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First-trimester screening markers in pregnancies complicated by cervical insufficiency: A comparative retrospective study

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MAIN POINTS

- Cervical insufficiency was associated with a significantly earlier gestational age at delivery compared to the control group.
- The study identified a distinct pattern in pregnancy outcomes among women with spontaneous preterm birth versus cervical insufficiency.
- A multi-group comparison revealed statistically significant differences in neonatal outcomes across all study groups.
- This research highlights the importance of early detection and classification of risk groups to prevent adverse perinatal outcomes.

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ABSTRACT

Aim: This retrospective study aimed to evaluate the relationship between first-trimester screening markers and cervical insufficiency, comparing biochemical parameters and pregnancy outcomes among women with cervical insufficiency, spontaneous preterm birth, and term pregnancies.

Materials and Methods: A total of 248 singleton pregnancies were included and divided into three groups: control (term deliveries, n=121), cervical insufficiency with cerclage (n=60), and spontaneous preterm birth (n=67). First-trimester serum markers including pregnancy-associated plasma protein A (PAPP-A), free beta-human chorionic gonadotropin (β-hCG), nuchal translucency (NT), and alpha-fetoprotein (AFP) were analyzed. Obstetric and neonatal outcomes such as gestational age at delivery, birth weight, Apgar scores, and adverse neonatal outcomes were recorded.

Results: No significant differences were observed in first-trimester PAPP-A, β-hCG, NT, and AFP levels between the cervical insufficiency and control groups. However, the spontaneous preterm birth group exhibited significantly lower PAPP-A and higher β-hCG levels compared to both other groups ($p<0.001$). Gestational age at delivery, birth weight, Apgar scores, and adverse neonatal outcomes were significantly worse in both cervical insufficiency and spontaneous preterm birth groups compared to controls ($p<0.05$).

Conclusion: First-trimester biochemical markers have limited predictive value for cervical insufficiency but show significant alterations in spontaneous preterm birth. Cervical insufficiency appears to be a localized structural pathology not reflected by early systemic biochemical changes. Clinical management should prioritize second-trimester cervical length assessment and appropriate interventions over reliance on first-trimester serum markers. Further research is needed to identify specific biomarkers for early detection of cervical insufficiency.

Keywords: Cervical insufficiency, First-trimester screening, Beta-human chorionic gonadotropin(β-hCG), Pregnancy-associated plasma protein A

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INTRODUCTION

Preterm birth is a major global obstetric problem, accounting for approximately 35% of all neonatal deaths worldwide [1]. Cervical insufficiency (CI) is of particular concern due to its impact on second-trimester pregnancy loss and preterm birth. CI is defined as painless cervical shortening and dilation occurring before 24–28 weeks of gestation without uterine contractions [2]. It affects approximately 1% of pregnant women but is the most common cause of recurrent second-trimester losses and extremely preterm births [2]. Given its serious effects on fetal health and neonatal morbidity, early diagnosis of women at risk of cervical incompetence is of great importance. Clinically, it is quite difficult to detect cervical incompetence before cervical changes become apparent.There is no reliable first-trimester diagnostic test for CI, and the condition is often recognised only after significant cervical shortening or dilation occurs in the second trimester [3]. The diagnosis is usually based on a characteristic obstetric history, such as two or more painless miscarriages or births during the second trimester, or on objective findings of cervical changes in the

middle of pregnancy [4,5]. In the second trimester, a cervical length of less than approximately 25 mm is one of the best clinical predictors of spontaneous preterm birth and may require prophylactic cerclage or vaginal progesterone to prevent preterm birth.

In routine prenatal care, the first trimester combined screening test is performed at 11–13 weeks of gestation to assess the risk of fetal aneuploidy [6]. This test measures fetal nuchal translucency (NT) on ultrasound, along with maternal serum pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) [7,8]. Specifically, abnormalities in these first trimester screening markers have been linked to numerous poor obstetric outcomes, indicating that they may offer early insights into placental function or developmental anomalies beyond chromosomal defects. Decreased PAPP-A levels in early gestation, together with elevated or diminished MoM (multiple of median) values of free β-hCG, have been correlated with a heightened risk of placental insufficiency syndromes, including preeclampsia, fetal growth restriction (FGR), and spontaneous premature birth [9,10,11]. However, it remains unclear whether first-trimester screening markers have any predictive value, particularly for cervical insufficiency.

This study aims to address this gap by evaluating whether first-trimester screening markers differ from other pregnancy outcomes in pregnancies complicated by cervical insufficiency. In conclusion, clarifying the relationship between first-trimester markers and cervical insufficiency may provide information for future strategies aimed at early diagnosis of high-risk pregnancies and the development of targeted preventive interventions.

MATERIALS AND METHODS

Study design

This study was designed as a retrospective cohort analysis to investigate the prognostic value of first-trimester screening markers in pregnancies complicated by cervical insufficiency, compared to spontaneous preterm birth and uncomplicated term deliveries. Data were collected from patients who applied to the Perinatology Department of Ankara Etlik City Hospital Hospital between January 1, 2023, and January 1, 2025. Ethical approval was obtained for the study from Ankara Etlik City Hospital Ethics Committee (approval number: AESH-BADEK-2025-028).

Selection of case and Selection of control

A total of 248 pregnancies were included in the study. The pregnant women were divided into three groups for comparison: those diagnosed with cervical insufficiency and who underwent cerclage, those who presented with spontaneous preterm labour, and a control group whose pregnancies ended without complications at term. The study included only patients who presented for ultrasound examination between 16+0 and 23+6 weeks of gestation due to an indication for cervical length measurement and who had a cervical length of <25 mm measured by transvaginal ultrasound during this period, followed by cerclage. Progesterone therapy was initiated in patients with a cervical length of <25 mm, and transvaginal cervical length monitoring was performed every 1–2 weeks until the 24th week of pregnancy. Cervical cerclage was performed in patients whose cervical length continued to shorten to <10 mm under progesterone therapy [3]. Patients with a history of second-trimester losses in previous pregnancies or a previous history of cerclage were excluded from the study. The spontaneous preterm birth group included cases with spontaneous labour onset before the 37th week of pregnancy and no diagnosis of cervical insufficiency. The control group included patients who had not experienced preterm birth threat throughout their pregnancy, had no cervical insufficiency or other complications, had a singleton and healthy pregnancy, and delivered at term. All patients were evaluated at our clinic and delivered their babies. All pregnant women were evaluated for first trimester screening tests (PAPP-A MoM, β-hCG MoM, NT MoM) between the 11th and 14th weeks of pregnancy as part of routine pregnancy follow-up. These values were obtained retrospectively from patient files. Additionally, second-trimester AFP MoM results and delivery information were obtained from hospital records. Cases with a history of cervical insufficiency who received prophylactic cerclage, multiple pregnancies, cases with fetal structural or chromosomal anomalies, cases with maternal chronic systemic diseases, and cases that did not complete the follow-up process or had insufficient medical records were excluded from the study.

Data collection and laboratory procedures

Patient data were obtained from medical records and the hospital's information management system. Maternal age, number of pregnancies, number of births, pre-pregnancy BMI (kg/m^2), in vitro fertilisation (IVF) pregnancy rates, history of previous preterm birth, PAPP-A MoM, β-hCG MoM, NT MoM, and Alpha-fetoprotein (AFP) MoM values,gestational age at birth (weeks), birth weight (g), 1-minute and 5-minute Apgar scores, and mode of delivery were obtained from the patients' medical records and compared between subgroups. Adverse neonatal outcomes included the presence of at least one of the following adverse outcomes: admission to the neonatal intensive care unit (NICU), neonatal hypoglycaemia, need for phototherapy, Apgar scores <7 at 1 and 5 minutes, caesarean section due to fetal distress, mechanical ventilation, sepsis, RDS, or IVH.

Statistical analysis

Statistical analysis was performed utilising IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess adherence to normal distribution. Since this was a retrospective study, no a priori sample size calculation was performed. However,

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a post-hoc power analysis based on the differences in PAPP-A and β-hCG MoM levels revealed an achieved power above 80% at a 0.95 confidence level with a medium effect size (Cohen's d ≈ 0.5). Descriptive statistics for continuous variables were reported as "mean ± standard deviation" for normally distributed data and "median (interquartile range)" for non-normally distributed data. Categorical variables were analysed using the chi-square test or Fisher's exact test. Continuous variables were analysed using the independent sample t-test or the Mann-Whitney U test, contingent upon their normal distribution status.The statistical analysis performed in this study involved the utilization of One-Way ANOVA, followed by post hoc tests to assess intergroup comparisons in cases where significant differences were observed. Pairwise comparisons were performed using Bonferroni-adjusted independent samples t-tests following one-way ANOVA and Bonferroni-corrected Mann–Whitney U tests following Kruskal–Wallis tests, as appropriate. Statistical significance for all tests was defined as a p value less than 0.05.

RESULTS

The study population consisted of 121 women in the control group, 60 women in the cervical insufficiency group, and 67 women in the spontaneous preterm birth group (Figure 1). There were no statistically significant differences between the groups in terms of maternal age, gravida, parity, or body mass index (p>0.05). In vitro fertilisation was more common in the control group and the preterm birth group, while none of the women in the cervical insufficiency group became pregnant through IVF (p = 0.037). A history of preterm birth was most common in the preterm birth group and significantly less common in the cervical insufficiency group and the control group (p<0.001). Gestational age at delivery was significantly lower in both the cervical insufficiency group and the preterm birth group compared to the control group (p<0.001). The caesarean section rate was also significantly higher in the cervical insufficiency group and the preterm birth group compared to the control group (p = 0.017). The birth weight of newborns was significantly lower in the preterm birth group and the cervical insufficiency group compared to the control group (p<0.001). Similarly, Apgar scores were significantly lower in both the cervical insufficiency and preterm birth groups at both the first and fifth minutes (p<0.001). The incidence of adverse neonatal complications, including admission to the neonatal intensive care unit, neonatal hypoglycaemia, need for phototherapy, low Apgar scores, and respiratory or infection complications, was significantly higher in the preterm birth group and the cervical insufficiency group compared to the control group (p<0.001). These results are summarised in Table 1. As shown in Table 2, there was no significant difference in gestational age among the three groups during the first-trimester screening (p = 0.719). There were also no significant differences in nuchal translucency (p = 0.255) or AFP MoM values (p = 0.197). However, beta-hCG MoM levels were significantly higher in the preterm birth group compared to the cervical insufficiency group and the control group (p<0.001). Conversely, PAPP-A MoM values were significantly lower in the preterm birth group compared to the other two groups (p<0.001). No significant differences were found between the cervical insufficiency group and the control group in these markers. The cervical insufficiency group was divided into two subgroups based on gestational age at delivery: those who delivered before 34 weeks (n = 22) and those who delivered at or after 34 weeks (n = 38). The results are presented in Table 3. There were no significant differences between the subgroups in terms of maternal age, BMI, PAPP-A MoM, NT MoM, or AFP MoM values. However, beta-hCG-MoM values were significantly higher in women who gave birth before 34 weeks compared to those who gave birth at or after 34 weeks (p<0.001). The birth weight of newborns in the group with gestational age less than 34 weeks was significantly lower than that of newborns in the group with gestational age 34 weeks or more (p = 0.003). The incidence of adverse neonatal outcomes was also higher in the <34-week group (35% vs. 10.5%; p = 0.024), although caesarean section rates and Apgar scores were similar in both subgroups.

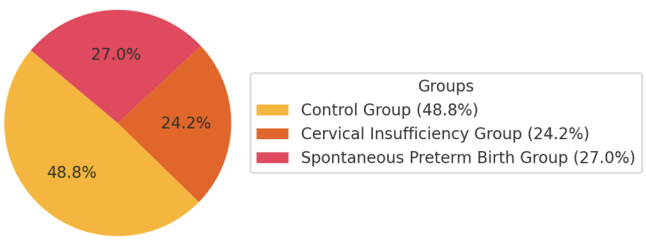

Figure 1. Distribution of study participants across groups.

DISCUSSION

First trimester screening markers, including PAPP-A and β-hCG, do not significantly differ in pregnancies with cervical insufficiency, highlighting the limited predictive value of these biomarkers for this condition. In this retrospective study, we investigated the relationship between first trimester screening tests and the development of cervical insufficiency. Our findings revealed that the first trimester biochemical parameters PAPP-A MoM, β-hCG MoM, and NT MoM in pregnant women diagnosed with cervical insufficiency did not differ significantly from those in the control group and the spontaneous preterm labour group. These results suggest that cervical insufficiency may not be predictable using first-trimester biomarkers, unlike preterm labour. Additionally, it was found that the cervical insufficiency and spontaneous preterm birth groups had significantly lower values compared to the control group in terms of gestational age and birth weight. These findings indicate that cervical insufficiency leads to preterm birth, resulting in newborns being born at a lower gestational age and having lower birth weights.

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Table 1. Demographic and clinical characteristics of the groups.

	Control Group n = 121	Cervical insufficiency Group n = 60	Preterm Birth Group n = 67	p value
Maternal age (year) (mean ± SD)	27.45± 4.59	29.13 ± 5.67	28.7 ± 5.12	0.308
Gravida (median, IQR)	2 (2)	2 (2)	2 (1)	0.181
Parity (median, IQR)	2 (1)	1 (1)	1 (2)	0.063
BMI (kg/m^2) (mean ± SD)	30.12 ± 4.84	30.46 ± 6	29.81 ± 5.4	0.860
In vitro fertilization (n,%)	12 (9.9%)	0 (0%)	7 (10.4%)	**0.037**[a,b]
History of Preterm Birth (n,%)	10 (8.3%)	14 (4.1%)	42 (62.7%)	**<0.001**[b,c]
GA at delivery (weeks) (mean ± SD)	39.12 ± 1.4	36.38 ± 1.71	35.4 ± 2.39	**<0.001**[a,c]
Gender				0.264
Male prevalance (n,%)	55 (45.5%)	35 (58.3%)	33 (49.3%)	
Female prevalance (n,%)	66 (54.5%)	25 (41.7%)	34 (50.7%)	
Cesarean section rate (n,%)	52 (43%)	33 (55%)	43 (64.2%)	0.017
Newborn birth weight (gram) (mean ± SD)	3230 ± 420	3005 ± 545	2700 ±710	**<0.001**[b,c]
Apgar score at 1st minute (mean ± SD)	8.76 ± 0.65	8.62 ± 0.61	8.12 ± 1.16	**<0.001**[b,c]
Apgar score at 5th minute (mean ± SD)	9.67 ± 1	9.63 ± 0.52	9 ± 1.16	**<0.001**[b,c]
Adverse CNO (n,%)	13 (10.8%)	11 (19%)	32 (47.8%)	**<0.001**[b,c]

Note: [a] The difference between Group 1 and Group 2 is significant; [b] The difference between Group 2 and Group 3 is significant; [c] The difference between Group 1 and Group 3 is significant. A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. Abbreviations: BMI, body mass index; GA, gestational age; CNO: composite neonatal outcome; SD: Standard deviation; IQR: İnterquartile range.

Table 2. Comparative analysis of first- and second-trimester maternal serum biomarkers and screening parameters across study groups.

	Control Group n = 121	Cervical insufficiency Group n = 60	Preterm Birth Group n = 67	p value
GA at Screening (weeks) (mean ± SD)	12.41 ± 0.75	12.31 ± 0.84	12.52 ±0.89	0.719
NT MoM (median, IQR)	0.71 (0.21)	0.75 (0.38)	0.88 (0.33)	0.255
B-hcg MoM (median, IQR)	0.75 (0.69)	0.64 (0.42)	2.12 (1.43)	**<0.001**[b,c]
PAPP-A MoM (median, IQR)	0.95 (0.6)	0.83 (0.73)	0.67 (0.9)	**<0.001**[b,c]
AFP MoM (median, IQR)	0.89 (0.3)	0.8 (0.66)	0.94 (0.59)	0.197

Note: [a] The difference between Group 1 and Group 2 is significant; [b] The difference between Group 2 and Group 3 is significant; [c] The difference between Group 1 and Group 3 is significant. A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. Abbreviations: GA: Gestational age; NT MoM: Nuchal translucency multiples of the median; B-hCG MoM: Beta-human chorionic gonadotropin multiples of the median; PAPP-A MoM: Pregnancy-associated plasma protein A multiples of the median; AFP MoM: Alpha-fetoprotein multiples of the median.

Table 3. Subgroup comparison of cervical insufficiency cases by gestational age at delivery (<34 vs ≥34 weeks).

	<34 weeks n= 22	≥34 weeks n=38	p value
Maternal age (years), mean ± SD	31 ± 5.74	28 ± 5.41	0.988
BMI (kg/m²), mean ± SD	29.76 ± 5.88	30.86 ± 6.17	0.516
GA at delivery (weeks) (mean ± SD)	34.27 ± 1.65	38.62 ± 1.99	**<0.001**
PAPP-A MoM, median (IQR)	0.84 (0.64)	0.78 (0.69)	0.434
β-hCG MoM, median (IQR)	1.91 (0.86)	0.46 (0.51)	**<0.001**
NT MoM (median, IQR)	0.72 (0.28)	0.73 (0.28)	0.690
AFP MoM (median, IQR)	0.81 (0.55)	0.82 (0.64)	0.380
Cesarean section rate (n,%)	12 (54.5%)	21 (55.3%)	0.957
Newborn birth weight (gram) (mean ± SD)	2755 ± 414	3225 ± 430	**0.003**
Apgar score at 1st minute (mean ± SD)	8.68 ± 0.66	8.63 ± 0.63	0.664
Apgar score at 5th minute (mean ± SD)	9.75 ± 0.53	9.68 ± 0.47	0.073
Adverse CNO (n,%)	7 (35%)	4 (10.5%)	**0.024**

Note: A p value of <0.05 indicates a significant difference and statistically significant p-values are in bold. Abbreviations: BMI, body mass index, GA: Gestational age; NT MoM: Nuchal translucency multiples of the median; B-hCG MoM: Beta-human chorionic gonadotropin multiples of the median; PAPP-A MoM: Pregnancy-associated plasma protein A multiples of the median; AFP MoM: Alpha-fetoprotein multiples of the median.

In the literature, cervical insufficiency and preterm birth are frequently highlighted as important risk factors for neonatal morbidity and mortality [12].

PAPP-A is a protease secreted by trophoblasts that increases insulin-like growth factor (IGF) bioavailability by breaking down IGF binding proteins [13,14]. With this feature, it plays an important role in placental growth, trophoblast invasion, and the regulation of uteroplacental circulation. Previous studies have investigated whether biochemical parameters measured in first-trimester screening tests can provide clues about the course of pregnancy [15]. It has been suggested

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that PAPP-A and free β-hCG levels may be associated with pregnancy complications because they reflect placental function. In the literature, diminished PAPP-A levels have been consistently associated with an elevated risk of preeclampsia and an increased probability of FGR in subsequent weeks. A study by Papamichail et al. indicated that the probability of developing preeclampsia or pregnancy-induced hypertension was markedly elevated when PAPP-A levels were 0.4 MoM in the first trimester; correspondingly, the incidence of FGR was also dramatically increased in these conditions [16]. In a similar manner, β-hCG promotes progesterone synthesis by sustaining the corpus luteum during early gestation and contributes to the proliferation and differentiation of trophoblastic cells. Pregnant women exhibiting markedly elevated β-hCG levels during the first trimester have an up to fivefold increased chance of subsequently developing preeclampsia [17]. In a study conducted by Younesi et al., statistical correlations were found between excessive β-hCG MoM values and various adverse outcomes such as low birth weight, premature birth, and gestational diabetes [7]. In our study, consistent with the literature, elevated β-hCG levels were noted in cases of preterm labour. Despite all this, many studies point to the limited value of first-trimester markers in predicting preterm birth. In a large cohort study by Swiercz et al., although low PAPP-A and abnormal β-hCG levels were found to statistically increase the risk of spontaneous preterm birth, it was noted that the diagnostic success of these markers alone remained moderate [18].

In our study, the lack of significant differences in the levels of these biomarkers in the cervical insufficiency group supports the notion that the pathophysiology of these cases is due to local structural cervical weakness rather than systemic or placental dysfunction. Cervical insufficiency primarily stems from weakness in the collagen structure of the cervical stroma, abnormal remodeling, or congenital connective tissue disorders [19]. This condition may not be directly linked to varying levels of PAPP-A or β-hCG associated with trophoblastic activity during the first trimester. However, the low PAPP-A and high β-hCG levels detected in the spontaneous preterm birth group suggest that some of the births in this group developed through placental dysfunction-based mechanisms. In addition, inflammation is also a possible mechanism in the pathophysiology of cervical insufficiency [20]. It is known that subclinical infection or inflammatory processes accelerate the early softening of cervical tissue by increasing collagen degradation enzymes such as MMP-9 and cytokines such as IL-6 and IL-8 in the cervix [21]. However, since the pathophysiology of cervical insufficiency is primarily associated with later-stage mechanisms such as accelerated local tissue remodelling and collagen matrix dissolution that occur in the second trimester, no significant changes in systemic biomarkers have been observed during weeks 11–14 of pregnancy. In this context, it is expected that first-trimester screening tests would fail to detect this late-onset process and, consequently, no significant differences would emerge in the cervical insufficiency group.

This study is significant as it is an original retrospective analysis examining the relationship between first trimester screening tests and obstetric outcomes in pregnancies with cervical insufficiency. The use of multiple group comparisons enhances the generalizability of the results. The detailed evaluation of both biochemical markers and neonatal outcomes demonstrates a multidisciplinary and comprehensive approach. In these aspects, the study provides important data contributing to the literature. However, the retrospective design of the study increases the risk of uncertainty in data collection and analysis processes. Furthermore, the limitation of first-trimester screening tests to specific biomarkers (PAPP-A, β-hCG, AFP, NT) and the failure to evaluate other potential biomarkers that could fully reflect the pathophysiology of cervical insufficiency can be considered a limitation. The fact that the sample was collected from a single center, along with the possibility that results may vary across different geographic and ethnic populations, may limit the universal validity of the study's findings. For these reasons, further prospective studies to validate the findings are important.

In conclusion, our study also demonstrates that first-trimester PAPP-A and β-hCG levels do not provide meaningful predictive value in cases of cervical insufficiency, thereby supporting the current guidelines' approach of focusing on clinical and ultrasonographic screening rather than biochemical markers [3]. These markers are more meaningful in preterm births associated with placental dysfunction but may not induce biochemical changes in the early stages of localized anatomical abnormalities such as cervical insufficiency.

CONCLUSION

First trimester screening markers did not show significant changes in cervical insufficiency cases, indicating their limited value for early prediction. However, altered biochemical profiles were observed in spontaneous preterm births. These findings support prioritizing second trimester ultrasound evaluation over reliance on early biochemical markers.

Ethics Committee Approval: The study was conducted in accordance with the principles stated in the Declaration of Helsinki and ethical approval was obtained from Ankara Etlik City Hospital Hospital Ethics Committee (approval number: AESH-BADEK-2025-028).

Informed Consent: Not applicable due to the retrospective design.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared that there are no conflicts of interest.

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Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization: D.D.B.

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