Research Article

Yasemin Üstündağ*, Kağan Huysal and Meryem Rümeysa Yeşil

Differences in second trimester risk estimates for trisomy 21 between Maglumi X3/Preaccu and Immulite/Prisca systems

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Abstract

Objectives: Maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG) or free β-HCG, and unconjugated estriol (uE3) concentrations are used to screen trisomy 21 in the second trimester. The performance of different analytical platforms has an impact on individual risk estimates. The aim of this study is to compare the multiple of median (MoM) values and risk estimates generated by Maglumi X3 analyzer/Preaccu software with the Immulite 2000 XPi device/Prisca software.

Methods: A total of 164 pregnant women (including 20 pregnants with risk estimates above ≥1 in 250 for trisomy 21) analyzed with both platforms.

Results: Passing–Bablok indicated proportional bias (0.75 [95 % CI 0.70 to 0.82]) between AFP MoMs and both systematic (−0.20 [95 % CI −0.33 to −0.05]) and proportional (1.25 [95 % CI 1.06 to 1.44]) differences between the HCG/free β-HCG MoMs, respectively. No significant differences (p=0.070) were present between calculated individual risks by both of the programmes (estimated median risk with Immulite/Prisca system was 1 in 1890 and 1 in 1220 with Maglumi X3/Preaccu system). The triple test result for three pregnant women was negative with the Prisca program, it was positive with the Preaccu.

Conclusions: Second trimester screening performance of Maglumi X3/Preaccu system achieves comparable performance. Determining regional median values before using will provide more accurate and reliable results.

***Corresponding author: Yasemin Üstündağ**, Department of Clinical Biochemistry, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, 16310, Bursa, Türkiye,
E-mail: yaseminustundagyieah@gmail.com. https://orcid.org/0000-0003-2415-0372
Kağan Huysal and Meryem Rümeysa Yeşil, Department of Biochemistry, University of Health Sciences Bursa Yuksek Ihtisas Research and Training Hospital, Bursa, Türkiye. https://orcid.org/0000-0003-3142-5944 (K. Huysal). https://orcid.org/0000-0002-6492-6094 (M.R. Yeşil)

Keywords: method comparison; Maglumi X3/Preaccu system; second trimester down screening; risk assessment; Immulite/Prisca system

Introduction

The triple test is a screening test used in the prenatal diagnosis of chromosomal abnormalities, such as trisomy 18, 21, as well as neural tube defects [1, 2]. This method is a simple, affordable, and noninvasive routine component of prenatal care that distinguishes affected pregnant women from a large group [1, 2]. Alpha fetoprotein (AFP), human chorionic gonadotropin (HCG) or free β-HCG instead of total HCG, and unconjugated estriol (uE3) are measured in the serum of pregnant women at 16 and 18 weeks of gestation and standardized as a multiple of the median (MoM) corrected for gestational week using special computer programs [2].

Patient-specific risk estimates with the likelihood ratio (LR; likelihood ratio) can modify the maternal age-specific risk for an affected pregnancy [2]. High-risk pregnancies can be definitively diagnosed by chromosome analysis (chorionic villus sampling or amniotic fluid cells). Individual risk levels should be determined as accurately as possible because amniocentesis may result in fetal loss or other pregnancy complications [3].

The expected distributions for maternal serum markers are generally based on studies performed with different populations and alternative testing platforms [4, 5]. Although these differences may affect the marker values, the risk assessments provided are generally believed to be accurate [6–8].

In Turkey, public procurement law requires that the lowest bid be accepted when equipment or reagents are ordered [9]. Thus, a new device, Maglumi X3 (Snibe Company, Shenzhen, China), along with the Preaccu 1.17.9.2 (Snibe diagnostics, Shenzhen, China) risk analysis program were installed in our laboratory [10].

The aim of our study is to compare the results of this new platform with the measurements, MoM values and risk estimates generated by the Immulite (Siemens, Eschborn, Germany) device and PRISCA 5.1.0.17 (Siemens Healthcare GmbH, Germany) program installed in our laboratory.

Materials and methods

This retrospective study involved 164 pregnant women (including 20 pregnants with risk estimates above ≥1 in 250 for trisomy 21) out of 354 who attended SBU Bursa Yuksek Ihtisas Education and Research Hospital Medical Biochemistry Department using fresh serum for second trimester screening for trisomy 21 between 19 December 2022 and 19 January 2023. The study was approved by the regional ethics committee (2011-KAEK-25 2023/02–12). The participants included pregnant women between 16 and 18 weeks of gestation (median age 28.4 ± 5.5, range 18–40 years). Biochemical biomarkers were tested using the Immulite 2000 XPi (Siemens, Eschborn, Germany) and Maglumi X3 (Snibe Company, Shenzhen, China) immunoassay analyzers. Results for both instruments were obtained using a single lot of commercial reagent sets. The Snibe kits were uE3 (unconjugated estriol) (Lot:130202008M), AFP (Lot:130201002M), and free β-HCG (Lot:130214005M) while the Immulite kits were HCG (Lot: L2KCG6) instead of free β-HCG, AFP (Lot: L2KAP2), and uE3 (Lot: L2KUE36).

The commercial screening software programs PRISCA 5.1.0.17 (Siemens Healthcare GmbH, Germany) and Preaccu 1.17.9.2 (Snibe Diagnostics, Shenzhen, China) were used to calculate Trisomy 21 risks. Both software programmes uses biochemical markers, ultrasound examination parameters and demographics such as patient's date of birth, maternal weight, smoking habits, first day of the last menstrual period, diabetes mellitus, twin pregnancy, sampling date, and pregnancies conceived by IVF to calculate risk and deliver reports. Fetal gestational ages were calculated using biparietal diameters (BPD) with both softwares [11]. The lower limit of BPD was reported as 26 mm at 14+0 weeks in both programs; the upper limit was reported as 49 mm (20w+6d) in the Preaccu software and 55 mm (22w+5d) in the Prisca software, respectively.

A Lyphochek immunoassay plus internal quality control materials (Bio-Rad, USA) were analyzed using the Immulite device. The level 1 internal quality control coefficient of variation (CV) values for 20 consecutive days were 12.1, 8.95, and 7.53 % for the HCG, uE3, and AFP tests, respectively. The level 2 internal quality control CV values were 9.18, 4.9 and 5.59 %, respectively.

We used Snibe's (Snibe Company, Shenzhen, China) two-level internal quality control materials for free β-HCG testing on the Maglumi X3 device. However, internal quality controls provided by Snibe (Snibe Company, Shenzhen, China) during the study period were only single-level for the Maglumi X3, AFP and uE3 tests. Multi-level internal quality control materials provided by Serocheck (Serocon, Konya, Turkey) were used for AFP and UE3 tests.

The level 1 internal quality control CV values for 20 consecutive days were 4.52, 5.11 and 6.76 % for the free β-HCG, uE3, and AFP tests, respectively. The level 2 internal quality control CV values were 4.74, 9.8, and 4.54 %, respectively. The external quality control data obtained from the RIQAS Proficiency Testing Maternal Screening, Cycle 14 (RIQAS, Randox®, County Crumlin, UK) quality control program were considered acceptable. A positive Trisomy 21 screening test result was defined as a value greater than 1:250 in Prisca and greater than 1:150 in Preaccu, respectively.

Statistics

Data were evaluated using MedCalc version 20.116 (MedCalc Software, Ostend, Belgium) and SPSS version 27 (SPSS, Chicago, IL). Data were tested for normality using the Kolmogorov–Smirnov test, and means, medians, and standard deviations were calculated. Passing–Bablok regression analysis was performed to assess constant and proportional biases between methods, including the Cusum test of linearity. If the 95 % confidence interval (CI) of the intercept was zero, there was no constant bias, whereas if the 95 % CI of the slope was one, there was no proportional bias between the two methods [12]. Spearman rank correlation coefficient (rho) was also used to determine correlation between the two variables. Agreement was assessed using Bland–Altman plots. An F test was used to identify significant differences in the standard deviations. Wilcoxon signed-rank test was used to compare median values. A p-value < 0.05 was considered statistically significant.

Results

The gestational ages of the pregnant women studied were distributed over all days between 16 and 18 (0–6 days) gestational weeks. The gestational age calculated based on BPD showed a small difference between the two programs (median difference of one day).

We observed lower levels of AFP and uE3 and higher levels of HCG/free β-HCG in screen positive pregnant women (Table 1).

The median MoM values of AFP of the unaffected pregnancies were 1.15 (1.07–1.19) with Immulite 2000 XPi and 0.79 (0.74–0.84) with Maglumi X3 (p<0.001), respectively (Table 1). The MoM values of uE3 were 0.67 (0.61–0.72) with Immulite 2000 XPi and 0.73 (0.68–0.77) with Maglumi X3 (p=0.003) in pregnant women with risk estimates 1: >250 (Table 1). MoM values of AFP of 20 pregnant women with screening results 1: ≤250 for trisomy 21 were statistically different (Table 1).

While the triple test result for three pregnant women was negative with the Prisca program, it was positive with the Preaccu (risk 1:78 to 1:115).

Table 1: Comparison of marker levels and MoM results from two different analyzers and programs.

Maternal biomarkers	Immulite/Prisca systems Group 1 n=144 Median (95 % CI)	Immulite/Prisca systems Group 2 n=20		Maglumi X3/Preaccu Group 1 n=144 Median (95 % CI)	Maglumi X3/Preaccu Group 2 n=20	p-Value[a]	p-Value[b]
AFP, ng/mL	42.0 (38.70–44.12)	24.6 (19.37–34.72)		38.11 (35.33–42.20)	24.4 (19.7–33.9)	0.006	0.126
MoM	1.15 (1.07–1.19)	0.70 (0.60–0.96)		0.79 (0.74–0.84)	0.52 (0.37–0.66)	<0.001	<0.001
HCG, IU/mL	17.702 (16.298–19.326)	23.393 (17.790–33.434)	Free β-HCG	12.68 (10.86–14.50)	14.60 (11.37–19.86)	–	–
MoM	0.78 (0.72–0.87)	1.13 (0.71–0.15)		0.68 (0.62–0.77)	1.14 (0.87–1.30)	0.554	0.717
UE3, ng/mL	0.66 (0.57–0.72)	0.30 (0.24–0.43)		0.79 (0.75–0.86)	0.48 (0.19–0.54)	<0.001	0.102
MoM	0.67 (0.61–0.72)	0.38 (0.33–0.40)		0.73 (0.68–0.77)	0.44 (0.30–0.46)	0.003	0.587

Group 1: low risk (1: >250), Group 2: high risk (1: ≤250); AFP, alpha-fetoprotein; free β-HCG, free beta human chorionic gonadotropin; uE3, unconjugated estriol; MoM, multiple of median; 95 % CI. p=Wilcoxon signed-rank, [a]screen negative, [b]screen positive.

We could not access the pregnancy outcomes for two women. A pregnant woman, with a risk ratio of 1:397 according to the Prisca program, was found to be at a risk ratio of 1:85 with the Preaccu program. Differences in HCG MoM (1.17) and free beta HCG MoM (1.92) values contributed to discordant results. Oligohydramnios was diagnosed in this woman, and her baby was born without Down syndrome.

A Bland–Altman comparison of the MoMs of AFP showed that the limit of agreement between the analyzer systems was −0.38 (−0.83 to 0.06). On average, the measured values uE3 values were about 0.2 MoM (9 %) higher with Maglumi than with Immulite in pregnant women with risk estimates below ≥1 in 250 (Figure 1). Difference between AFP and HCG/free B HCG MoM values tend to get larger as the average gets higher.

The standard deviations of MoMs were slightly lower for AFP (F=1.91, p=0.001), uE3 (F=1.90, p=0.001) and slightly higher for HCG (Immulite) instead of free β-HCG (F=1.74, p=0.004) with Maglumi, respectively. Even if we used different tests (HCG on one platform free beta HCG on the other) MoM values (deviation of individual test from median value) were smilar.

Passing–Bablok indicated proportional bias (0.75 95 % CI 0.70 to 0.82) between AFP MoMs and both systematic (−0.20 95 % CI −0.33 to −0.05) and proportional (1.25 95 % CI 1.06 to 1.44) differences between the HCG/free β-HCG MoMs, respectively. The p-values from the linear model validity Cusum test for uE3 and AFP were 0.55 and 0.92, respectively (Table 2). For maternal serum AFP and uE3 values, the relationship between both platforms were linear (r=0.91 and r=0.80, p<0.001 respectively) (Table 2).

Statistical analysis revealed that no significant differences (p=0.070) were present between calculated individual risks by both of the programmes (estimated median risk with Immulite/Prisca system was 1 in 1890 and 1 in 1220 with Maglumi X3/Preaccu system).

Discussion

We observed a significant correlation between free β-HCG analyzed with Maglumi X3 or HCG values with Immulite 2000 XPi device; and AFP, uE3 MoM values analyzed with two different platforms. However, the MoM distributions of

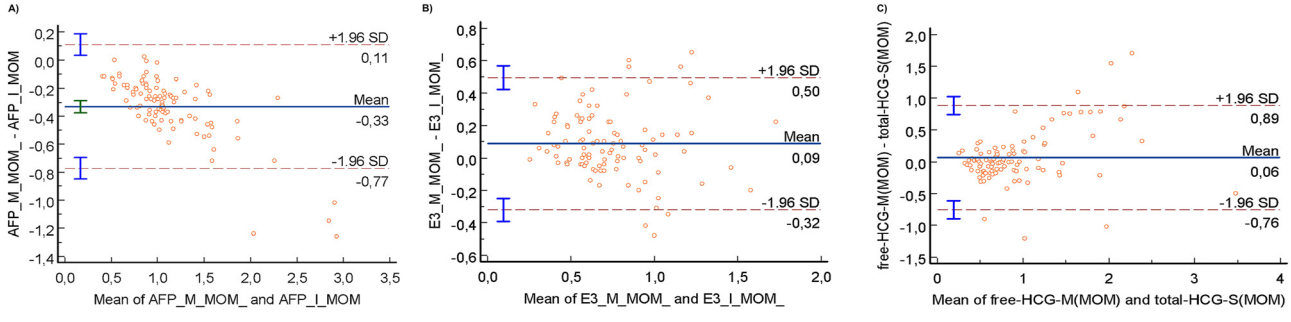

Figure 1: Bland and Altman plots of the MOM values of Maglumi X3 and Immulite 2000 XPi, with the representation of the limits of agreement in pregnants with risk estimates below ≥1 in 250 (A) AFP, (B) uE3, and (C) HCG/free β-HCG.

Table 2: Intercept and slope from the Passing-Bablok regression analysis.

	Marker levels			MoM values		
	All n=164	Group 1 n=144	Group 2 n=20	All n=164	Group 1 n=144	Group 2 n=20
AFP, ng/mL				**AFP (MoM)**		
rho	0.914	0.904	0.940	0.853	0.850	0.661
p-Value	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
Slope	1.04	1.07	0.95	0.75	0.79	0.68
95 % CI	0.98 to 1.11	1.00 to 1.16	0.86 to 1.14	0.70 to 0.82	0.72 to 0.87	0.52 to 1.07
Intercept	−2.47	−4.69	−0.28	−0.05	−0.10	0.03
95 % CI	−6.28 to −0.16	−8.15 to −1.01	−4.86 to 1.92	−0.14 to 0.00	−0.2 to −0.02	−0.2 to 0.15
Cusum test, p	0.81	0.87		0.92	0.75	0.97
uE3, ng/mL				**uE3 (MoM)**		
rho	0.808	0.783	0.462	0.669	0.657	0.005
p-Value	<0.001	<0.001	0.04	<0.001	<0.001	0.982
Slope	1.09	1.04	2.00	1.02	1.50	2.7
95 % CI	0.98 to 1.22	0.92 to 1.18	1.25 to 6.00	0.90 to 1.17	1.25 to 1.80	–
Intercept	0.07	0.09	−0.26	0.01	−0.23	−0.58
95 % CI	0.00 to 0.14	0.01 to 0.16	−1.59 to −0.01	−0.07 to 0.09	−0.40 to −0.05	–
Cusum heike	0.32	0.47	0.66	0.55	0.35	0.30
				HCG/free β-hCG (MoM)		
			rho	0.769	0.766	0.692
			p	<0.001	<0.001	0.001
			Slope	1.25	1.25	1.0
			95 % CI	1.06 to 1.44	1.06 to 1.46	0.73 to 1.82
			Intercept	−0.20	−0.19	−0.14
			95 % CI	−0.33 to −0.05	−0.34 to −0.05	−0.93 to 0.24
			Cusum test	0.17	0.07	0.97

Group 1: high risk (1: ≤250); Group 2: low risk (1: >250) AFP, alpha-fetoprotein; free β-HCG, free beta human chorionic gonadotropin; uE3, unconjugated estriol; MoM, multiple of median.

AFP and uE3 in the unaffected pregnant women analyzed with the new platform were not close to the well-established population parameters that we have used for many years. The differences in the MoM values calculated by the two platforms were, on average, 0.38 (38 %) for AFP and 0.2 (9 %) for uE3. A constant deviation between test methods will not affect the diagnostic effectiveness of MoMs calculated by either method. However, difference between AFP and HCG/free B-HCG MoM values tend to get larger as the average gets higher. Risk estimation models assume that maternal serum AFP and uE3 are 30 % lower in Down syndrome pregnancies compared to unaffected pregnancies. However, the bias between the established and new MoM values should not exceed 10 % [13]. A 10 % deviation in the median MoM for individual markers can result in up to a fourfold increase in the risk of Down syndrome. Even a 5 % bias in a single marker can result in up to a 2 % change in the false positive rate (FPR) [14]. Although the use of the MoM value aims to reduce the differences between analytical systems and screened populations, it is still sensitive to these variables. Other studies have also shown a significant difference in risk assessment results when using different screening platforms. It has been shown that even laboratories with the same platform can report different risk assessments [15]. Detection rate of the fetal trisomy 21 depends the accuracy of the MoM values of each marker. In our study, while the tests of three pregnant women were negative with the Prisca program, they were positive with Preaccu. Oligohydramnios was diagnosed in one of these woman, and her baby was born without Down syndrome. Similar to our finding; Godbole et al. reported that abnormal serum HCG levels from mothers reported as high risk for Down syndrome (with a normal fetus) were associated with adverse pregnancy outcomes as well as oligohydramnios [16].

In the unaffected population, MoM values must be between 0.95 and 1.05 while values outside this range have been shown to affect the FPR [17]. It is recommended that each laboratory should calculate its own MoM values for each analyte [18] The extent to which prenatal triple antenatal screening of a pregnant woman by different laboratories using different analytical systems affects the calculated individual risk is a matter of debate. There are many reports

comparing the estimated median values obtained using different devices [19, 20]. Previous studies has shown that there are significant differences in uE3 performance between different analytes [19, 20]. Mannings et al. found that falsely decreased AFP due to interference from the automated time-resolution fluorescence analyzer led to an increase in the calculated risk of Down syndrome pregnancies [21].

In our study, we used median data reported by the commercial software provider Preaccu. However, we could not find any study showing how the Preccau program derived the median MoM values [22]. Taking MoM values from the literature that do not combine knowledge obtained from assays, analyzers, and programs may exhibit unsatisfactory performance [23]. It is important to note that laboratories implementing the new platform need to determine new medians that are representative of the population [24, 25].

HCG or free β-HCG were analyzed using the two platforms. Although total HCG serum concentrations are 100 times higher than the free beta subunit in normal pregnancies, it has been reported that free β-HCG is preferable for evaluating Down syndrome [26]. We found that free β-HCG MoM is 0.03 higher than HCG MoM. Risk estimation models assume that maternal serum HCG/free β-HCG is two times higher in Down syndrome pregnancies compared to unaffected pregnancies.

The gestational age calculated based on BPD showed a small difference between the two programs (median difference of one day). Ethnicity, environmental, and socioeconomic factors may result in underestimation or overestimation of gestational age calculated with BPD [27]. We could not find information in the literature about the nomogram used for the accurate estimation of gestational age based on BPD for either software.

In this study, serum AFP, uE3, and HCG MoM values were varied using the two methods. Such differences in the performance of analytical instruments have a significant impact on individual risks. Studies with a larger number of patients that determine regional median values are needed to ensure more accurate and reliable prenatal screening test results. Clinicians should be aware of this issue, and methodological changes should be interpreted at the national level.

Limitations

An important limitation of the present study is that the accuracy of the Maglumi X3 data was not evaluated via any external quality assurance program during the study period because both analyzers were only in the laboratory for a short demonstration period. As there are no guidelines for institutions involved in nationwide prenatal screening tests or recommendations for different analytical platforms in our country, FPR results can only be reduced by studies [28, 29]. In this study, we used the findings of a user-conducted method comparison study in accordance with previously established performance specifications. The minimum sample size for method comparison and estimation of bias using patient samples is 40; while the new method use a different principle a sample size of 100–200 is recommended [30]. However; larger prospective studies are needed to test Maglumi X3/Preaccu platforms for effectiveness. In addition, instead of the software's medians from other populations we must calculate our own population-specific medians and weight correction factors. Therefore, It is necessary to develop a set of median values for each biochemical marker for each week of the second trimester.

Conclusions

Second trimester screening performance of Maglumi X3/Preaccu system achieves comparable performance. Determining regional median values by increasing the number of patients before using will provide more accurate and reliable results.

Research ethics: The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital, with Ethics Committee approval number 2011-KAEK-25, February 12,2023 dated.
Informed consent: Not applicable.
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