ORIGINAL ARTICLE

10.2478/AMB-2026-0057

HIDDEN SIGNALS IN PLACENTAL BIOCHEMISTRY: PAPP-A MOM AS AN EARLY INDICATOR OF TRISOMY 21

B. Ilkovska[1], B. K. Trifunova[2], F. Ilkovski[3], D. Gramatkovski[1], M. Avramovska[4], P. Avramovski[5], L. Todorovska[6]

[1]Sv. Kliment Ohridski University, High Medical School, PHO Clinical Hospital Dr. Trifun Panovski, Department of Laboratory Medicine, Bitola – North Macedonia
[2]Acibadem City Clinic UMHAT Tokuda, Department of Dermatovenerology – Sofia, Bulgaria
[3]High Medical School Dr. Trifun Panovski, Bitola – North Macedonia
[4]Sv. Kliment Ohridski University, High Medical School, PHO Clinical Hospital Dr. Trifun Panovski, Department of Obstetrics and Gynecology, Bitola – North Macedonia
[5]PHO Clinical Hospital Dr. Trifun Panovski, Department of Internal Medicine, Bitola – North Macedonia
[6]PHO Clinical Hospital Dr. Trifun Panovski, Department of Nuclear Medicine, Bitola – North Macedonia

Abstract. Purpose: *Trisomy 21, or Down Syndrome, is one of the most common chromosomal abnormalities in newborns, appearing in approximately 1 in 700 births, with risk increasing with maternal age. It is a condition of particular importance during first-trimester screening.* ***Materials and Methods:*** *We conducted a retrospective cohort study of 2,849 pregnant women at 11+0 and 13+6 weeks of gestation to assess the indicative values of Pregnancy-associated plasma protein-A (PAPP-A) expressed as multiples of the median (MoM), as well as the influence of maternal factors. Differences within groups were made using t-tests or Mann-Whitney U tests for continuous variables, with $p < 0.05$ considered statistically significant.* ***Results:*** *Out of the 2,849 pregnant women examined, 293 were classified as high-risk pregnancies (risk for screening in the first trimester ≥ 1:250). We confirmed that PAPP-A MoM values were significantly lower in high-risk pregnancies (median 0.68, IQR 0.4-1.1) compared with the low-risk group (median 1.81, IQR 1.2-2.5; $p < 0.0001$). Nuchal translucency MoM was slightly lower in high-risk pregnancies (0.87, IQR 0.43-1.20) compared with the low-risk group (0.98, IQR 0.86-1.10; $p = 0.0394$), while CRL did not differ significantly between groups (70.3 mm vs. 63.1 mm; $p = 0.4037$).* ***Conclusions:*** *These findings support the use of combined screening with maternal demographics, ultrasound, and biochemical markers for accurate first-trimester risk assessment. Further studies suggest adjusting MoM values for maternal characteristics to enhance screening performance, reduce false positives, and enable individualized counseling. Early identification is crucial in high-risk pregnancies to facilitate informed decision-making, targeted check-ups, and reinforce the role of integrated, personalized prenatal screening for optimizing maternal and fetal outcomes.*

Key words: *Trisomy 21, PAPP-A, first-trimester screening, maternal age, nuchal translucency*

Corresponding author: *Biljana Ilkovska PhD MD, St. Dimce Lahcanski No.29, 7000 Bitola, North Macedonia, email: drbiljanailkovska@yahoo.com*

ORCID: *0000-0002-6287-3830 – Biljana Ilkovska*

ORCID: *0000-0003-0437-6526 – Bisera Kotevska Trifunova*

ORCID: *0009-0002-9271-3608* – *Filip Ilkovski*
ORCID: *0009-0004-0562-7045* – *Dejan Gramatkovski*
ORCID: *0000-0003-1129-1205* – *Maja Avramovska*
ORCID: *0000-0003-2816-3365* – *Petar Avramovski*

Received: *15 October 2025;* ***Accepted:*** *23 January 2026*

INTRODUCTION

Trisomy 21, or Down syndrome, is the most common chromosomal abnormality in newborns, with an incidence of approximately 1 in 700 pregnancies, and the risk of Down syndrome is strongly associated with advancing maternal age [1]. First-trimester screening of pregnant women provides an opportunity for early detection of Down syndrome, and includes maternal age, measurement of fetal nuchal translucency (NT) and CRL, and key biochemical markers in maternal serum, including pregnancy-associated plasma protein A (PAPP-A) and free β-human chorionic gonadotropin (free β-hCG) [1, 2]. Numerous scientific studies indicate that PAPP-A levels (especially when expressed as corrected multiples of the median (MoM)) are significantly reduced in pregnancies with trisomy 21 [1, 2].

A prospective cohort study conducted in 2020 further solidifies this fact as it reported significantly lower PAPP-A MoM values in pregnancies with positive Down syndrome, with detection rates of over 88% and a false-positive rate of approximately 5% [1]. Similarly, a large retrospective analysis from China conducted in 2023 further highlights that the combination of PAPP-A MoM ≤ 0.5 and free β-hCG MoM ≥ 2.75 is greatly useful for detecting Trisomy 21, even in low-risk populations [2]. These findings are furthermore supported by a conducted meta-analysis of over 72,000 pregnancies, which confirmed significant differences in PAPP-A, free β-hCG, and NT values between healthy pregnant women and pregnant women at risk of Down syndrome [3].

An international cohort study conducted in 2023 consisting of 13,000 singleton pregnancies had presented that the inclusion of placental growth factor (PlGF) and alpha-fetoprotein (AFP) together with PAPP-A, free β-hCG and NT increased the detection rate of Trisomy 21 to 96% [4]. When highlighting PAPP-A concentrations, their reduced values are associated with adverse obstetric outcomes, such as preterm birth, small-for-gestational-age infants and preeclampsia [5]. Furthermore, in pregnant women with pregestational diabetes mellitus we observed how their PAPP-A MoM decreased by 12%. This is a finding which is best taken into consideration when screening as it may lead to an increase in false-positive screening rates when appropriate adjustments are not made [6]. This decrease is thought to be caused by impaired placental function, as reduced PAPP-A levels are associated with abnormal trophoblast activity and dysregulation of the insulin-like growth factor (IGF) pathway – mechanisms, which leads to further contribution to both trisomy 21 and placental insufficiency [7].

The aim of this study was to assess the predictive efficacy of PAPP-A, expressed as multiples of the median (MoM), in identifying the risk of trisomy 21 during the first trimester of pregnancy. In addition to these markers the study is aimed to assess how age, body weight, smoking status, in vitro fertilization (IVF), and pregestational diabetes are to be taken into consideration due to their influence over biomarker levels.

MATERIALS AND METHODS

Study design and Population

This retrospective cohort study includes data collected from 2,849 pregnant women who underwent combined first-trimester screening at the Public Health Institution Clinical Hospital "Dr. Trifun Panovski" – Bitola, Department of Medical Biochemistry, between January 1, 2020, and December 31, 2024. Screening was performed between 11+0 and 13+6 weeks of gestation. Ethical approval was obtained from the Institutional Ethics Committee of Clinical Hospital "Dr. Trifun Panovski," Bitola, North Macedonia (Approval No. 27/2020). High-risk pregnancies were defined as those with a first-trimester screening risk ≥1:250 for trisomy 21, calculated using PRISCA software. Invasive diagnostic testing (chorionic villus sampling or amniocentesis) was performed in a subset of these high-risk pregnancies to confirm chromosomal abnormalities.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Singleton pregnancies undergoing routine screening in the first trimester between 11+0 and 13+6 weeks of gestation.

- Availability of maternal serum levels of PAPP-A with appropriate MoM values.
- Ultrasound measurements, including nuchal translucency (NT) and crown-rump length (CRL), performed according to standardized protocols.
- Demographic and clinical data of the pregnant women that included: age, weight, smoking status, mode of conception (spontaneous or IVF), and pregestational diabetes status.

Exclusion Criteria:

- Twin pregnancy.
- Pregnancies with confirmed fetal anomalies identified before biochemical testing.
- Incomplete or missing ultrasound measurements.
- Women who refuse to participate or have incomplete consent for the use of clinical data.

Biochemical Analysis

Maternal blood samples were collected at the Department of Medical Biochemistry following referral by primary gynecologists. Serum levels of pregnancy-associated plasma protein A (PAPP-A) was measured using the Immulite 2000 XPi immunoassay system (Siemens Healthcare Diagnostics), in accordance with the manufacturer's protocol. The results were expressed as multiples of the median with values adjusted for gestational age and maternal characteristics.

Ultrasound Examination

Ultrasound examinations, including nuchal translucency (NT) and crown–rump length (CRL) measurements, were performed by the women's primary gynecologists using standardized first-trimester screening protocols.

Maternal Demographic and Clinical Data

Information on maternal age, body weight, smoking status, in vitro fertilization (IVF), and pregestational diabetes mellitus was obtained from standardized questionnaires completed by the referring gynecologists.

Risk Assessment

Risk for trisomy 21 was calculated using PRISCA software (Prenatal Risk Calculation Software, Typolog Software, Germany). The software in question uses a combination of maternal age, ultrasound findings (e.g., NT), and biochemical marker MoM values (using population-specific medians and correction factors) to provide risk estimates for chromosomal abnormalities personalized to every patient.

Statistical Analysis

The collected data were analyzed using IBM SPSS Statistics version 13 alongside *DES*criptive statistics as to summarize demographic, clinical, and biochemical data. Group comparisons (high-risk vs. low-risk) were performed using independent t-tests or Mann–Whitney U tests to account for continuous variables and Chi-square tests for categorical variables. Correlations between maternal characteristics and biomarker MoM values were evaluated using Pearson or Spearman correlation coefficients, as appropriate. A two-tailed p-value < 0.05 was considered statistically significant. No logistic regression was performed; associations between PAPP-A MoM, NT, CRL, and high-risk status were evaluated using group comparisons (t-tests, Mann–Whitney U tests) and correlation analysis, with $p<0.05$ considered significant.

RESULTS

Our study included two groups of pregnant women: healthy pregnant women (low-risk group) and a group of pregnant women at high risk of Down syndrome. Maternal age was significantly higher in the high-risk group. Due to the skewed distribution, median and interquartile range (IQR) are shown: low-risk pregnant women were 27.3 years old (IQR 25-30), while high-risk pregnant women were 32.0 years old (IQR 30-34). Maternal weight and gestational age showed similar patterns and are also presented as median ± IQR. Other maternal characteristics: smoking, mode of conception, and diabetes status are presented as summary numbers (Table 1).

When assessing the history of the disease, related to previous pregnancies with Trisomy 21, 1,402 low-risk pregnant women had no such history, while 3 pregnant women reported a positive history, and 779 had an unknown history. In the high-risk group, 185 pregnant women reported no previous pregnancies with Trisomy 21, while 2 pregnant women had a positive history, and 106 had an unknown status.

Maternal weight showed similar distributions between the two groups with a median of 67.5 kg (IQR 60–75) in the low-risk group and 66.5 kg (IQR 58–75) in the high-risk group, indicating no significant difference between them.

Measurement of CRL showed differences that were not statistically significant ($p = 0.4037$), although CRL was slightly lower in the high-risk group. The median CRL in low-risk pregnant women was 70.3 mm (IQR 66–74) while in high-risk pregnant women the CRL was 63.1 mm (IQR 58–68) (Table 2, Figure 1).

Table 1. Maternal Characteristics and First-Trimester Screening Variables

Variable	Healthy pregnant women with low risk (n=2556) median (IQR)	Pregnant women with high risk for Down syndrome (n=293) median (IQR)
Maternal age (years)	27 (25–30)	32 (30–34)
Gestational age (weeks)	12 (12–13)	12 (11–13)
Smoking status	1821 non-smoker (71%) 348 smokers (14%) 387 unknown (15%)	253 non-smoker (86%) 40 smokers (14%)
Mode of conception	2156 spontaneous (84%) 17 IVF (1%) 12 unknown (0.5%)	286 spontaneous (98%) 4 IVF (1%) 3 unknown (1%)
Diabetes status	2165 non-diabetic (85%) 5 diabetic (<1%) 15 unknown (1%)	292 non-diabetic (99%) 1 diabetic (<1%)
History of previous trisomy 21	1402 no (55%) 3 yes (<1%) 779 unknown (30%)	185 no (63%) 2 yes (<1%) 106 unknown (36%)
Maternal weight- kg	67.5 (60–75)	66.5 (58–75)

High-risk pregnancies: first-trimester screening risk ≥ 1:250

Table 2. Ultrasound and Biochemical Parameters in Healthy and High-Risk Pregnancies

Variable	Healthy pregnant women with low risk (n=2556) median (IQR)	Pregnant women with high risk for Down syndrome (n=293) median (IQR)	P
Crown - rump length (CRL) mm	70.3 (66–74)	63.1 (58–68)	0.4037
Nuchal translucency (NT) mm	1.72 (1.65–1.78)	1.41 (1.10–1.70)	0.0581
Nuchal translucency multiple of the median (NT MoM)	0.98 (0.86–1.10)	0.87 (0.43–1.20)	0.0394
PAPP-A	2.20 (1.3–3.0)	0.61 (0.3–1.2)	<0.0001
PAPP-A MoM	1.81 (1.2–2.5)	0.68 (0.4–1.1)	<0.0001

High-risk pregnancies: first-trimester screening risk ≥ 1:250

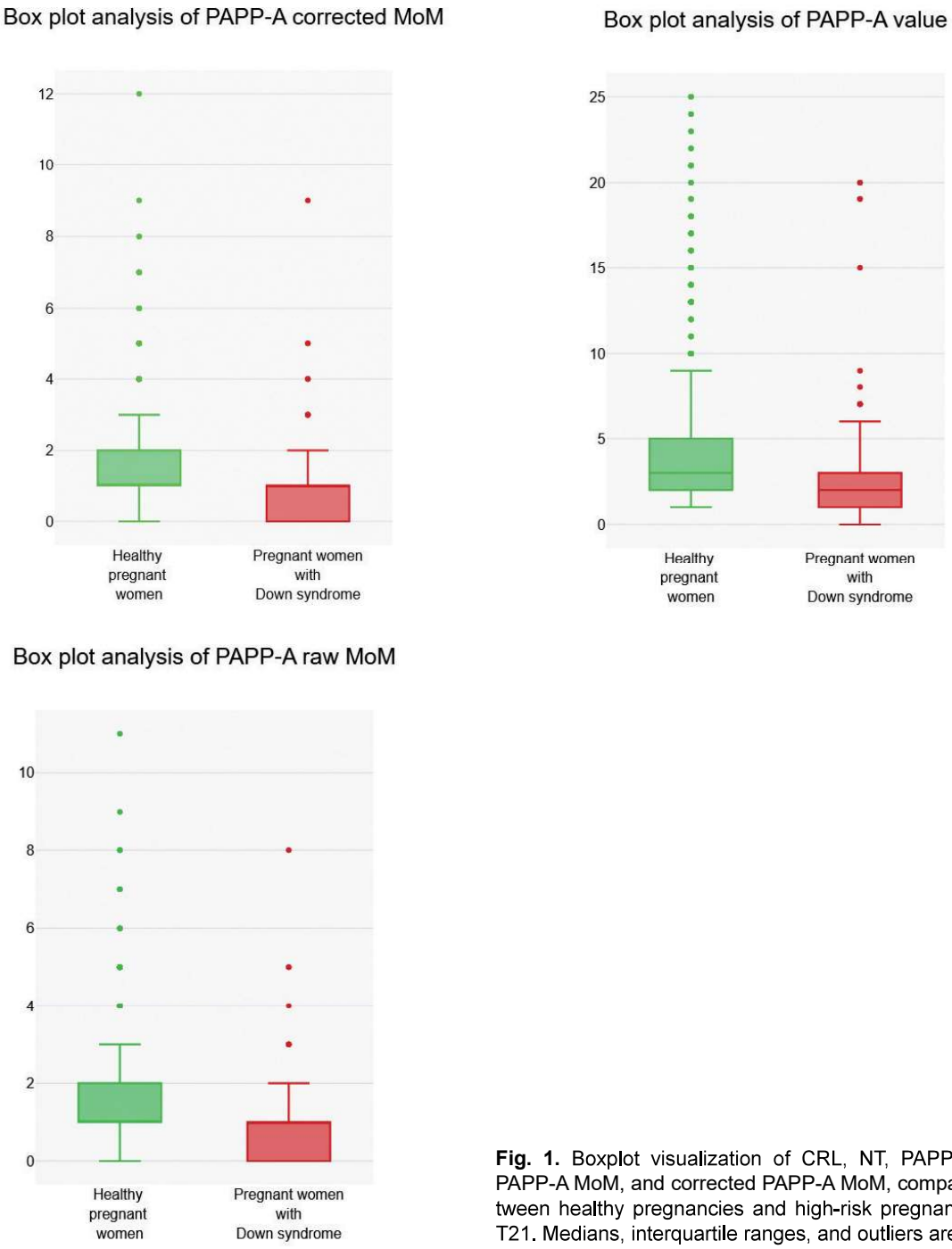

Fig. 1. Boxplot visualization of CRL, NT, PAPP-A, raw PAPP-A MoM, and corrected PAPP-A MoM, compared between healthy pregnancies and high-risk pregnancies for T21. Medians, interquartile ranges, and outliers are shown

Nuchal translucency (NT) also varied between groups, with higher values observed in low-risk pregnancies. In low-risk pregnancies, NT had a median of 1.72 mm (IQR 1.65–1.78), while in high-risk pregnancies, the median was 1.41 mm (IQR 1.10–1.70), with a borderline non-significant difference (P = 0.0581). NT multiples of the median (NT MoM) were slightly lower in the high-risk group (0.87, IQR 0.43–1.20) compared with the low-risk group (0.98, IQR 0.86–1.10), and this difference reached statistical significance (P = 0.0394).

PAPP-A values were significantly lower in high-risk pregnancies. The median PAPP-A was 2.20 (IQR 1.3–3.0) in low-risk pregnancies, while in high-risk pregnancies it was 0.61 (IQR 0.3–1.2) (P < 0.0001). Similarly, the corrected PAPP-A MoM values were lower in high-risk pregnancies (median 0.68, IQR 0.4–1.1) compared with low-risk pregnancies (median 1.81, IQR 1.2–2.5), confirming the importance of this marker in the detection of Trisomy 21 (P < 0.0001).

DISCUSSION

This study provides a comprehensive analysis through the use of maternal, biochemical, and ultrasound parameters in healthy pregnancies in comparison to those at increased risk for Trisomy 21, highlighting how early indicators may be used to optimize first-trimester prenatal screening and risk awareness.

Our findings are in line with the study by Kirovakov et al., which made the same observations in a Bulgarian population and supports the application of combined screening protocols in the early detection of chromosomal abnormalities [8].

Maternal age was significantly higher in the high-risk group, with a mean value of 32.39 years compared to 27.32 years in the healthy group. This finding is consistent with prior epidemiological studies demonstrating that the risk of Trisomy 21 increases with maternal age, particularly after 35 years [9]. Although most women in this study that fell inside the higher-risk group were under the age of 35, they still presented a measureable increase inside the baseline risk, despite there only being a minimal increase in maternal age. Showing how age-specific risk calculations need to be supported with in risk calculations for first-trimester screening procedures.

An interesting finding is that smokers presented a slightly higher percentage inside the high-risk group. However, this did not lead to any findings supporting a direct connection or association between smoking and increase in Trisomy 21. This finding further supports previous research that found that lifestyle factors (such as smoking) have minimal influence on the appearance of chromosomal abnormalities in comparison to maternal age, despite these factors having a possible effect on pregnancy outcomes. Future studies that involve a large sample size could further shed light or explain the effects of maternal smoking and its effects over biomarkers or other pregnancy risk factors. These findings are in line with the Bulgarian study by Antonova et al, who evaluated fertility treatments and oocyte competence and who noted that maternal age remains a dominant risk factor for Trisomy 21, and in vitro fertilization and other assisted reproductive techniques may require careful consideration when interpreting biochemical markers [10]. Although some meta-analyses do raise a flag on major birth defects in ART pregnancies, they are not specific to Trisomy 21 [11] with other studies instead highlighting how maternal age and underlying infertility are the main determinants of risk rather than ART procedures themselves [12]. Noticeably however, it has shown that preimplantation genetic testing on embryos before transfer lowers the likelihood of chromosomal abnormalities, underscoring the potential of genetic screening to limit risk.

The presence of maternal diabetes was infrequent and limited in the data collected thus limiting the ability to assess its, impact on the Trisomy 21 risk. But it is still known that maternal diabetes does have a negative influence over pregnancy outcomes, such as congenital anomalies, macrosomia and varied prenatal complications [13]. However, a direct relationship cannot be created between diabetes and chromosomal abnormalities, as hyperglycemia could have an impact in the early development of the embryo that contributes to the rise of risk for abnormalities. Further studies are needed as to give a clear view and definition of the effect of maternal diabetes in association with the risk of Trisomy 21 with emphasis on type of diabetes, glycemic control, as well as other confounding factors.

Within the high-risk group of women were women that have reported previous pregnancies with positive Trisomy 21. An observation that stays consistent with previous findings saying an increase chance of reoccurrence and risk with following pregnancies with special emphasis on cases where there were involved parental chromosomal deformations [14]. However, the large amounts of missing obstetric data within the healthy group limit the potential of interpretation of these findings, leading to a critical need for accurate and comprehensive data collection for future counseling and guiding for targeted screening and monitoring for chromosomal abnormalities [16].

The study by Hristova et al. conducted in pregnant women in Bulgaria confirms the association of variations in fetal growth related to maternal weight and BMI and PAPP-A values, which reinforces the need to adjust MoM values for maternal characteristics [17].

Interestingly, NT values were slightly lower in the high-risk group in our cohort. This observation differs from most published studies and may reflect algorithm-based risk classification rather than confirmed Trisomy 21 cases, as well as interobserver variability in NT measurements. Furthermore, this observation is supported by NT MoM values, as they as well were more stable in healthy pregnancies while showing a much wider range within high-risk pregnancies, thus reinforcing NT screening as a reliable indicator in early pregnancies.

Although we observed slightly lower CRL values in high-risk pregnant women compared to healthy pregnant women, this difference was not statistically significant ($p = 0.4037$). Therefore, CRL alone should not be considered a reliable early marker of trisomy 21, but it can provide additional information

when interpreted together with NT and biochemical markers [18, 19].

Both raw and corrected PAPP-A MoM values were recorded to be significantly lower with-in the high-risk group, supporting the markers role as an early indicator of increased risk of Trisomy 21 [20, 21]. A decrease in PAPP-A values likely reflect impaired placental function and dysregulation of the insulin-like growth factor (IGF) pathway (processes implicated in both chromosomal abnormalities and placental insufficiency). These findings underscore the importance of adjusting and personalizing MoM values for maternal factors such as weight, age, and diabetes status, as uncorrected values may lead to false-positive or false-negative results. MoM adjustments, along with integrated PAPP-A and NT screening and results further enhances predictive accuracy, consistent with international screening protocols. The variability observed in biochemical risk estimates (median 177, mean 235.75) highlights the heterogeneity of high-risk pregnancies and the necessity for individualized risk assessment during prenatal screening.

Limitations of the Study

This study has several limitations that should be considered. First, the sample size, the study included a relatively small number of subjects and was conducted at only one health facility, which may limit the generalizability of the findings to broader populations with different demographic or clinical characteristics.

Second, the study did not evaluate the influence of smoking status, socioeconomic status, and ethnicity of the participants, which may affect biomarker levels, including PAPP-A. Also, the ultrasound measurements were performed by a larger number of gynecologists, and this poses a risk of subjective factors in the measurement.

The findings of this study imply the need for reinforcing the use of combined first-trimester screening, which inclu*DES* maternal age, biochemical markers, ultrasound parameters as baseline risk assessment. Also, there is an inclusion and use of NT and PAPP-A markers for early detection thanks to their sensitive nature as well as CRL as a supportive finding in assessing presence of chromosomal anomalies; Careful collection and study of the patient's maternal history such as previous pregnancies, use of ART methods, presence of diabetes and mixed lifestyle factors. Collectively, these findings contribute to a better understanding of the mechanisms underlying chromosomal abnormalities and may facilitate further refinement and personalization of prenatal screening algorithms.

This study has several limitations, including its retrospective design and the fact that it was conducted at a single center, which may limit the generalizability of the findings.

Future prospective multicenter studies with larger cohorts are needed to further validate the predictive value of PAPP-A MoM and its role in optimizing first-trimester screening strategies.

CONCLUSION

This study highlights the effectiveness of combined first-trimester screening using methods mentioned above, in identifying pregnancies at increased risk for Trisomy 21, with our findings illustrating that key points of interest for increased risk are advanced maternal age and decreased PAPP-A MoM which emerged as the strongest indicators of chromosomal abnormality.

The results also emphasize the importance of considering maternal characteristics such as the patient's body weight, presence of diabetes, smoking, mode of conception and biochemical marker results in deciding a patient's risk group. Also taking into account the need for personalization of these findings for MoM values as to lower the chance of false positives/negatives appearing with in testing.

Additionally, the study underlines the importance of integrated risk evaluation, combining biochemical and ultrasound markers with maternal demographics, to improve early detection of high-risk pregnancies. Early identification allows for timely counseling, informed decision-making, and, where appropriate, targeted follow-up and diagnostic testing, ultimately contributing to improved maternal and fetal outcomes.

While our findings support the robustness of combined first-trimester screening, future prospective studies with larger and more diverse populations are needed to refine cut-off values, validate predictive algorithms, and further enhance the sensitivity and specificity of screening for Trisomy 21. Overall, this study reinforces the critical role of a comprehensive, individualized approach to prenatal screening and highlights the continuing importance of PAPP-A, NT, and maternal age as cornerstones of early risk assessment.

Acknowledgements: *We would like to thank the staff of the Department of Medical Biochemistry at the Clinical Hospital "Dr. Trifun Panovski" – Bitola, as well as all participating gynecologists and patients, for their contribution to data collection and support throughout this study.*

Funding Statement: *The authors declare that this research received no funding from public, private, or commercial sources. There was no financial support that could have influenced the results or their interpretation.*

Declaration of Interest: *The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.*

REFERENCES

1. Mazer Zumaeta A, Wright A, Syngelaki A et al. Screening for trisomies at 11–13 weeks' gestation: use of PAPP-A, PlGF or both. Prenat Diagn. 2020;40(11):1421-9.
2. Kagan KO, Wright D, Spencer K et al. First-trimester screening for trisomy 21 by free β-hCG and PAPP-A: impact of maternal and pregnancy characteristics. Ultrasound Obstet Gynecol. 2008;31(5):493-502. doi:10.1002/uog.5332
3. Zhang Y, Li H, Wang Q et al. Chinese cohort evaluation of PAPP-A ≤0.5 MoM and β-hCG ≥2.75 MoM in trisomy 21 detection. BMC Pregnancy Childbirth. 2023;23:363.
4. Wang J, Li X, Chen Y et al. Multimarker approach (PAPP-A, free β-hCG, PlGF, AFP + NT) detection rates in 13,000 women. Prenat Diagn. 2023;43(4):473-80.
5. Ranganathan A, Fresen J, Sarkar P. Association of low first-trimester pregnancy-associated plasma protein A with adverse pregnancy outcomes: an observational study. Obstet Gynecol Rep. 2016;1(1):1-6. doi:10.15761/OGR.1000116
6. Gonzalez-Gonzalez NL, Gonzalez Davila E, Castro A et al. Effect of pregestational diabetes mellitus on first-trimester placental characteristics: three-dimensional placental volume and power Doppler indices. Placenta. 2014;35(3):147-51. doi:10.1016/j.placenta.2014.01.002
7. Guibourdenche J, Leguy MC, Pidoux G et al. Biochemical screening for fetal trisomy 21: pathophysiology of maternal serum markers and involvement of the placenta. Int J Mol Sci. 2023;24(8):7669. doi:10.3390/ijms24087669
8. Kirovakov Z, Hinkova N, Konova E. The impact of inherited thrombophilia on first trimester combined aneuploidy screening parameters. Acta Medica Bulgarica. 2024;51(4):22-27. doi:10.2478/AMB-2024-0073.
9. Jensen TK, Andersen AN, Bjerregaard B et al. Maternal age and the risk of fetal aneuploidy: a nationwide cohort study in Denmark. Acta Obstet Gynecol Scand. 2023. doi:10.1111/aogs.14713
10. Hristova I, Naseva E, Yunakova M. Fetal growth abnormalities in overweight and obese pregnant women: a study among Bulgarian pregnant women. Acta Medica Bulgarica. 2026;53(Suppl 1):6-14. doi:10.2478/AMB-2026-0001.
11. Aiken CE, Smith GC, Best C. Assisted reproductive technology and the risk of birth defects: a systematic review and meta-analysis. JAMA Pediatr. 2016;170(9):890-7. doi:10.1001/jamapediatrics.2016.1011
12. Tannir G, Boulet S, Jamieson DJ. Genetic risks and outcomes in assisted reproductive technologies. Fertil Steril. 2021;115(5):1101-9. doi:10.1016/j.fertnstert.2021.01.017
13. Ornoy A. Prenatal origin of obesity and diabetes: an update. Reprod Toxicol. 2015;56:98-106. doi:10.1016/j.reprotox.2015.05.002
14. Robinson DO, Hall B, Jacobs PA. Parental origin of extra chromosomes in trisomy 21 and its relationship to maternal age. Hum Genet. 2009;126(2):231-7. doi:10.1007/s00439-009-0703-0
15. Khoshnood B, Loane M, de Vigan C, Dolk H. Long-term trends in prevalence of Down syndrome in Europe. Prenat Diagn. 2011;31(5):487-94. doi:10.1002/pd.2725
16. Zhu X, Li H, Wang J et al. Association of nuchal translucency with chromosomal abnormalities in a large Chinese cohort. JAMA Netw Open. 2023;6(3):e231234. doi:10.1001/jamanetworkopen.2023.1234
17. Antonova I, Ivanov D, Yaneva G, et al. Body mass index as a factor influencing oocyte competence and implantation potential – distribution and results in 4,882 women undergoing fertility treatment. Acta Medica Bulgarica. 2024;51(2):8-13. doi:10.2478/AMB-2024-0024.
18. Souka AP, Snijders RJ, Novakov A et al. Deficient growth in fetuses with trisomy 21 at 11–13+6 weeks of gestation. Ultrasound Obstet Gynecol. 2002;19(2):117-20. doi:10.1002/pd.643
19. Liao AW, Snijders RJ, Geerts L et al. Fetal growth in chromosomally abnormal fetuses. Ultrasound Obstet Gynecol. 2000;15(1):9-13. doi:10.1046/j.1469-0705.2000.00002.x
20. Spencer K, Spencer CE, Power M et al. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: three years' prospective experience. BJOG. 2003;110(3):281-6. doi:10.1046/j.1471-0528.2003.02292.x
21. Krantz DA, Hallahan TW, Orlandi F et al. First-trimester Down syndrome screening using dried blood biochemistry and nuchal translucency. Obstet Gynecol. 2000;96(2):207-13. doi:10.1016/S0029-7844(00)00895-1