Screening for Hypertensive Pregnancy Complications through Maternal Serum PAPP-A 5th and 10th Percentiles during the 11-14 Weeks Gestational Age Interval

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The aim of our study was to assess the predictive values for hypertensive complications of pregnancy of the multiples of median (MoM) of serum pregnancy associated plasma protein A (PAPP-A), measured in 128 pregnant patients between 11 and 14 weeks gestational age. The 5th and the 10th percentile for MoM PAPP-A were 0.27 and 0.33, respectively. The detection rate for pregnancy induced hypertension, mild preeclampsia, severe preeclampsia, all preeclampsia and all hypertensive complications was 0%, 9.09%, 0%, 7.69%, and 6.25% for MoM PAPP-A below the 5th percentile (for a false positive rate of 5%), and 33.33%, 9.09%, 0%, 7.69%, and 12.5% for MoM PAPP-A below the 10th percentile (for a false positive rate of 10%), respectively. The specificity ranged from 89.57% to 95.73%, the positive predictive value from 0% to 16.67%, and the negative predictive value from 87.70% to 98.36%.

Keywords: pregnancy, preeclampsia, screening, detection rate, PAPP-A

Pregnancy-associated plasma protein-A (PAPP-A) is the largest of the pregnancy associated proteins produced by the syncytiocytotrophoblast [1]. This protein has several different functions, including preventing recognition of the fetus by the maternal immune system, matrix mineralization and angiogenesis1. The serum levels of PAPP-A rise from first detection in the first trimester until term [1].

Maternal serum concentrations are related to subsequent fetal growth and it can be used as a diagnostic test for adverse pregnancy outcomes, including intrauterine growth restriction, premature birth, preeclampsia, and stillbirth [1].

The plasmatic concentrations of PAPP-A are altered in pregnant patients who will develop preeclampsia (PE), the predictive value being high especially for the preterm type 2,3. The accuracy of PAPP-A is low for term PE, most probably because this type of PE is due to maternal cardiovascular disease and/or placental insufficiency at term4-6.

The value of MoM PAPP-A was statistically significantly decreased in the 224 pateients who developed PE in a study comprising 47994 pregnant women with the gestational age between 11 and 13 weeks7.

Another study on 3663 pregnant patients demonstrated that the ones with MoM PAPP-A below the 10th percentile had a relative risk for PE and preterm PE of 3.27 and 9.26, respectively, with the frequency thereof statistically significantly increased compared to the other patients in the study group8.

PAPP-A used separately or combined with uterine artery PI revealed higher AUC for preterm PE than for term PE9.

Experimental part
Materials and methods
The study included 128 pregnant patients with gestational ages between 11 weeks and 13 weeks+6 days, who were examined by ultrasound, including uterine artery Doppler, and who had the plasmatic concentration of PAPP-A determined. Plasmatic PAPP-A was determined with the ELISA Sunrise device, Tecan, Switzerland, and Pregnancy Associated Plasma Protein A reactant, MBS026323, MyBioSource, Inc., USA.

Results and discussions
The 128 in our study had a total of 16 pregnancies with different types of hypertensive complications (12.5%), the number and frequency thereof being detailed in table 1.

The demographics of the paients (total, with complications and with normal outcome) are shown in table 2; Student's t-test was used to compare mean values and standard deviations, while the statistical significance for differences in frequencies was assessed with the Chi-square test.

The 5th and the 10th percentile for MoM PAPP-A were 0.27 and 0.33, respectively.

Table 1
COMPLICATIONS

Type	Number	%
PIH	3	2.34
Mild PE	11	8.59
Severe PE	2	1.56
PE	13	11.15
Total hypertension	16	12.50

PIH pregnancy induced hypertension; PE: preeclampsia

Table 2
DEMOGRAPHICS

	Total (128 de pacients)	Complications (16 pacients)	Normal outcome (112 pacients)	p (normal vs. complications)
Age	27.55±4.93	29.13±6.68	27.33±4.58	0.1698
Gesta	2.27±1.90	1.50±0.87	2.38±1.98	0.0827
Para	0.81±1.40	0.31±0.58	0.88±1.47	0.1286
BMI	24.56±5.69	27.97±5.87	24.52±4.49	**0.0066**
Pre pregnancy BMI	23.78±5.58	26.58±5.87	23.81±4.45	0.0273
Perimetru abdominal	87.77±13.56	91.25±19.87	87.28±12.32	0.2713
Systolic BP	109.69±11.89	117.81±12.62	108.53±11.31	**0.0030**
Diastolic BP	68.87±8.01	73.75±9.27	68.17±7.56	**0.0083**
Mean BP	81.20±13.28	88.44±8.74	81.62±8.08	**0.0022**
CRL	58.42±13.15	57.46±12.60	58.56±13.02	0.7515
MoM PAPP-A	0.831±0.52	0.80±0.53	0.84±0.52	0.7745
Mean PI	1.72±0.64	1.67±0.62	1.73±0.64	0.7254
Meanm RI	0.71±0.14	0.71±0.12	0.72±0.11	0.7372
Mean PI/RI	2.33±0.58	2.27±0.56	2.34±0.58	0.6510
Primigesta	46.09% (59/128)	68.75% (11/16)	42.86% (48/112)	0.0529
Nullipara	55.50% (71/128)	75% (12/16)	52.68% (59/112)	0.0942
Primigesta+nullipara	45.93% (59/128)	68.75% (11/16)	42.86% (48/112)	0.0529
Previous PIH	0.78% (1/128)	-	0.89% (1/112)	0.7055
Chronic HTN	3.91% (5/128)	25% (4/16)	0.89% (1/112)	**0.0001**
Total personal history of HTN	4.69% (6/128)	25% (4/16)	1.79% (2/112)	**0.0001**
Smoking	28.91% (37/128)	25% (4/16)	29.46% (33/112)	0.8624
Family history of HTN	42.19% (54/128)	43.75% (7/16)	41.96% (47/112)	0.6883
Family history of DM	27.34%(35/128)	43.75% (7/16)	25% (28/112)	0.1169

BMI: body mass index; BP: blood pressure; PI: pulsatility index; RI: resistivity index; HTN: hypertension; DM: diabetes mellitus

The distribution of the MoM PAPP-A values is shown by figures 1 and 2, while figure 3 shows the cvartiles thereof
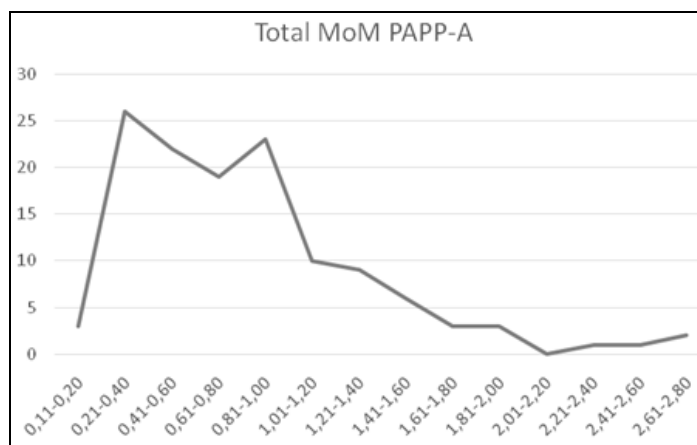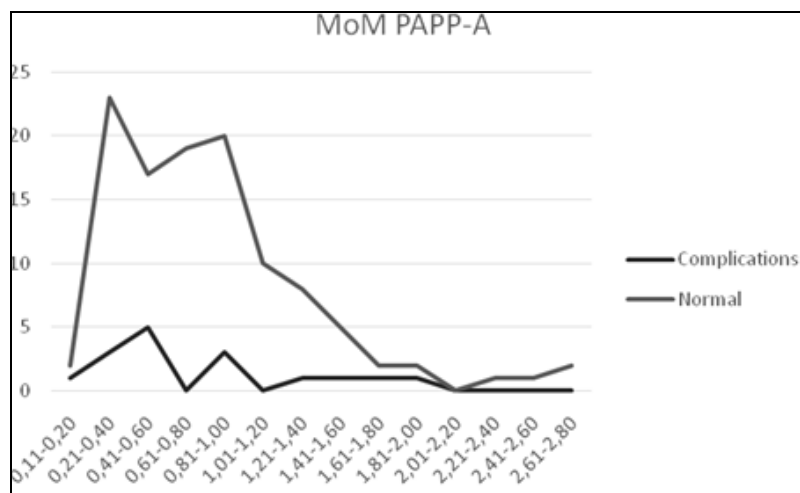

Fig. 1 The distribution of MoM PAPP-A

Fig. 2 The distribution of MoM PAPP-A for complicated and normal outcome pregnancies
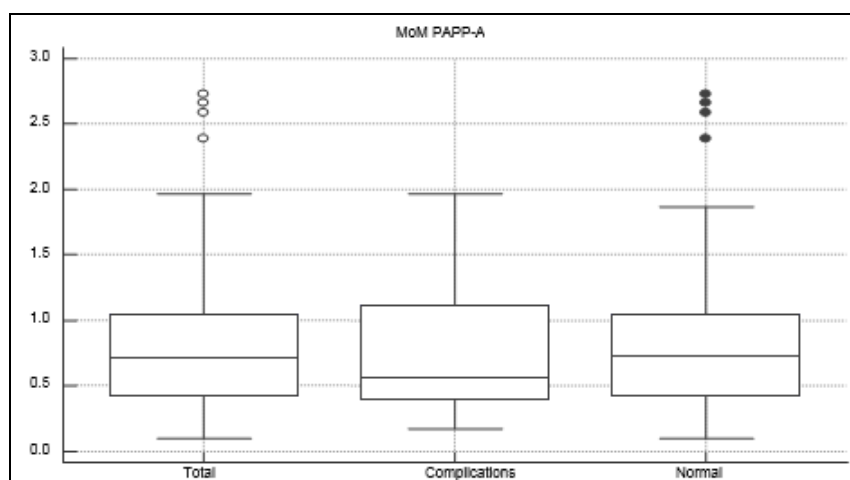

Fig. 3 The distribution of MoM PAPP-A cvartiles

We have calculated the predictive values for hypertensive complications for values of MoM PAPP-A below the 5th and the 10th percentile are detailed in tables 3 and 4. Table 5 shows the detection rate of these complications for a false positive rate of 5% and 10%.

Table 3
PREDICTIVE VALUES OF MOM PAPP-A BELOW THE 5th PERCENTILE

Complication	Sensitivity	Specificity	PPV	NPV	FPR	OR (95% CI)
PIH	0.00%	95.20%	0.00%	97.54%	4.80%	4.345 (0.185 to 101.857)
Mild PE	9.09%	95.73%	16.67%	91.80%	4.27%	2.240 (0.238 to 21.092)
Severe PE	0.00%	95.24%	0.00%	98.36%	4.76%	7.303 (0.266 to 200.554)
PE	7.69%	95.65%	16.67%	90.16%	4.35%	1.833 (0.197 to 17.019)
Total hypertension	6.25%	95.54%	16.67%	87.70%	4.46%	1.427 (0.156 to 13.058)

PIH pregnancy induced hypertension; PE: preeclampsia; PPV: positive predictive value;
NPV: negative predictive value; FPR false positive rate

Table 4
PREDICTIVE VALUES OF MOM PAPP-A BELOW THE 10th PERCENTILE

Complication	Sensitivity	Specificity	PPV	NPV	FPR	OR (95% CI)
PIH	33.33%	90.40%	7.69%	98.26%	9.60%	4.708 (0.397 to 55.840)
Mild PE	9.09%	89.74%	7.69%	91.30%	10.26%	0.875 (0.103 to 7.442)
Severe PE	0.00%	89.68%	0.00%	98.26%	10.32%	3.027 (0.117 to 78.335)
PE	7.69%	89.57%	7.69%	89.57%	10.43%	0.715 (0.085 to 5.994)
Total hypertension	12.50%	90.18%	15.38%	87.83%	9.82%	1.312 (0.263 to 6.543)

PIH pregnancy induced hypertension; PE: preeclampsia; PPV: positive predictive value;
NPV: negative predictive value; FPR false positive rate

Table 5
DETECTION RATE FOR 5% AND 10% FALSE POZITIVE RATES

	Detection rate for 5% FPR	Detection rate for 10% FPR
PIH	0.00%	33.33%
Mild PE	9.09%	9.09%
Severe PE	0.00%	0.00%
PE	7.69%	7.69%
Total hypertension	6.25%	12.50%

PIH pregnancy induced hypertension; PE: preeclampsia; FPR false positive rate

The prevalence of preeclampsia was 11.15% and PIH appeared in 2.34%. The detection rate for PE was 7.69% for all PE cases for both 5% and 10% FPR, with 0% for severe and 9.09% for mild PE for both FPR rates. The sensitivity and PPV were low, while the specificity and NPV were high.

The detection rate for PE, mild PE and severe PE was the same for MoM PAPP-A below the 5th and the 10th percentile, while PIH and all hypertensive complications had a higher detection rate for MoM PAPP-A below the 10th percentile.

The only statistical significant differences between the patients with and without hypertensive complications were for the values of blood pressure, BMI, and for the personal history of chronic hypertension and any type of hypertension.

The prevalence of PE, the detection rate and the OR for PAPP-A below the 5th percentile in several studies were:
- prevalence 1.9%. detection rate 9.6%, with an OR of 2.0[10]
- prevalence 1.5%. detection rate 23.1%, with an OR of 4.6[11]
- prevalence 2.6%. detection rate 11.1%, with an OR of 2.1[12]
- prevalence 3.7%. detection rate 10.6%, with an OR of 2.3[13]
- prevalence 1.5%. detection rate 14.1%, with an OR of 2.8[14]
- prevalence 0.5%. detection rate 14.6%, with an OR of 3.7[15]
The values of MoM PAPP-A were 0,903 for PE and 0,837 for PIH in another study[16].

Conclusions

Although the size of the population in our study was small, the results, including prevalence, OR and detection rate, are very similar to those in literature.

The detection rate for PIH and for all hypertensive complications of pregnancy is higher for values of MoM PAPP-A below the 10th percentile compared to values thereof below the 5th percentile, but the FPR is higher (10% versus 5%).

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