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RESEARCH ARTICLE

The effect of maternal asthma on serum PAPP-A levels and first trimester aneuploidy screening test running

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Abstract

Introduction: PAPP-A (Pregnancy-associated plasma protein-A) is considered a pro-inflammatory marker and its serum levels are elevated in non-pregnant patients with asthma. In the current research, we aimed to investigate whether maternal serum PAPP-A levels, a biomarker for first-trimester aneuploidy screening, differ in pregnant women with asthma compared to healthy pregnant women.

Methods: In the first step, maternal serum PAPP-A MoM values, used as the first-trimester fetal aneuploidy screening marker, were compared between pregnant women with asthma and a healthy pregnant group. In the second step, the groups compared whether PAPP-A and fβ-HCG (free β human chorionic gonadotropin) levels were below or above the cut-off values for Trisomy 21 and compared them according to maternal age (<35; ≥35).

Results: The median PAPP-A level was found to be 2.15 IU/L (0.41-9.91) in the asthma group and 2.54 IU/L (0.56-11.40) in the control group, and there was no difference between the groups (P=0.363). The median PAPP-A MoM value was 0.99 (0.15-3.28) in the asthma group and 1.07 (0.33-3.37) in the control group. This result did not show a statistically significant difference (P = 0.694). No statistically significant difference was shown between the groups below and above 35 age (P=0.456).

Conclusion: Maternal serum PAPP-A levels in pregnant women with asthma do not vary compared to the healthy pregnant group without asthma. Based on the results of our study, the first-trimester fetal aneuploidy screening test is a reliable screening method for pregnant women with asthma.

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Introduction

Asthma is a disease accompanied by chronic airway inflammation characterized by hyperreactivity to stimuli and reversible obstruction. It is associated with significant maternal morbidity. In a large prospective study, the exacerbation rate of the disease in pregnant women followed up with mild asthma, moderate asthma, and severe asthma were 12.6%, 25.7%, and 51.9%, respectively.[1] In the same study, it was observed that 23% of asthma in pregnant women improved and 30% became worse. While the effects of pregnancy on asthma vary, pregnant women with asthma are at high risk for pregnancy complications. The first trimester is generally well-tolerated in patients with asthma since acute episodes are not very frequent. The National Asthma Education and Prevention Program (NAEPP) classified asthma as mild intermittent, mild persistent, moderate persistent, and severe persistent. Asthma is observed at approximately 8% during pregnancy.[2]

Prenatal screening for fetal aneuploidy such as Trisomy 21,13 and 18 is recommended in the first trimester of pregnancy. In this aneuploidy screening test performed when the crown-rump length (CRL) is 45-84 mm between 11+0 and 13+6 weeks of gestation, two maternal serum markers are used.[3] It is known that pregnancy-associated plasma protein-A (PAPP-A) has a median value (MoM) of 0.4 times in pregnancies with trisomy 21 fetuses, and the free β subunit (fβ-hCG) of human chorionic gonadotropin is known to increase to a median MoM value of 1.8 in pregnancies with Down's syndrome. PAPP-A and fβ-hCG together can identify 60-65% of Down's syndrome in the first trimester with a 5% false-positive rate. When these maternal serum markers are combined with the measurement of nuchal translucency (NT) in ultrasonography and the positive threshold value is traditionally accepted as 1/270, the trisomy 21 detection rate of the test reaches 87.5-88.9%.[4]

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein and its concentration in the maternal circulation increases throughout pregnancy. Due to its proteolytic activity in the insulin-like growth factor system, it functions as a regulatory protein. Low PAPP-A levels were associated with adverse pregnancy outcomes such as preeclampsia and intrauterine growth retardation (IUGR).[5] PAPP-A is a pro-atherosclerotic metalloproteinase and an inflammatory marker. It has been shown that its serum level is elevated in non-pregnant asthma patients. Furthermore, a significant correlation has been revealed between PAPP-A concentration and the severity of asthma.[6]

In light of this information, we aimed to investigate whether first-trimester maternal serum PAPP-A levels varied in pregnant women with asthma compared to the healthy pregnant population and the findings' impacts on first-trimester aneuploidy screening results.

Material and Methods

This research is a case-control study. . The ethics committee approval was obtained with the decision number E2-22-1569 on 30/03/2022. Eighty-seven pregnant women with asthma aged between 18-45 years, who attended their routine check-ups regularly in the Perinatology Outpatient Clinic of Ankara City Hospital in the two years between January 2020 and January 2022, and had the first-trimester fetal aneuploidy screening between 11th and 14th gestational weeks in our hospital, were determined as the case group. Randomly selected 97 healthy pregnant women, who continued their follow-ups regularly in the antenatal outpatient clinic in the same age and gestational week range and did not have any chronic or pregnancy-related disease, were determined as the control group. In the case group, pregnant women with additional chronic and pregnancy-related conditions other than asthma were excluded from the study. The study did not include pregnant women with suspected or diagnosed with fetal chromosomal or structural abnormality in the first trimester. Informed consent was obtained from all the participants.

First-trimester serum PAPP-A level and MoM range, fβ-hCG level and MoM range for each patient in the case and control groups, and biochemical Trisomy 21 risk ratio determined due to aneuploidy screening were recorded. PAPP-A and fβ-hCG levels were studied by the chemiluminescent immunoassay method. The patient's age, parity, smoking consumption status, body mass index (BMI), sociodemographic characteristics, and medical history were examined. Routine obstetric and ultrasonographic examinations of the patients were performed. The groups of medicines they used were classified according to the lines of treatment. Patients who were followed up and treated in the chest diseases outpatient clinic were divided into groups according to the treatments they received. The patients who did not

need drugs due to asthma during pregnancy were taken as Group 1. The patients who have mild intermittent and mild persistent asthma which received 1.-2. step treatment using low-dose inhaled corticosteroids (ICS) or short-acting beta-agonist alone were taken as Group 2. The moderate and severe persistent asthma patients who received 3rd step and above asthma treatment using leukotriene receptor agonist (LTRA) together with medium-high dose ICS and long-acting beta-agonist (LABA) were taken as Group 3.

Statistical analysis

Statistical analyses were performed with the help of IBM SPSS version 25 software. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were presented using the median and interquartile range for non-normally distributed variables. Independent groups were compared using the Mann-Whitney U test since they did not show a normal distribution. Since the variables were non-normally distributed, Spearman's test was used for correlation coefficients. The Chi-square test was used to compare the ratios between the groups. Cases with a p-value below 0.05 were accepted as statistically significant results.

Results

The sociodemographic characteristics of the pregnant women with asthma and healthy control groups were compared. There was no significant difference between the groups in terms of mean age (P=0.951), mean BMI (P=0.615), parity (P=0.298), and smoking status (P=0.635) (Table 1).

Table 1. Comparison of the sociodemographic characteristics of asthma and control groups

		ASTHMA GROUP (n=87)	CONTROL GROUP (n=97)	P-VALUE
Age Median (min-max)		27.0 (20-45)	27 (19-40)	0.951[a]
BMI Median (min-max)		24.9 (18.9-32.3)	25.2 (18.2-31.1)	0.615[a]
Parity N (%)				
	primiparity	32 (36.8%)	43 (44.3%)	0.298[b]
	multiparity	55 (63.2%)	54 (55.7%)	
Smoking N (%)				
	yes	4 (4.6%)	6 (6.2%)	0.635[b]
	no	83 (95.4%)	91 (93.8%)	

Table 1.
BMI: body mass index. aMann Whitney U test was used to compare the measurement values of two independent groups. b Chi-square test was used to compare the ratios between the groups

The biochemical parameters of the first-trimester fetal aneuploidy screening test were compared between asthma and control groups. The median (min-max) values of the parameters examined are presented in Table 2. The median PAPP-A levels (P=0.363) and the median PAPP-A MoM values (P= 0.694) were compared between asthma and control groups. The results were similar between the groups. When fβ-HCG levels (P= 0.338) and fβ-HCG MoM values (P=0.278) were compared between the groups, the result was not found to be statistically significant (Table 2).

Table 2. Comparison of serum biochemical parameters in the first-trimester aneuploidy screening between the groups

	Asthma Group N: 87 Median (min-max)	Control Group N:97 Median (min-max)	P-value
PAPP-A (IU/L)	2.15 (0.41-9.91)	2.54 (0.56-11.40)	0.363[a]
PAPP-A MoM	0.99 (0.15-3.28)	1.07 (0.33-3.37)	0.694[a]
fβ-HCG (ng/ml)	31.10 (10.40-136.00)	35.70 (11.20-155.00)	0.338[a]
fβ-HCG MoM	0.81 (0.23-3.37)	0.97 (0.22-3.63)	0.278[a]

PAPP-A: Pregnancy-associated plasma protein-A; fβ-HCG: free β human chorionic gonadotropin; MoM: Multiples of median. aMann Whitney U test was used to compare the measurement values of two independent groups.

PAPP-A MoM values were compared between asthma and control groups at the cut-off value below and above 0.4 MoM. 3 (3.4%) pregnant women in the asthma group and 2 (2.1%) pregnant women in the control group were below 0.4 MoM. In comparison, there were 84 (96.6%) pregnant women in the asthma group and 95 (97.9%) pregnant women in the control group above 0.4 MoM, and the result was not statistically significant (P=0.564). fβ-HCG values were compared between asthma and control groups at the cut-off value below and above 2 MoM. The result was not statistically significant (P=0.244) (Table 3).

Table 3. Comparison of asthma and control groups according to PAPP-A MoM and fβ-HCG MoM Trisomy 21 cut-off values

		ASTHMA GROUP N (%)	CONTROL GROUP N (%)	P-VALUE
PAPP-A	< 0,4 MoM	3 (3.4%)	2 (2.1%)	0.564[b]
	> 0,4 MoM	84 (96.6%)	95 (97.9%)	
TOTAL		87 (100%)	97 (100%)	
fβ-HCG	> 2 MoM	7 (8%)	13 (13.4%)	0.244[b]
	< 2 MoM	80 (92%)	84 (86.6%)	
TOTAL		87 (100%)	97 (100%)	

PAPP-A: Pregnancy-associated plasma protein-A; fβ-HCG: free β human chorionic gonadotropin; MoM: Multiples of median. b Chi-square test was used to compare the ratios between the groups.

PAPP-A and PAPP-A MoM values were separately compared between the groups under and over 35 years of age. While the median PAPP-A value was found to be 2.10 IU/L (0.41-9.91) in the asthma group under 35 years of age, the median value was found to be 2.48 IU/L (0.56-11.40) in the control group, and the results were similar between the groups (P=0.225). While the median PAPP-A MoM value was 0.97 MoM (0.15-3.28) in the asthma group, the median value was 1.03 MoM (0.33-3.37) in the control group, and no significant difference was determined between the groups (P=0.431). Whereas the median PAPP-A value was found to be 3.24 IU/L (1.20-6.98) in the asthma group over 35 years of age, the median value was 4.19 IU/L (1.20-5.34) in the control group, and the results were similar between the groups (P=1.0). While the median PAPP-A MoM value was found to be 1.32 MoM (0.75-2.75) in the asthma group, the median value was found to be 1.28 MoM (0.53-2.75) in the control group, and no statistically significant difference was shown between the groups (P=0.456) (Table 4).

Table 4. Comparison of PAPP-A (IU/L) and PAPP-A MoM values between the groups under and over 35 years of age

GROUP	AGE	PAPP-A (IU/L) Median (min-max)	P-value	PAPP-A MoM Median (min-max)	P-value
ASTHMA N:87	< 35 years N:76	2.10 (0.41-9.91)	0.225[a]	0.97 (0.15-3.28)	0.431[a]
CONTROL N:97	< 35 years N:88	2.48 (0.56-11.40)		1.03 (0.33-3.37)	
ASTHMA N:87	≥ 35 years N:11	3.24 (1.20-6.98)	1.0[a]	1.32 (0.75-2.75)	0.456[a]
CONTROL N:97	≥ 35 years N:9	4.19 (1.20-5.34)		1.28 (0.53-2.75)	

PAPP-A: Pregnancy-associated plasma protein-A;-MoM: Multiples of median. aMann Whitney U test was used to compare the measurement values of two independent groups.

The asthma group was divided into treatment groups according to the type of asthma treatment provided to the patients during pregnancy. PAPP-A MoM and PAPP-A IU/L levels were compared between the groups. There was no statistically significant difference in PAPP-A MoM (P=0.738) and PAPP-A (IU/L) levels (P=0.588) among the first group that did not receive asthma treatment during pregnancy, the second group that used either a short-acting beta-agonist or low-dose inhaled corticosteroids alone, and the third group that received combined treatment with LABA + ICS (Table 5).

Table 5. Comparison of PAPP-A MoM and PAPP-A (IU/L) levels according to the steps of treatment provided in the asthma group

Medication	N (%)	PAPP-A MoM Median (min-max)	P-value	PAPP-A (IU/L) Median (min-max)	P-value
None	7 (8%)	0.84 (0.48-1.49)	0.738[a]	1.73 (0.76-4.07)	0.588[a]
1.-2. Step medication	37 (%42.5)	1.01 (0.15-2.75)		2.34 (0.41-7.02)	
≥3. Step Medication	43 (%49.4)	0.95 (0.39-3.28)		2.15 (0.53-9.91)	

1st - 2nd step treatment: treatment with a short-acting beta-agonist or low-dose ICS alone
≥3rd step treatment: combined treatment using LABA + ICS together. aMann Whitney U test was used to compare the measurement values of two independent groups.

Discussion

Based on the literature data showing that serum PAPP-A levels are elevated in asthma patients, we compared first-trimester PAPP-A levels between pregnant women with asthma and the healthy control group without asthma. Both groups' mean age, BMI, and smoking status were similar in our study. We did not reveal a significant difference in PAPP-A level, PAPP-A MoM values independent of the gestational week, fβ-HCG level, and fβ-HCG MoM value between pregnant women in asthma and healthy control group. Upon comparing the cut-off values taken as a basis for Down's syndrome (PAPP-A 0.4 MoM, fβ-HCG 2.0 MoM), there was no statistical difference between the groups below and above the cut-off values. When maternal age under and over 35 years was evaluated separately between the groups, the biochemical parameters were similar. When we divided asthma patients into groups according to the medical treatments and compared them, we revealed that the treatment type or severity did not affect PAPP-A levels and PAPP-A MoM values.

PAPP-A was defined in 1974 for the first time.[7] Circulating PAPP-A was primarily derived from syncytiotrophoblasts. Nowadays, it is included in the screening program for Trisomy 21 since low maternal serum levels are associated with Trisomy 21,18,13. The multiple of the median (MoM) unit, which shows the expression of PAPP-A concentration independent of the gestational week. This screening program determines which pregnant group should be recommended for diagnostic chorionic villus sampling (CVS) or amniocentesis. In the screening test for trisomy 21, the PAPP-A cut-off value was accepted as 0.405 MoM (95% confidence interval 0.28 to 0.67),[8] while it was 0.25 MoM for trisomy 13, Patau syndrome[9] and 0.15–0.22 MoM for trisomy 18, Edward's syndrome.[10] PAPP-A levels have been used as a parameter for screening tests in obstetrics and have also become a marker used to evaluate the prognosis of pregnancy. Based on the results of the FASTER study, PAPP-A MoM levels β 5th percentile were associated with spontaneous pregnancy loss, low birth weight, preeclampsia, gestational HT, preterm birth, PPROM, and ablatio placenta. It was concluded that low maternal serum PAPP-A levels in the first trimester were strongly associated with poor pregnancy outcomes.[11] Other studies in the literature support this result.[12,13]

Insulin-like growth factor (IGF) binding protein (IGFBP)-4 is an essential regulator of the IGF system and a substrate for the pregnancy-associated plasma protein-A (PAPP-A) enzyme, which is a dimeric protein detected in high concentrations in the plasma of pregnant women. PAPP-A is a local regulatory protein for IGF bioavailability. PAPP-A is secreted as a disulfide-linked homodimer and is classified as a metzincin metalloproteinase linked to the matrix metalloproteinase family.[14] The bioactivity of IGFBP-4 and PAPP-A has biological significance because it is associated with several pathological conditions such as metabolic disorders, type 2 diabetes mellitus, atherosclerotic/cardiovascular diseases (CVD), and tumorigenesis. At the posttranslational stage, IGFBP-4 is regulated by the proteolytic degradation of the PAPP-A enzyme.[15] PAPP-A is expressed and presented in various tissues and fluids, including adipose tissue, human osteoblasts, fibroblasts, ascitic fluids, and pleura. It reaches detectable levels in maternal blood after embryo implantation following fertilization and increases throughout pregnancy, reaching its highest level at term.[16] Its level is significantly lower in healthy non-pregnant women, but it is found in higher serum concentrations in males and females. PAPP-A is not a pregnancy-specific protein and is synthesized in many different cell types in males and females, such as fibroblasts, osteoblasts, vascular smooth muscle cells, testis, ovary, endometrium, fallopian tubes, kidney, bone, and colon.[17] PAPP-A is associated with inflammatory conditions, and its expression level is upregulated by proinflammatory cytokines such as IL-1β and tumor necrosis factor (TNF)-α.[18]

A study carried out in 2007 investigated the importance of the PAPP-A level in asthma disease. Because PAPP-A is a potential pro-atherosclerotic metalloproteinase and a new inflammatory marker, PAPP-A levels were compared in 35 asthma patients and 20 healthy subjects. Patients using only B2 agonists were included in the study, while those using corticosteroids or other anti-inflammatory drugs were excluded. PAPP-A concentrations were found to be 8.1±5.0 mU/L in the asthmatic group and 4.9±2.1 mU/L in the control group, statistically significantly higher in the asthmatic group. When compared according to the severity of asthma, it was considerably higher in stage 3 asthma patients than in the control group and other first and second-stage

asthma patients.[6] In another study investigating the relationship between PAPP-A levels and the severity of the disease in patients with Chronic Obstructive pulmonary disease (COPD), which is defined by chronic airflow limitation and increased airway inflammation, the average PAPP-A level in the group of 75 people with COPD was 33.7±36.8 ng/ml, and in the control group with 35 people was 13.8±9.9 ng/mL. This difference was statistically significant between the groups. PAPP-A levels were higher in stage 1 and 2 COPD groups than in stage 3 and 4 COPD patients. This study stated that PAPP-A could be a new marker showing inflammation in diseases such as asthma, pulmonary embolism, and lung cancer.[19] A study on 36 severe allergic asthma patients and 36 healthy control subjects from Turkey determined that PAPP-A and IGFB-4 levels were higher in patients with allergic asthma. In contrast, IGF-1 levels were similar between the groups. Omalizumab treatment was applied to the allergic asthma case group for six months. A significant decrease was observed in PAPP-A, IGFBP-4, and IGF-1 levels after treatment.[20] Studies state that PAPP-A levels may be a sensitive and specific early diagnostic biomarker in acute coronary syndrome, coronary artery diseases,[21,22] and cardiovascular diseases.23 The limitations of our study are that our sample size is relatively small, and the study is a single-center study.

Conclusion

This is the first study that evaluates serum PAPP-A levels in pregnant women with asthma to the best of our knowledge. Maternal serum PAPP-A level in pregnant women with asthma was not observed to vary compared to the healthy pregnant group without asthma. We revealed that medical treatments used for asthma treatment did not influence PAPP-A levels. Based on the results of our study, although first-trimester fetal aneuploidy screening seems to be a reliable screening method in pregnant women with asthma, more extensive studies are needed.

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Statements & Declarations

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Conflict of interest disclosure

The authors declare that they have no conflicts of interest.

Ethics approval

The study protocol was approved by Ankara City Hospital No. 2 Clinical Research Ethics Department and was performed in line with the Declaration of Helsinki. The ethics committee approval was obtained with the decision number E2-22-1569 on 30/03/2022.

Informed consent

Informed consent was obtained from all participants.

Author Contribution

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by [Bergen Laleli Koc], [Ozgur Kara], [Atakan Tanacan], [Deniz Oluklu], [Betul Akgun Aktas], [Ecem Kaya], [Dilek Sahin]. The first draft of the manuscript was written by [Bergen Laleli Koc] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Schatz M, Dombrowski MP, Wise R, et al.: Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol. 2003, 112:283-288. 10.1067/mai.2003.1516
2. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol. 2005, 115:34-46. 10.1016/j.jaci.2004.10.023
3. Canick JA, Lambert-Messerlian GM, Palomaki GE, et al.: Comparison of serum markers in first-trimester down syndrome screening. Obstet Gynecol. 2006, 108:1192-1199. 10.1097/01.AOG.0000241095.19638.f2
4. Wapner R, Thom E, Simpson JL, et al.: First-trimester screening for trisomies 21 and 18. N Engl J Med. 2003, 349:1405-1413. 10.1056/NEJMoa025273

5. Kirkegaard I, Uldbjerg N, Oxvig C: Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview. Acta Obstet Gynecol Scand. 2010, 89:1118-1125. 10.3109/00016349.2010.505639
6. Coskun A, Balbay O, Duran S, et al.: Pregnancy-associated plasma protein-A and asthma. Adv Ther. 2007, 24:362-367. 10.1007/bf02849905
7. Lin TM, Galbert SP, Kiefer D, Spellacy WN, Gall S: Characterization of four human pregnancy-associated plasma proteins. Am J Obstet Gynecol. 1974, 118:223-236. 10.1016/0002-9378(74)90553-5
8. Krantz DA, Larsen JW, Buchanan PD, Macri JN: First-trimester Down syndrome screening: free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Am J Obstet Gynecol. 1996, 174:612-616. 10.1016/s0002-9378(96)70436-2
9. Spencer K, Ong C, Skentou H, Liao AW, K HN: Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn. 2000, 20:411-416.
10. Tul N, Spencer K, Noble P, Chan C, Nicolaides K: Screening for trisomy 18 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn. 1999, 19:1035-1042. 10.1002/(sici)1097-0223(199911)19:11<1035::aid-pd694>3.0.co;2-2
11. Dugoff L, Hobbins JC, Malone FD, et al.: First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol. 2004, 191:1446-1451. 10.1016/j.ajog.2004.06.052
12. ATAMAN YILDIRIM Z, TUĞRUL ERSAK D, TİMUR B, KAHYAOĞLU S: The Predictive Value of First and Second Trimester Screening Test Biomarkers in Preeclampsia. Forbes Journal of Medicine. 2022, 3.
13. D'Antonio F, Rijo C, Thilaganathan B, et al.: Association between first-trimester maternal serum pregnancy-associated plasma protein-A and obstetric complications. Prenat Diagn. 2013, 33:839-847. 10.1002/pd.4141
14. Overgaard MT, Boldt HB, Laursen LS, Sottrup-Jensen L, Conover CA, Oxvig C: Pregnancy-associated plasma protein-A2 (PAPP-A2), a novel insulin-like growth factor-binding protein-5 proteinase. J Biol Chem. 2001, 276:21849-21853. 10.1074/jbc.M102191200
15. Hjortebjerg R: IGFBP-4 and PAPP-A in normal physiology and disease. Growth Horm IGF Res. 2018, 41:7-22. 10.1016/j.ghir.2018.05.002
16. Bischof P, DuBerg S, Herrmann W, Sizonenko PC: Pregnancy-associated plasma protein-A (PAPP-A) and hCG in early pregnancy. Br J Obstet Gynaecol. 1981, 88:973-975. 10.1111/j.1471-0528.1981.tb01683.x
17. Overgaard MT, Oxvig C, Christiansen M, et al.: Messenger ribonucleic acid levels of pregnancy-associated plasma protein-A and the proform of eosinophil major basic protein: expression in human reproductive and nonreproductive tissues. Biol Reprod. 1999, 61:1083-1089. 10.1095/biolreprod61.4.1083
18. Conover CA, Harrington SC, Bale LK: Differential regulation of pregnancy associated plasma protein-A in human coronary artery endothelial cells and smooth muscle cells. Growth Horm IGF Res. 2008, 18:213-220. 10.1016/j.ghir.2007.09.001
19. Talay F, Tosun M, Yaşar ZA, et al.: Evaluation of Pregnancy-Associated Plasma Protein-A Levels in Patients with Chronic Obstructive Pulmonary Disease and Associations with Disease Severity. Inflammation. 2016, 39:1130-1133. 10.1007/s10753-016-0345-z
20. Bulut I, Ozseker ZF, Coskun A, Serteser M, Unsal I: Pregnancy-associated plasma protein-A (PAPP-A) levels in patients with severe allergic asthma are reduced by omalizumab. J Asthma. 2018, 55:1116-1121. 10.1080/02770903.2017.1396471
21. Li Y, Zhou C, Zhou X, Song L, Hui R: PAPP-A in cardiac and non-cardiac conditions. Clin Chim Acta. 2013, 417:67-72. 10.1016/j.cca.2012.12.006
22. Gutiérrez-Leonard H, Martínez-Lara E, Fierro-Macías AE, et al.: Pregnancy-associated plasma protein-A (PAPP-A) as a possible biomarker in patients with coronary artery disease. Ir J Med Sci. 2017, 186:597-605. 10.1007/s11845-016-1515-6
23. Hjortebjerg R, Rasmussen LM, Gude MF, et al.: Local IGF Bioactivity Associates with High PAPP-A Activity in the Pericardial Cavity of Cardiovascular Disease Patients. J Clin Endocrinol Metab. 2020, 105. 10.1210/clinem/dgaa617