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Research paper

# Maternal heart examination in pregnancy affected by low PAPP-A MoM in the first trimester

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## Abstract

**Introduction:** Pregnancy-associated plasma protein A (PAPP-A) protease is known for its role as a key regulator of insulin-like growth factors and hence of foetal development. With the present study we intend to investigate its role in the maternal haemodynamic adaptation to the state of pregnancy.
**Material and methods:** We selected 18 patients referred to our unit between February 2017 and July 2017, of whom 10 showed low PAPP-A values at the first trimester screening for chromosomal anomalies. Each patient had 3 serial echocardiographic evaluations at the 13th, 24th, and 33rd week of pregnancy. On the basis of the plasma values of PAPP-A, the patients were divided into cases ($n = 10$) and controls ($n = 8$), where cases had a mean PAPP-A concentration of 0.345 with a standard deviation of 0.086, while the controls were characterised by a mean PAPP-A concentration of 1.380 with a standard deviation of 0.613. The main outcome measures were peripheral vascular resistance (PVR), cardiac output (CO), systolic excursion of the tricuspid ring (TAPSE), and E/E' ratio. Systolic and diastolic arterial blood pressure and heart rate (HR) were measured at each visit. Mono- and bidimensional, Doppler, and TDI images were acquired and analysed blindly by a single sonographer.
**Results:** A slight increase in heart rate (HR, + 12%, $p < 0.05$) was observed in the control group at the 33rd week visit, while there was no change in the group with low levels of PAPP-A. Cardiac output and PVR also changed in the high-value PAPP-A group (ANOVA for repeated measures, $p < 0.05$), while they remained unchanged in the group with low PAPP-A values. It was observed that in the case group, the lower the PAPP-A values, the lower the extent of the haemodynamic adjustment in terms of PVR drop and increase in CO. A lack of physiological adaptation to pregnancy was also observed in the systolic function of the right ventricle. Women with normal PAPP-A showed a slight reduction ($t$ test, $p < 0.05$) of TAPSE, while in women with low PAPP-A no change was observed. The E/E' ratio was significantly increased in the control group at the last two visits ($p < 0.005$ and $p < 0.05$, respectively).
**Conclusions:** This study shows that the physiological haemodynamic adaptation and the morphofunctional changes in the heart are incomplete in women with low PAPP-A levels, creating a favourable substrate for the development of preeclampsia. The assay of PAPP-A in the first trimester can therefore be used as a screening method to select at-risk pregnancies, with the aim of creating a specific path and a closer follow-up.

**Key words:** PAPP-A, maternal heart, preeclampsia, haemodynamics in pregnancy.

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## Introduction

### Pregnancy-associated plasma protein A

Pregnancy-associated plasma protein A (PAPP-A) is a glycoprotein produced in high concentrations by the liver and the trophoblast cells. It is released at increasing concentrations in the maternal circulation at the beginning of pregnancy [1]. PAPP-A can act as an important factor in regulating growth by influencing the insulin-like growth factor (IGF) system [2]; it is also believed to play a significant role in the autocrine and paracrine control of trophoblast invasion during the placentation phase [3, 4].

The concentration of PAPP-A (reported as a multiple of the median – MoM) measured in the first trimester of pregnancy (11-14 weeks) was demonstrated to be associated with low neonatal weight at birth, preterm premature rupture of membranes (PPROM), and preterm birth [5, 6]. In addition, a low concentration of PAPP-A seems to be associated with preeclampsia.

The 2004 FASTER trial [7] found that PAPP-A values are significantly lower in patients who develop preeclampsia later in pregnancy. Because the *primum movens* of preeclampsia is indeed an alteration of the vascular organisation, the determination of PAPP-A values can represent an important marker in the early diagnosis of this affection [8].

Numerous studies have elaborated on the role of PAPP-A protease during the placentation phase, specifically in correlation with placental size, placental vascularisation, and CD flow and its consequences on maternal blood pressure and foetal growth.

Rizzo G et al. [5] in 2009 suggested that low maternal serum levels of PAPP-A at gestational ages of 11 weeks to 13 weeks and 6 days may be an early sign of impaired placental development leading to a subsequent reduction of foetal growth. In their study they found that low maternal serum PAPP-A concentrations are associated with a significant reduction of the placental volume and its vascularisation.

In a subsequent study, Rizzo et al. [9] studied placental 3-dimensional power Doppler ultrasonographic vascularisation, the histomorphometric characteristics of first-trimester chorionic villi at CVS and their correlation with low maternal serum PAPP-A concentrations.

They found that the chorionic villi capillaries obtained at CVS from these pregnancies are fewer and smaller, with greater differences in those pregnancies developing IUGR foetuses secondary to uteroplacental insufficiency. These studies ascertain the role of PAPP-A as one of the regulators of placentation, influencing the histopathologic structure of the placenta and its function, and hence foetal growth.

On the other hand, in a systematic review and meta-analysis by Morris et al. [10] the association and predictive ability of first-trimester maternal serum PAPP-A with adverse pregnancy outcomes was analysed. It was found that low maternal serum PAPP-A in the first trimester is associated with adverse pregnancy outcome, particularly if levels are very low (< 1$^{st}$ centile). They also highlighted that, for the individual, predictive values are poor, and the majority of adverse outcomes will occur in women without an abnormally low PAPP-A.

Our work integrates these previous studies on the PAPP-A, investigating its role in the maternal haemodynamic adaptation to the state of pregnancy.

PAPP-A is also known among cardiologists for being a sensitive, specific, and early marker for acute coronary syndrome diagnosis, because it has been demonstrated that higher PAPP-A values are associated with an increased short-term risk of cardiovascular events [11]. Elevated PAPP-A levels are also associated with systemic atherosclerosis: serum PAPP-A is elevated in symptomatic peripheral arterial disease, and it also correlates with early indicators for peripheral vascular disease, such as carotid intima-media wall thickness and toe-brachial index [12].

PAPP-A, playing a role in the vascular organisation of the foetoplacental unit, can consequently be the link between the development of hypertensive disorders of pregnancy and the progression of maternal cardiovascular disease.

### Physiological haemodynamic adaptation to pregnancy

The basic haemodynamic parameters can help differentiate between normal subjects and women at risk of impaired foetoplacental perfusion and preeclampsia.

Systemic vascular resistance (SVR): pregnancy is associated with systemic and renal vasodilation, due to a fall in SVR. The process is multifactorial and mediated by endothelium-dependent factors, including the synthesis of nitric oxide stimulated by oestradiol and probably by prostaglandins with vasodilating action (PGI2) [13].

Cardiac output (CO) = stroke volume (SV) × heart rate (HR). In parallel with the reduction of systemic resistance, there is an increase in CO. In the first part of pregnancy, this change seems to be attributable to an increase in SV, while later in pregnancy it is probably due to an increase in HR. The heart is physiologically dilated, and myocardial contractility is increased. While stroke volume tends to decrease towards the end of pregnancy, the increase in heart rate remains continuous and ensures a constant preservation of the increase in cardiac output [13].

Blood pressure: blood pressure drops by about 10 mm Hg in the second trimester, with a greater decrease in the diastolic component compared to the systolic one. Values reach a minimum during this period [14], while in the third trimester there is a slight increase.

### Systolic function during pregnancy

Estensen et al. [15] considered a large cohort of healthy patients in 3 moments of pregnancy and at 6 months after delivery. They studied, with non-invasive methods, left ventricular contractility, and global and regional systolic and diastolic function. The study showed a 23% increase in the left ventricular end-diastolic volume (LVEDV) and an 11% reduction in the ejection fraction (LVEF), which both regressed 6 months after delivery. Even the left ventricular myocardial thickness slowly increases between 14-16 weeks and the 36$^{th}$ week and remained

unchanged at 6 months after delivery. The left ventricular mass (LV mass) increases by 14% during pregnancy, reaching a peak at 36 weeks. Also, the ventricular dimensions in end-diastole (LVIDd) and end-systole (LVIDs) were increased.

These findings suggest that the state of pregnancy can be comparable to moderate exercise, with an increase in cardiac output, peripheral perfusion (at the uterine rather than muscular level), and oxygen demand.

## Diastolic function during pregnancy

Evidence shows a discrepancy in results regarding diastolic function during pregnancy.

The study by Estensen et al. [15] showed a reduction in E' (peak velocity of early diastolic mitral annular motion). It is not clear whether this represents a real change in diastolic function or it is the result of a preload alteration due to pregnancy. The same study also showed a decrease in the peak velocity of early diastolic transmitral flow (E) and the E/A ratio, not observing any change in A, the peak velocity of late transmitral flow. The ratio E/E' remains unchanged, although the area of the left atrium increases during pregnancy. These data suggest that left ventricular filling pressures remain unchanged during pregnancy and postpartum. As a consequence of the plasma expansion and therefore of the stretch of the myocardial fibres, there is also a 40% increase in the secretion of the atrial natriuretic peptide (BNP) in the third trimester and in the first postpartum week [16].

# Material and methods

## Study population

The study recruited 18 consecutive pregnant women referred to our unit between February 2017 and July 2017. All were evaluated 3 times at 12-week intervals. Median gestational age values were as follows: 13 weeks (range 11-20), 24 weeks (range 22-26), and 32 weeks (range 30-35). For each woman the following data were collected: parity and type of conception, ethnicity, weight, height, smoking habits, presence of diseases and pharmacological treatment, and first-degree family history for trisomy and malformations. In cases of multiparity, the outcome of previous pregnancies was recorded with regard to complications such as preterm birth, preeclampsia, gestational diabetes, and presence of chromosomal and/or structural abnormalities of the newborn. The plasma assay of PAPP-A was performed in the first trimester, during the screening test for chromosomopathies, by using BRAHMS KRYPTOR technique, certified by the Foetal Medicine Foundation (FMF). The biochemical parameters obtained were converted into multiples of the median (MoM) with the software ASTRAIA 2.8.0_3, which uses algorithms established by the FMF.

On the basis of the plasma values of PAPP-A the patients were divided into cases ($n$ = 10) and controls ($n$ = 8), where cases had a mean PAPP-A concentration of 0.345 with a standard deviation of 0.086, while the controls were characterised by a mean PAPP-A concentration of 1.380 with a standard deviation of 0.613.

## Echocardiography

Systolic and diastolic arterial blood pressure and heart rate were measured at each visit, in a clinostatic position, and using a digital sphygmomanometer. The cardiac examination was performed with an echocardiograph (Vivid 7 Pro, GE Healthcare) equipped with a 3.5 MHz probe and equipped to process the second tissue harmonic in accordance with the recommendations of the American Society of Echocardiography. Mono- and bidimensional, Doppler, and TDI images were acquired and analysed blindly by a single sonographer (Caputo MT).

In greater detail, the following parameters were collected.

### *Left ventricle morphology and volumes*

Left ventricle parameters were obtained in M-Mode in the left parasternal window long axis:

- IVSd – interventricular septal width in end-diastole (interventricular septum thickness in tele-diastole),
- IVSs – interventricular septal width in end-systole (interventricular septum thickness in tele-systole),
- LVIDd – left ventricular internal dimension in end-diastole (left ventricular internal diameter in tele-diastole),
- LVIDs – left ventricular internal dimension in end-systole (left ventricular internal diameter in tele-systole),
- LVPWd – left ventricular posterior wall dimensions in end-diastole (thickness of the posterior wall of the left ventricle in tele-diastole),
- LVPWs – left ventricular posterior wall dimensions in end-systole (thickness of the posterior wall of the left ventricle in end-systole),
- EDV – end-diastolic volume,
- ESV – end-systolic volume,
- SV – stroke volume,
- LVM – left ventricular mass was obtained through the Penn convention formula: mass VS (g) = 1.04 × [(diameter of diastolic canvases VS + thickness of diastolic canvases of the interventricular septum and the posterior wall of the VS)$^3$ – diameter diastolic canvases VS$^3$] –13.6. The mass is then indexed both as a function of the body surface (LVMI: g/m$^2$) and of the height (LVMI/h$^{2.7}$). For the diagnosis of ventricular hypertrophy, we have considered the thresholds reported in the guidelines of the European Society of Hypertension and Cardiology of 2013,
- RWT – relative wall thickness = 2LVPW/EDV, where 2LVPW is twice the wall thickness value and EDV is the left ventricular end diastolic diameter. This ratio allows us to differentiate between ventricular concentric (RWT > 0.42) and eccentric (RWT ≤ 0.42) hypertrophy (LVH).

### *Global systolic function*

Endocardial shortening fraction (FS) was calculated as FS = (DTD – DTS)/DTD × 100, where DTD: end-diastolic diameter LV and DTS: end-systolic LV diameter.

Ejection fraction (FE) was calculated by entering the volumes calculated by the Teicholtz formula into the Simpson formula: FE = (EDV – ESV)/EDV × 100.

Cardiac output was estimated as the difference between the EDV and the ESV of the left ventricle, multiplied by the HR, according to the following formula: PC = (EDV – ESV) × HR.

### *Diastolic function*

The diastolic function of the left ventricle was evaluated by measuring the velocity peaks of the transmitral flow during the ventricular filling phase (pulsed Doppler) and the mitral ring excursions (tissue Doppler):

- transmitral diastolic flow (E wawe, A wawe),
- TDI of the mitral ring (E' – lateral, septal).

### *Right ventricle function*

As for the right ventricle, we measured the systolic excursion of the tricuspid ring or TAPSE (tricuspid annular plane systolic excursion, normal value ≥ 18 mm). It reflects the longitudinal shortening of the cardiac fibres that drag the tricuspid ring towards the ventricular apex during the systole. The greater the systolic excursion of the ring, the more vigorous the systole. The values were obtained in apical window 4-chamber view measuring the systolic diastolic excursion of the tricuspid ring in M-mode.

### *Left atrium*

The left atrium was evaluated by measuring the diameter with a mono-dimensional method in the left parasternal long-axis projection, while the area and volume were measured by two-dimensional method in an apical window with 4 chambers.

### *Valves and aorta*

The aortic systolic flow velocity and the maximum tricuspid regurgitation flow rate were measured by continuous Doppler in 4 chamber projection. The annular aortic diameter (bulb) was measured by sampling perpendicular to the long axis of the vessel at the point of union between the cusps, with 1-dimensional method in a parasternal long-axis projection.

**Table 1.** Clinical features of the population

| Parameter | Cases mean ± SD | Controls mean ± SD |
|---|---|---|
| *N* | 10 | 8 |
| Age (years) | 33 ±5.4 | 35 ±2.9 |
| Height (cm) | 163 ±5 | 168 ±4.9 |
| Weight (kg) | 60 ±9.4 | 63 ±8.8 |
| BMI (kg/m$^2$) | 22.5 ±2.9 | 22.2 ±2.1 |
| Parity (0/1/2) | 8/1/1 | 5/3/0 |
| PAPP-A (MoM) | 0.345 ±0.1 | 1.380 ±0.6** |
| SBP (mm Hg) | 118 ±12.3 | 114 ±15.6 |
| DBP (mm Hg) | 73 ±7 | 68 ±6 |
| MBP (mm Hg) | 88 ±7 | 84 ±9 |
| HR (bpm) | 75 ±9.8 | 74 ±8.4 |

*$p < 0.05$ between s 13 and 24, **$p < 0.005$ between s 13 and 24, °$p < 0.05$ between s 13 and 32, °°$p < 0.005$ between s 13 and 32.

Also, the diameter of the aortic arch was evaluated in the suprasternal projection of the long axis, while the diameter of the ascending tract was measured in the parasternal long axis.

## Statistics and data analysis

For each visit and for each group of women, the mean, deviation, and standard error of all the anatomical and functional parameters were calculated. The variables were compared between the groups and within the groups related to time by means of a paired Student's *t* test, with 2-tailed distribution. Tests with p values less than 0.05 were considered statistically significant. For those parameters that did not reach statistical significance in paired comparisons, but which changed throughout the 3 visits, we used the analysis of variance for repeated measurements using JMP statistical software. The same software was used for the simple linear regression analysis and to create the scatter plot graphs.

## Results

In terms of clinical features (Table 1), the 2 groups were similar with respect to age, height, weight, BMI, blood pressure (SBP, DBP, MBP), and heart rate (HR). They instead differed with regard to parity ($c^2$, $p < 0.05$) and PAPP-A (*t* test, $p < 0.005$).

With respect to anatomic-structural cardiac features (Table 2) we did not observe significant differences between the groups concerning the main parameters at the first ultrasound scan. These same parameters showed no variation in the two subsequent evaluations, except for the diameter of the left atrium (left atrium D), which increased slightly (+ 10%) in both groups but without being associated with significant changes in atrial surface and volume or with differences between the two groups.

The systemic haemodynamic and systolic function parameters of the left ventricle (Table 3) measured in the first 2 visits in patients with low PAPP-A values were also not different from the controls. At the third visit, a slight increase in heart rate was observed (HR, + 12%, $p < 0.05$) only in women from the control group, while there was no change in the group with low levels of PAPP-A. Although at the *t* test the between-visit variations were not significant, cardiac output and peripheral vascular resistance (PVR) also changed, in a manner consistent with that expected during pregnancy, only in the high-value PAPP-A group (ANOVA for repeated measures, $p < 0.05$), while they remained unchanged in the group with low PAPP- A values (Figures 1 and 2).

Of note, in subjects with altered PAPP-A, it was observed that the lower the PAPP-A values, the lower the extent of haemodynamic adjustment in terms of PVR drop and increase in cardiac output (Figures 3 and 4).

A lack of physiological adaptation to pregnancy was also observed in the systolic function of the right ventricle (Table 3). Women with normal PAPP-A showed a slight reduction (*t* test, $p < 0.05$) of tricuspid ring excursion (TAPSE), while in women with low PAPP-A no change was observed (Figure 5).

**Table 2.** Anatomic structural cardiac parameters

| Parameter | Cases mean ± SE | | | Controls mean ± SE | | |
|---|---|---|---|---|---|---|
| | Week 13 | Week 24 | Week 32 | Week 13 | Week 24 | Week 32 |
| Weight (kg) | 60.1 ±3 | 64.9 ±3.2** | 67.2 ±2.9*°° | 63.1 ±2.8 | 68.3 ±2.7** | 71.7 ±2.8**°° |
| Arch (cm) | 2.03 ±0.04 | 2.06 ±0.06 | 2.08 ±0.07 | 2.18 ±0.10 | 2.15 ±0.08 | 2.14 ±0.06 |
| Ascending (cm) | 2.51 ±0.05 | 2.53 ±0.06 | 2.67 ±0.07 | 2.56 ±0.075 | 2.63 ±0.05 | 2.69 ±0.06 |
| Bulb (cm) | 2.68 ±0.06 | 2.64 ±0.06 | 2.71 ±0.04 | 2.68 ±0.077 | 2.71 ±0.07 | 2.83 ±0.08 |
| L atrium D (cm) | 2.85 ±0.11 | 2.98 ±0.13* | 3.17 ±0.11**°° | 2.99 ±0.12 | 3.25 ±0.12** | 3.23 ±0.10°° |
| L atrium S ($cm^2$) | 11.4 ±0.9 | 11.5 ±0.8 | 12.1 ±0.7 | 12.6 ±0.9 | 13.7 ±0.9 | 13.2 ±0.7 |
| L atrium V ($cm^3$) | 27.5 ±3.1 | 28.5 ±3.1 | 29.7 ±2.4 | 31.4 ±3.08 | 35.1 ±3.8 | 33.1 ±2.8 |
| IVSd (cm) | 0.81 ±0.033 | 0.82 ±0.03 | 0.86 ±0.03 | 0.85 ±0.03 | 0.86 ±0.03 | 0.89 ±0.02 |
| LVIDd (cm) | 4.58 ±0.13 | 4.58 ±0.16 | 4.61 ±0.14 | 4.55 ±0.178 | 4.56 ±0.18 | 4.69 ±0.15 |
| LVPWd (cm) | 0.83 ±0.03 | 0.77 ±0.03 | 0.75 ±0.02 | 0.80 ±0.034 | 0.84 ±0.04 | 0.84 ±0.05 |
| IVSs (cm) | 1.41 ±0.04 | 1.38 ±0.06 | 1.41 ±0.03 | 1.53 ±0.069 | 1.46 ±0.09 | 1.55 ±0.04 |
| LVIDs (cm) | 2.54 ±0.092 | 2.65 ±0.12 | 2.67 ±0.14 | 2.54 ±0.136 | 2.53 ±0.16 | 2.79 ±0.15 |
| LVPWs (cm) | 1.39 ±0.05 | 1.39 ±0.07 | 1.40 ±0.06 | 1.41 ±0.049 | 1.48 ±0.09 | 1.48 ±0.05 |
| LVd mass (g) | 137 ±10 | 133 ±11 | 136 ±8 | 140 ±12 | 146 ±15 | 156 ±17 |
| RWT | 0.17 ±0.01 | 0.17 ±0.02 | 0.16 ±0.01 | 0.18 ±0.011 | 0.18 ±0.01 | 0.17 ±0.01 |

**p < 0.05 between s 13 and 24, **p < 0.005 between s 13 and 24, °p < 0.05 between s 13 and 32, °°p < 0.005 between s 13 and 32.*

**Table 3.** Basal haemodynamic parameters and cardiac systolic function

| Parameter | Cases AV ± SE | | | Controls AV ± SE | | |
|---|---|---|---|---|---|---|
| | Sett 13 | Sett 24 | Sett 32 | Sett 13 | Sett 24 | Sett 32 |
| MBP (mm Hg) | 88 ±2 | 85 ±2 | 86 ±2 | 84 ±3 | 84 ±4 | 83 ±3 |
| HR (bpm) | 82 ±4 | 85 ±2 | 83 ±2 | 74 ±3 | 76 ±3 | 83 ±3° |
| SV (ml) | 74 ±6 | 71 ±6 | 72 ±4 | 72 ±6 | 74 ±7 | 72 ±5 |
| PVR | 15.5 ±1.4 | 15.2 ±1.6 | 15.1 ±1.0 | 16.8 ±1.4 | 15.7 ±1.0 | 14.6 ±1.3 |
| Cardiac output (l/min) | 6.0 ±0.6 | 6.1 ±0.6 | 5.9 ±0.3 | 5.2 ±0.4 | 5.5 ±0.3 | 6.0 ±0.5 |
| EF (%) | 76 ±2 | 73 ±2 | 73 ±2 | 75 ±2 | 75 ±3 | 71 ±2 |
| SF (%) | 45 ±2 | 42 ±2 | 42 ±2 | 44 ±1 | 45 ±2 | 41 ±2* |
| TAPSE (mm) | 26.6 ±0.7 | 26.5 ±1.0 | 26.0 ±0.8 | 28.0 ±0.9 | 26.1 ±0.9* | 25.4 ±0.6° |

**p < 0.05 between s 13 and 24, **p < 0.005 between s 13 and 24, °p < 0.05 between s 13 and 32, °°p < 0.005 between s 13 and 32.*

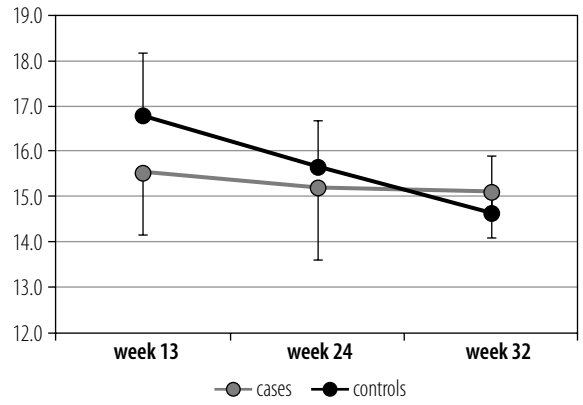


**Figure 1.** Trend of the PVRs of the two groups over time

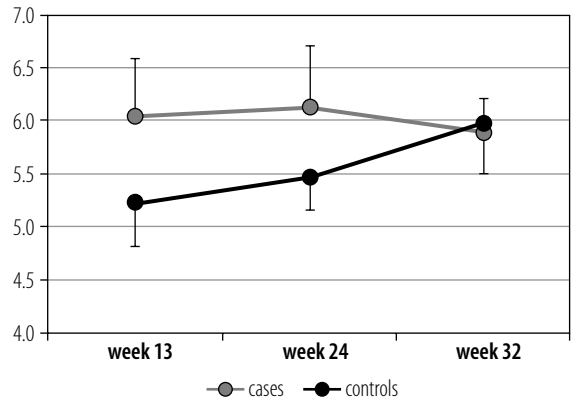


**Figure 2.** Trend of cardiac output over time

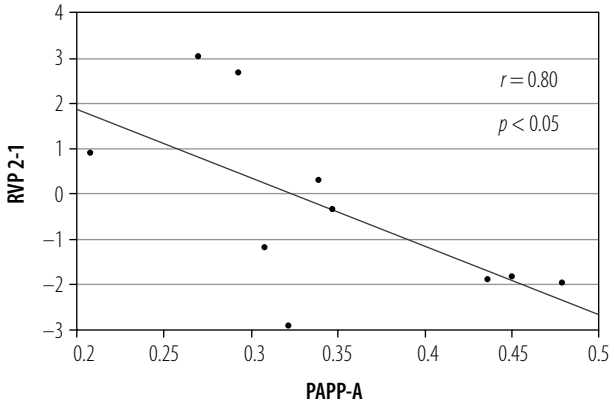


**Figure 3.** Correlation between the difference in RVP values in the first two visits and the PAPP-A plasmatic levels

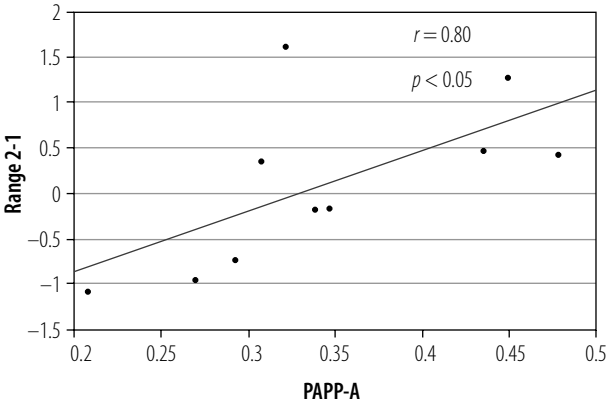


**Figure 4.** Correlation between the difference in cardiac output values in the first two visits and the PAPP-A plasmatic levels

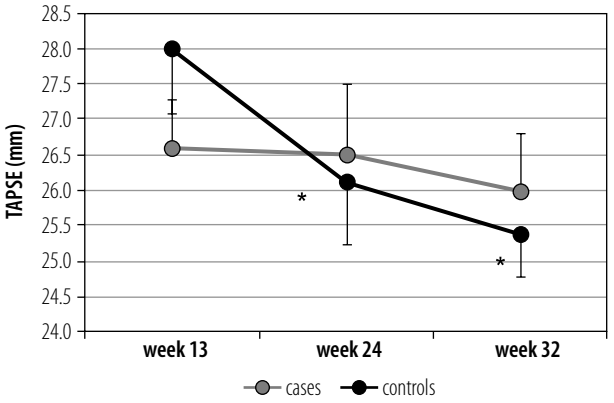


**Figure 5.** TAPSE trend over time

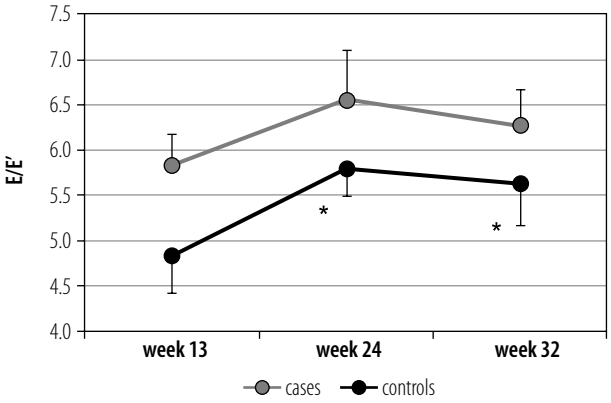


**Figure 6.** Trend of the E/E' ratio over time

With respect to the left ventricular diastolic function (Table 4), a slight and similar decrease of transmitral E and A flow rates was observed in both groups (12%).

Conversely, a significant difference was observed in the tissue Doppler measurements of the transmitral flow at parietal and septal level (E'), and consequently of the E/E' ratio. In both groups there was a decrease across visits of the transmitral velocity (E' average), obtained from the velocities at the septal and parietal level, which was statistically significant only in the control group. Consequently, also the E/E' ratio was significantly increased in the control group at the last 2 visits ($p < 0.005$ and $p < 0.05$, respectively), while a minor and non-significant increase was observed in the group with low PAPP-A levels (Figure 6).

## Discussion

This study shows that the presence of low plasma PAPP-A values measured in the first trimester is associated with a relative lack of haemodynamic adaptation to pregnancy. The parameters indicating this phenomenon are: PVR, CO, TAPSE, and the E/E' ratio.

Among the other data analysed, small differences at the limit of statistical significance were observed in the diameter of the left atrium (left atrium D) and HR.

**Table 4.** Parameters of ventricular diastolic function

| Parameter | Cases mean ± SE | | | Controls mean ± SE | | |
|---|---|---|---|---|---|---|
| | Week 13 | Week 24 | Week 32 | Week 13 | Week 24 | Week 32 |
| L atrium V (ml) | 27.5 ±3.1 | 28.5 ±3.1 | 29.7 ±2.4 | 31.4 ±3.0 | 35.1 ±3.7 | 33.1 ±2.7 |
| E (cm/s) | 90.1 ±5.9 | 84.0 ±3.7 | 82.0 ±5.0 | 87.9 ±6.1 | 84.6 ±5.5 | 77.4 ±4.5° |
| A (cm/s) | 68.2 ±5.8 | 60.0 ±2.9 | 57.6 ±3.5 | 61.5 ±3.0 | 60.6 ±3.1 | 58.8 ±3.5 |
| E/A | 1.34 ±0.06 | 1.41 ±0.06 | 1.44 ±0.07 | 1.44 ±0.09 | 1.40 ±0.09 | 1.36 ±0.10 |
| E' medium (cm/s) | 15.5 ±0.7 | 13.1 ±0.9 | 13.2 ±1.0 | 18.4 ±1.2 | 14.7 ±1.0** | 14.0 ±0.9°° |
| E/E' | 5.8 ±0.3 | 6.6 ±0.5 | 6.3 ±0.4 | 4.8 ±0.3 | 5.8 ±0.3** | 5.6 ±0.4° |

*$p < 0.05$ between s 13 and 24, **$p < 0.005$ between s 13 and 24, °$p < 0.05$ between s 13 and 32, °°$p < 0.005$ between s 13 and 32.

In contrast to what was observed in some studies [15, 17], no difference was observed in cardiac anatomical and structural variables. However, consistent with the literature, we observed slight increases (5-10%) in almost all ultrasound measurements related to cardiac anatomy, none of which, however, reached statistical significance. This is probably due to the fact that the haemodynamic changes of pregnancy determine progressive and minor anatomical-structural changes that are quantitatively too small to be evaluated in a short study with a small sample size.

One of the first signs of the physiological adaptation to pregnancy is a moderate decrease in peripheral resistance, detectable as early as in the first trimester and presumably responsible for a large part of the consequent haemodynamic alterations. In this regard, we observed a difference in the PVR trend over time in the 2 populations, which, however, did not reach statistical significance (*t* test within the groups or analysis of variance for repeated measures) (Figure 1). To try to understand if the failure to achieve statistical significance was due to the heterogeneity in terms of PAPP-A values in the group with abnormal ones, we performed a simple regression analysis (Figure 3), which showed a strong ($r = 0.83$, $p < 0.05$) negative correlation between PAPP-A values and the extent of haemodynamic adjustment (delta PVR), suggesting that the failure in adaptation is observed particularly in women with very low PAPP-A levels.

Considering also that in the control group this relationship was not confirmed, a further corollary is that this protein seems to play a permissive role on the development of haemodynamic adaptations in pregnancy. A minimum level of PAPP-A is necessary and sufficient for the normal pregnant body's response to take place. The reduced decrease in systemic PVRs in patients with low PAPP-A values could therefore be one of the first causes of inadequate maternal haemodynamic adaptation, whose exasperation would then translate into the development of hypertensive pathology. This finding suggests a possible role of PAPP-A as a cofactor in the set of mechanisms responsible for systemic vasodilation typical of the early stages of pregnancy, because its deficit results in a reduced plasma concentration of IGF-1 and IGF-2. This data would confirm, as observed by Irwin et al. [4], the role of IGF-2-IGFBP in the correct trophoblastic invasion, but also suggests a possible direct implication of IGF-1 in the physiological PVR decrease and in the typical blood pressure lowering of the early stages of pregnancy. These data are also consistent with those reported by Pete et al. [18] on the mechanism of NO-mediated vasodilation induced by the binding of IGF-1 to the endothelial receptor IGFr-1. The altered trophoblastic invasion, with the consequent lack of complete formation of the low-resistance placental circle, cannot in fact represent by itself the only physiopathological cause of preeclampsia, which, being a systemic phenomenon, necessarily involves large sectors of the circulatory system.

Cardiac output is the second parameter the trend of which is significantly different within the 2 groups (Figure 2). However, it is important to underline how the values related to cardiac output increase with the progression of pregnancy in the control group, while they show a slight decrease in patients with low PAPP-A values. The regression analysis showed a significant correlation ($r = 0.80$, $p < 0.05$) between the PAPP-A values and the variation in the cardiac output (Figure 4), implying that the lower the concentration of PAPP-A, the smaller the cardiac output increase during pregnancy. Considering the increase in cardiac output as a first response to the PVR decrease and to the subsequent hyperdynamic state, these data are also consistent with the idea that women with pathological PAPP-A have an insufficient haemodynamic adaptation. Heart rate displayed a trend in the 2 groups that was similar to cardiac output.

The study of the systolic function of the right ventricle evaluated by TAPSE had never been taken into consideration by recent literature, and this is the most original result of our study. The trend of this parameter suggests a progressive reduction of right ventricular systolic function in women from the control group, while no change was evident in women with pathological PAPP-A, in whom the values of TAPSE remained almost unchanged over time (Figure 5).

The fall in peripheral resistance during a normal pregnancy determines, through the stimulation of arterial baroreceptors, a substantial activation of the renin-angiotensin-aldosterone system and of other autonomic mechanisms. This activation results in an increase in sodium renal retentive mechanisms and in a non-osmotic release of vasopressin from the hypothalamus. The final result of these changes is an increase in plasma volume, of which, however, 85% is in the venous circulation. Because the right ventricle is passively affected by volumetric variations, there is no adaptation of the ejection fraction based on the extent of the myocardial fibre stretch, but rather, in the presence of an increase in venous return and therefore in the ventricular chamber size, the ejection fraction tends to decrease. This will correspond to a reduction in contractility and therefore in TAPSE, which is closely related to it. The reduction in TAPSE values observed in the control group is statistically significant (*t* test, $p < 0.05$); therefore, it is consistent with the haemodynamic changes that characterise pregnancy.

The lack of change of the values of TAPSE in women with pathological PAPP-A is compatible with the imperfect haemodynamic adaptation, including in the first place the smaller PVR fall, which would not be followed by the consequent activation of the previously mentioned autonomic mechanisms. This would explain why the right systolic function remains unchanged, not being affected, like a normal pregnancy, by the increase in plasma volume and the consequent increase in venous return.

Contrary to what was observed by Estensen et al., who reported a decrease in E' transmitral peak velocity without a corresponding decrease in the E/E' ratio, our study showed a decrease in the value of this ratio in both groups, resulting in significant statistical significance between the first and subsequent visits ($p < 0.005$ and $p < 0.05$) only in the control group (Figure 6). It is not clear whether the slight deterioration of ventricular diastolic function is due exclusively to the altered loading conditions typical for pregnancy or if there are other responsible factors, but in any case, being a common finding in most normal pregnancies, it must be considered a paraphysi-

ological condition. We can hypothesise that the absence of this finding in patients with pathological PAPP-A may have importance in the context of the differences between physiological and pathological haemodynamic adaptation. As reported in the literature, the value of the left atrium diameter increases over time in both groups but with different timing. In the control group the greatest increase is observed between the first and second visit (*t* test, $p < 0.005$), followed by a slight but continuous increase up to the third visit ($p < 0.005$ between weeks 13 and 33). In the group of patients with pathological PAPP-A, on the other hand, there is a first minor increase between the first and second visit ($p < 0.05$) followed by a greater increase in the following ones ($p < 0.005$ between week 24 and 33 and $p < 0.005$ between weeks 13 and 33).

This different trend may be due again to the lack of early haemodynamic adaptation in women with low PAPP-A values, responsible for the reduced increase in plasma volume and consequently for the reduced distension of the left atrium walls. The fact that the atrial dilation is not entirely absent but late can be a sign of a process that in this case would result not so much from the physiological overload induced by the pregnancy, but from a process of adaptation to a pathological condition of chronic increase of peripheral resistance and inefficiency of haemodynamic adaptation mechanisms, among which we find the concentration of PAPP-A.

The major limitations of our study were the relatively small number of patients enrolled and the lack of data on pregnancy outcomes, such as the development of preeclampsia or IUGR.

Morris et al. [10] found that, as we mentioned in our introduction, the majority of adverse outcomes of pregnancy will occur in women without an abnormally low PAPP-A.

We believe it would be of interest to widen the present study to fully understand the role of PAPP-A in placentation and further examine its effects on foetal growth. Another important topic would have been the follow-up of the patients after delivery, in order to understand if they developed hypertension outside of pregnancy or if there were some morpho-functional cardiac changes after delivery. We believe it would be of interest to widen the present study to reproduce and confirm our data, in addition to including pregnancy outcomes and a maternal echocardiography 6 months after delivery.

## Conclusions

This study shows that the haemodynamic adaptation that occurs during a normal pregnancy, and determines morphological and functional changes also in the heart, is incomplete in women with low PAPP-A levels. In particular, the decrease in peripheral resistance and the increase in cardiac output were lower compared to a normal pregnancy, with different consequences for ventricular systolic and diastolic function. The systolic function of the right ventricle and the diastolic function of the left ventricle are not reduced, demonstrating that the lesser systemic vasodilation is not followed by the physiological cardiac adaptation. Whether PAPP-A is directly involved in haemodynamic pregnancy changes or is only an indicator cannot be clarified by this study, both for the small size of the population and for the interruption of the study at the 32$^{th}$ week of gestation. The fact remains that low plasmatic levels of PAPP-A in pregnant women were found to be in association with a missed haemodynamic adaptation, which, due to its characteristics, creates a favourable substrate for the development of pre-eclampsia.

Based on the results of our study it is believed that the assay of PAPP-A in the first trimester can help to identify women with a greater risk of preeclampsia and can be used as a screening method to select at-risk pregnancies, with the aim of creating a specific path and a closer follow-up. Considering the scarcity of data in the literature and the controversies surrounding the subject, the expansion of the study to a greater number of patients as well as the inclusion of an echocardiographic reassessment at 6 months after the delivery could allow a better understanding of the relationships between PAPP-A and haemodynamic adaptation in pregnancy.

Highlights:

- The decrease in peripheral resistance and the increase in cardiac output are lower in women with low PAPP-A values compared to those with a normal pregnancy.
- Haemodynamic adaptation to pregnancy is incomplete in women with low PAPP-A values.
- Low plasmatic levels of PAPP-A in pregnant women were found to be associated with a missed haemodynamic adaptation.
- The assay of PAPP-A in the first trimester can identify women at greater risk of preeclampsia.

## Conflict of interest

The authors declare no conflict of interest.

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