:10000	1:99433	0,00000009
1:10000	1:61401	0,00000014
1:1455	1:3338	0,00001161
1:10000	1:39748	0,00000019
1:10000	1:100000	0,00000009
1:1074	1:5307	0,00001399
1:10000	1:22314	0,00000025
1:10000	1:63103	0,00000201
1:5148	1:5642	0,00000041
1:10000	1:100000	0,00000009
1:4052	1:4982	0,00000092
1:128	1:150	0,00002732
1:10000	1:29864	0,00000022
1:2677	1:3865	0,00000297

1:8114	1:23149	0,00000035
1:10000	1:39480	0,00000019
1:1223	1:2626	0,00001638

Table 5. Calculation results for 90 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:780	1:2344	0,00000086
1:111	1:10	0,90990991
1:1399	1:3066	0,00001268
1:1282	1:2079	0,00001438
1:989	1:1476	0,00002260
1:5	1:10	1,00000000
1:10000	1:100000	0,00000009
1:867	1:17369	0,00000631
1:4954	1:8902	0,00000101
1:10000	1:56628	0,00000015
1:2716	1:3244	0,00000185
1:10000	1:30418	0,00000022
1:10000	1:40366	0,00000019
1:10000	1:15046	0,00000003
1:10000	1:30222	0,00000007

Table 6. Calculation results for 91 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:4194	1:2863	0,00000387
1:10000	1:4886	0,00000214
1:10000	1:91741	0,000000097
1:10000	1:13203	0,00000018
1:318	1:395	0,02245701
1:2872	1:4153	0,00000259
1:9593	1:19039	0,00000007
1:5954	1:11067	0,00000070
1:10000	1:23251	0,00000025
1:1308	1:3312	0,00000518
1:10000	1:42849	0,00000018
1:3149	1:3084	0,00000022
1:4101	1:7136	0,00000145
1:10000	1:31214	0,00000022
1:1500	1:2775	0,00001104
1:10000	1:33681	0,00000021
1:10000	1:39545	0,00000019

1:10000	1:33681	0,00000021
1:10000	1:59228	0,00000014
1:1942	1:100000	0,00000415

Table 7. Calculation results for 92 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:369	1:1147	0.0004982%
1:69	1:341	0.0167539%
1:10000	1:99285	0.0000009%
1:7743	1:28260	0.0000012%
1:10000	1:56284	0.0000223%
1:78	1:275	0.0117746%
1:4119	1:24673	0.0000049%
1:8104	1:25085	0.0000010%
1:100000	1:100000	0.0000000%
1:2426	1:18354	0.0000147%
1:909	1:7628	0.0001066%
1:1215	1:11623	0.0000607%
1:1901	1:10740	0.0000228%
1:909	1:7496	0.0001063%
1:711	1:28087	0.0003715%
1:2106	1:7737	0.0000164%
1:5209	1:16088	0.0000025%
1:4137	1:20625	0.0000047%
1:10000	1:21108	0.0000005%
1:2427	1:5362	0.0000093%

Table 8. Calculation results for 93 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:10000	1:56594	0.0000008%
1:10000	1:10249	0.00000002%
1:10000	1:12794	0.0000002%
1:1647	1:1914	0.0000051%
1:569	1:1196	0.0001619%
1:10000	1:21140	0.0000005%
1:3866	1:8861	0.0000038%
1:10000	1:26970	0.0000006%
1:10000	1:35722	0.0000007%
1:10000	1:37453	0.0000007%
1:10000	1:28967	0.0000007%

Table 9. Calculation results for 94 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:9399	1:36157	0.00000084%
1:2417	1:2821	0.00000245%
1:4379	1:15752	0.00000377%
1:6268	1:5027	0.00000063%
1:606	1:730	0.00004625%
1:1362	1:8546	0.00004532%
1:10000	1:40020	0.00000075%
1:22	1:21	0.00983865%
1:5143	1:12205	0.00000219%
1:155	1:6123	0.00405696%
1:988	1:6434	0.00008672%
1:1988	1:2084	0.00000117%
1:10000	1:37032	0.00000073%
1:350	1:18510	0.00080089%
1:3464	1:4107	0.00000130%
1:10000	1:74590	0.00000087%
1:10000	1:100000	0.00000090%
1:1955	1:4916	0.00001576%
1:10000	1:7562	0.00000032%
1:10000	1:46102	0.00000078%
1:10000	1:65615	0.00000078%
1:7720	1:5355	0.00000074%
1:6526	1:1433	0.00000835%

Table 10. Calculation results for 95 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:3350	1:1539	0.0000763%
1:10000	1:100000	0.0000009%
1:1895	1:4296	0.0000156%
1:100000	1:100000	0.0000009%
1:827	1:8171	0.0001314%
1:1566	1:6543	0.0001512%
1:10000	1:28265	0.0000006%
1:425	1:1609	0.0004074%
1:1251	1:1914	0.0004074%
1:1785	1:12565	0.0000269%
1:1544	1:8926	0.0003946%
1:10000	1:34317	0.0000007%
1:10000	1:10000	0.0000000%
1:10000	1:14105	0.0000003%
1:8571	1:12506	0.0002342%

1:74	1:209	0.0117957%
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Table 11. Calculation results for 98 days for risk T21

COBAS riskT21 values	Albanian risk T21	Relative error ABS η (%)
1:731	1:414	0.0001433%
1:6242	1:8415	0.0000007%
1:1450	1:1375	0.0000026%
1:1977	1:411	0.0000975%
1:647	1:4399	0.0002038%
1:10000	1:100000	0.0000009%
1:7105	1:4947	0.0000009%
1:10000	1:10000	0.0000009%
1:10000	1:12043	0.0000002%

Table 12. Comparison of Standard Deviation (STDEV)

Age-group(gestational age)	COBAS STDEV	Albanian STDEV
84	1.312	1.115
86	1.016	1.115
89	0.77	0.86
90	0.736	0,657
91	0.915	0.81
92	0.719	0.706
93	0.683	1.069
94	1.19	1.285
95	0.798	0.804
98	1.507	1.570

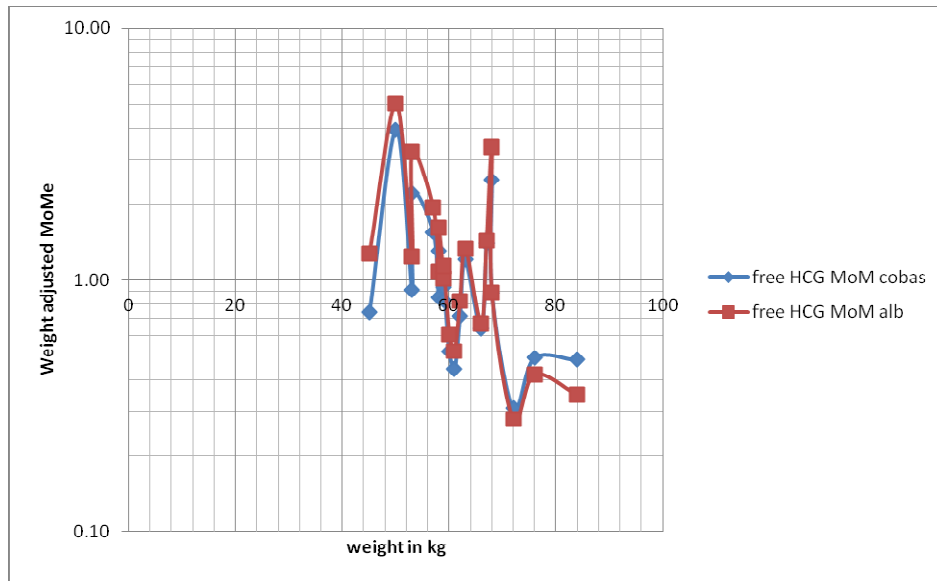


Figure 1. Trend comparison of two calculated weight corrected MoMs in age group 89 days.