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Research Article

Morphofunctional Study of the Maternal Heart in Pregnancies Complicated by Low PAPP-A Values

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Abstract

Background: PAPP-A protease is known for its role as a key regulator of the insulin-like growth factor and hence of the fetal development. With the present study we intend to investigate its role in the maternal haemodynamic adaptation to the state of pregnancy.

Methods: We selected 18 patients referred to our unit between February 2017 and July 2017, who showed low PAPP-A values at the first trimester screening for chromosomal anomalies. Each patient had three serial echocardiographic evaluations at 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 characterized by a mean PAPP-A concentration of 1.380 with a standard deviation of 0.613. The main outcome measures were Peripheral Vascular Resistances (PVR), Cardiac Output (CO), the systolic excursion of the Tricuspid Ring (TAPSE) and the E/E' ratio. Systolic and diastolic arterial blood pressure and heart rate were measured at each visit. Mono, 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's visit, while there was no change in the group with low levels of PAPP-A. Cardiac output and Peripheral Vascular Resistance (PVR) also changed in the high values 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 were the PAPP-A values, the lower was the extent of the hemodynamic adjustment in terms of PVR drop and increase in cardiac output. 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 Tricuspid Ring Excursion (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 hemodynamic 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.

Keywords: PAPP-A; Maternal heart; Preeclampsia; Heamodynamics in pregnancy

Introduction

PAPP-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 IGF system (Insulin-like Growth Factor) [2]; it is also believed to have 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, with 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], supported by a more recent work by Ayse Kirbas et al. [8] 50, found that PAPP-A values are significantly lower in patients who develop preeclampsia later in pregnancy. Since the *primum movens* of preeclampsia is indeed an alteration of the vascular organization, the determination of PAPP-A values can represent an important marker in the early diagnosis of this affection. PAPP-A is also known among cardiologists for being a sensitive, specific and early marker for acute coronary syndrome diagnosis, as it is demonstrated that higher PAPP-A values are associated with an increased short-term risk of cardiovascular events [9]. 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 [10]. PAPP-A, playing a role in the vascular organization of the fetoplacental unit, can consequently be the link between the development of hypertensive disorders of pregnancy and the progression of maternal cardiovascular disease.

Physiological hemodynamic adaptation to pregnancy

The basic hemodynamic parameters can help differentiate

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between normal subjects and women at risk of impaired feto-placental 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 estradiol and probably by prostaglandins with vasodilating action (PGI2) [11].

Cardiac output (CO) = SV(stroke volume) x HR(heart rate): In parallel with the reduction of systemic resistance, there is an increase in cardiac output. In the first part of pregnancy, this change seems to be attributable to an increase in Stroke Volume (SV), while later in pregnancy it is probably due to an increase in Heart Rate (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 [11].

Blood pressure: Blood pressure drops by about 10 mmHg in the second trimester, with a greater decrease in the diastolic component compared to the systolic one. Values reach a minimum during this period [12], while in the third trimester there is a slight increase.

Systolic function during pregnancy

Estensen et al. [13] considered a large cohort of healthy patients in three moments of pregnancy and six months after delivery. They studied, with non-invasive methods, left ventricular contractility, global and regional systolic and diastolic function. The study showed a 23% increase in the Left Ventricular End-Diastolic Volume (LVEDV) and a 11% reduction in the Ejection Fraction (LVEF), both regressed 6 months after delivery. Even the left ventricular myocardial thickness slowly increases between 14-16 weeks and the 36th and remains 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) are 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 discrepancy in results regarding diastolic function during pregnancy.

The study by Estensen et al. [13], showed a reduction in E' (peak velocity of early diastolic mitral annular motion). It is not certain 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 fibers, 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 [14].

Methods

Study population

The study recruited 18 consecutive pregnant women referred to our unit between February 2017 and July 2017. All were evaluated three times at 12-weeks intervals. Median gestational age values were: 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, 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 Fetal 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 characterized 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, bidimensional, Doppler and TDI images were acquired and analysed blindly by a single sonographer (Caputo MT).

More in detail, the following parameters were collected.

Left Ventricle (LV) 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 telesole)
- EDV: End diastolic Volume (Telediastolic volume)
- ESV: End Systolic Volume (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/m2) and of the height (LVMI/h2,7). 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 = 2 LVPW/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 entering the volumes calculated by *Teicholtz formula* into the *Simpson formula*: FE = (EDV- ESV)/EDV x 100
- Cardiac output was estimated as the difference between the End-Diastolic Volume (EDV) and the end-systolic volume (ESV) of the left ventricle, times the heart rate (HR) according to the formula:
- PC = (EDV - ESV) x 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 Wave
    - A Wave
- TDI of the mitral ring
    - E' (lateral, septal)

Right Ventricle (RV) 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 fibers that drag the tricuspid ring towards the ventricular apex during the systole. As the systolic excursion of the ring is greater the more vigorous is the systole. The values were obtained in apical window 4 chambers measuring the systolic diastolic excursion of the tricuspid ring in M-Mode.

Left Atrium (LA)

The left atrium was evaluated by measuring the diameter with a mono-dimensional method in the left parasternal long-axis projection, while 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 one-dimensional method in a parasternal long-axis projection. Also the diameter of the aortic arch was evaluated in the suprasternal projection of the long axis while the diameter of the ascending tract 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 Test *t*, with 2-tails distribution. We have considered statistically significant the test with p values less than 0.05. For those parameters that did not reach statistical significance, in paired comparisons, but that changed throughout the three visits, we have 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 two groups were similar with repect to age, height, weight, BMI, Blood Pressure (SBP, DBP, MBP) and Heart Rate (HR). They instead differed with regard to: parity (*Chi2*, 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, without, however, being associated neither with significant changes in atrial surface and volume nor with differences between the two groups. The systemic haemodynamic and systolic function parameters of the left ventricle (Table 3) measured in the first two visits in patients with low PAPP-A values were also not different from the controls. At the third visit, instead, a slight increase in heart rate was observed (HR, + 12%, p <0.05) only in women of the control group, while there was no change in the group with low levels of PAPP-A. Although at the *t test* the between-visits variations were not significant, cardiac output and peripheral vascular resistance (PVR) also changed, in a manner consistent with what expected during pregnancy, only in the high values PAPP-A group (ANOVA for repeated measures, p<0.05), while they remained unchanged in the group with low PAPP- A values (Figure 1 and 2). Of note, in subjects with altered PAPP-A, it was observed that the lower were the PAPP-A values, the lower was the extent of hemodynamic adjustment in terms of PVR drop and increase in cardiac output (Figure 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). 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%). On the contrary, 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 two 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).

Table 1: Clinical features of the population.

	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 (mmHg)	118±12.3	114±15.6
DBP (mmHg)	73±7	68±6
MBP (mmHg)	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

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 hemodynamic adaptation to pregnancy. The parameters indicating this phenomenon are: Peripheral Vascular Resistances (PVR), Cardiac Output (CO), the systolic excursion of the tricuspid ring (TAPSE) and the E/E' ratio. Among the other data analyzed, small differences at the limit of statistical significance were observed in the diameter of the left atrium (Left atrium D) and in Heart rate (HR). In contrast to what was observed in some studies (30, 31), 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, already detectable in the first trimester and presumably responsible for a large part of the consequent hemodynamic alterations. In this regard we observed a difference in the PVRs trend over time in the two 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) that showed a strong (r = 0.83, p <0.05) negative correlation between PAPP-A values and the extent of hemodynamic 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 hemodynamic adaptations in pregnancy. A minimum level of PAPP-A is necessary and sufficient for the normal pregnancy 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 hemodynamic 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

Table 2: Anatomic structural cardiac parameters.

	CASES			CONTROLS		
	MEAN ± SE			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±0.07	2.63±0.05	2.69±0.06
Bulb (cm)	2.68±0.06	2.64±0.06	2.71±0.04	2.68±0.07	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±3.0	35.1±3.8	33.1±2.8
IVSd (cm)	0.81±0.03	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±0.17	4.56±0.18	4.69±0.15
LVPWd (cm)	0.83±0.03	0.77±0.03	0.75±0.02	0.80±0.03	0.84±0.04	0.84±0.05
IVSs (cm)	1.41±0.04	1.38±0.06	1.41±0.03	1.53±0.06	1.46±0.09	1.55±0.04
LVIDs (cm)	2.54±0.09	2.65±0.12	2.67±0.14	2.54±0.13	2.53±0.16	2.79±0.15
LVPWs (cm)	1.39±0.05	1.39±0.07	1.40±0.06	1.41±0.04	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±0.01	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 hemodynamic parameters and cardiac systolic function.

	CASES			CONTROLS		
	AV±SE			AV±SE		
	Sett 13	Sett 24	Sett 32	Sett 13	Sett 24	Sett 32
MBP (mmHg)	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°

Table 4: Parameters of ventricular diastolic function.

	CASES			CONTROLS		
	MEAN ± SE			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°

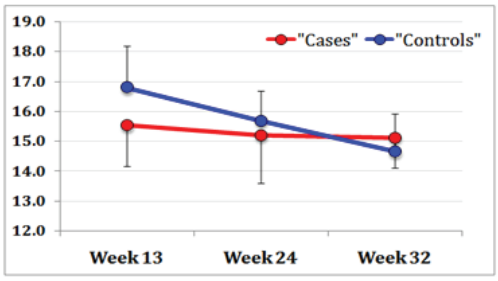

Figure 1: Trend of the PVRs of the two groups over time.

responsible for systemic vasodilation typical of the early stages of pregnancy, since its deficit results in a reduced plasma concentration of IGF-1 and IGF-2. This data would confirm, as observed by Irwin JC 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. This data are also consistent with what reported by Pete G 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 whose trend is significantly different within the two groups (Figure 2). However, it is important to underline how the values related to cardiac output are increasing, 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 is, the smaller is 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, this data is also consistent with the idea that women with pathological PAPP-A have an insufficient hemodynamic adaptation. Heart rate displays a trend in the two groups that was similar to cardiac output. The study of the systolic function of the right ventricle evaluated by TAPSE had never been

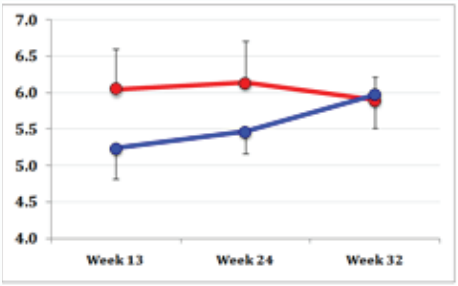

Figure 2: Trend of cardiac output over time.

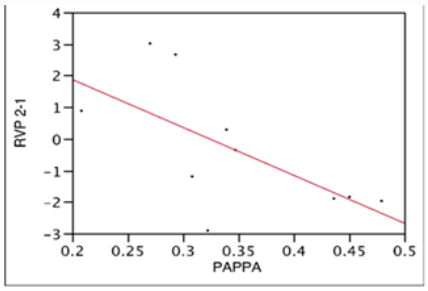

Figure 3: Correlation between the difference in RVP values in the first two visits and the PAPP-A plasmatic levels.

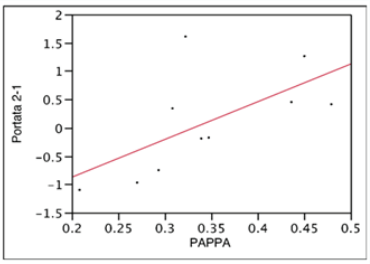

Figure 4: Correlation between the difference in Cardiac Output values in the first two visits and the PAPP-A plasmatic levels.

taken into consideration by recent literature, and is the most original result of our study. The trend of this

parameter suggests a progressive reduction of right ventricular systolic function in women of the control group, while no change is evident in women with pathological PAPP-A, in whom the values of TAPSE remain 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. Since the right ventricle is passively affected by volumetric variations, there is no adaptation of the ejection fraction based on the extent of the myocardial fiber 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 hemodynamic changes that characterise pregnancy. The lack of change of the values of TAPSE in women with pathological PAPP-A is compatible with the imperfect hemodynamic adaptation, including in the first place the smaller PVR fall, which would not be followed by the consequent activation of the before 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 which 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 of 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 paraphysiological condition. We can hypothesize that the absence of this finding in patients with pathological PAPP-A may have an importance in the context of the differences between physiological and pathological hemodynamic 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

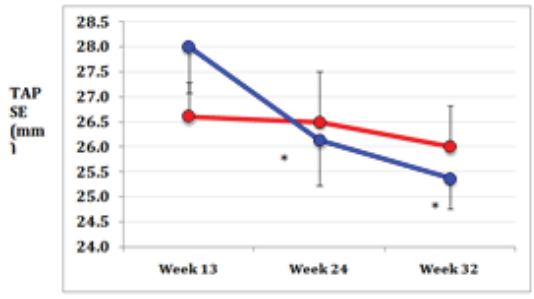

Figure 5: TAPSE trend over time.

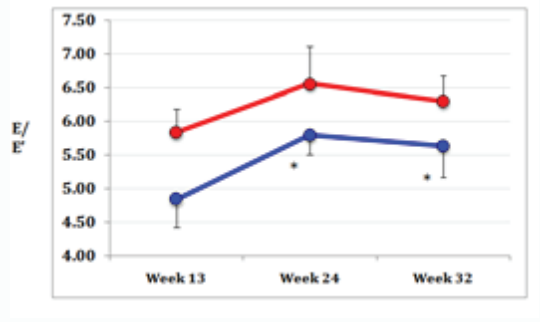

Figure 6: Trend of the E / E' ratio over time.

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 hemodynamic 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, as much from a process of adaptation to a pathological

condition of chronic increase of peripheral resistance and inefficiency of hemodynamic adaptation mechanisms, among which we find the concentration of PAPP-A.

Conclusions

This study shows that the hemodynamic adaptation that occurs during a normal pregnancy, and that 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 on 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 hemodynamic 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 32th 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, is such as to create a favorable 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 therefore 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 create a specific path and a closer follow-up. Considering the scarcity of data in the literature and the controversies on 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 from the delivery, could allow a better understanding of the relationships between PAPP -A and hemodynamic 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 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 in association with a missed haemodynamic adaptation
- The assay of PAPP-A in the first trimester can identify women at a greater risk of preeclampsia

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