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Correlation of PAPP-A values with maternal characteristics, biochemical and ultrasonographic markers of pregnancy

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ABSTRACT

Objective: Our aim is to investigate whether there is a correlation of pregnancy-associated plasma protein A (PAPP-A) values with other variables in pregnancy and maternal characteristics.

Materials and Methods: We retrospectively analyzed the relation between the PAPP-A levels, demographics, biochemical and ultrasonographic markers of the first trimester screening of 11,842 pregnant women seen at a tertiary hospital between November 2002 and November 2008.

Results: A significant difference between PAPP-A values of the diabetic and non-diabetic pregnant women were observed (p=0.0005, Mann-Whitney U test). In terms of weight, crown-rump length, Beta-hCG values, significant differences were observed between low and medium level PAPP-A subgroups and between low and high level PAPP-A subgroups. PAPP-A levels were found to differ significantly between the pregnant women of Caucasian origin and other racial origins.

Conclusions: Pregnant women with different ethnic and medical backgrounds have different PAPP-A values and other markers of the aneuploidy screening. To make patient specific risk predictions, understanding these interactions and differences is important. Future studies are needed to understand the pathopyhsiology behind these differences.

Keywords: Pregnancy-associated plasma protein A (PAPP-A), Maternal characteristics, Aneuploidy screening, Biochemical markers, Ultrasonographic markers

1. INTRODUCTION

Pregnancy-associated plasma protein A (PAPP-A) is one of the markers used in aneuploidy screening. It can be used alone or with other markers. Used alone, low PAPP-A levels can indicate adverse pregnancy outcomes such as small for gestational age babies, preterm delivery, intrauterine growth retardation and large for gestational age babies in high PAPP-A levels [1-3]. High levels of PAPP-A (PAPP-A more than 4 multiples of median (MoM) are rarely observed and there are a few studies on the outcomes of pregnancies with extremely high PAPP-A levels (More than 5 MoM) [4].

Previous studies demonstrated that there is an effect of different PAPP-A levels on maternal characteristics [5-8]. Westergaard et al., found statistically significant correlation between PAPP-A concentrations and maternal weight, placental weight, fetal sex and gravidity [5]. Several studies showed that PAPP-A level is higher in women of Afro-Caribbean, South Asian and East Asian racial origin, than in Caucasian women [7,8].

The relation between gestational diabetes and PAPP-A is an active research area [9]. Syngelaki et al., reported that PAPP-A levels of patients who developed gestational diabetes were 5.1–30.8% lower than other pregnant women [10]. Lovati et al. showed that low PAPP-A was associated with gestational diabetes mellitus (DM) and lower values were found in insulin dependent diabetic women [11].

The objectives of this study with its large cohort is to identify and quantify the effects of maternal characteristics and biochemical and ultrasonographic markers of first trimester screening on PAPP-A levels to make better predictions for pregnancy outcome and therefore to give better counselling and follow up.

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2. MATERIALS and METHODS

We retrospectively collected first trimester screening data from 11,824 singleton pregnant women followed between November 2002 and November 2008 after approval by the Yale University Ethics Commitee (September 23, 2008, protocol number HIC 080.900.4229). In this study group, there were only 23 pregnancies (0.18%) with PAPP-A above 5 MoM .

As part of first trimester aneuploidy screening, free beta human chorionic gonadotrophin (Beta-hCG) and PAPP-A measurements of pregnant women were collected. Free Beta-hCG and PAPP-A were measured using IMMULITE 1,000 analyzer (BioDPC, USA). The concentrations of these markers were converted to MoMs. Features such as age, weight, diabetes status, age group risk, down syndrome risk, nuchal translucency (NT), and crown-rump length (CRL) were recorded.

Mean, median, minimum and maximum values of 11,842 patients' age, weight, gestational week, crown-rump length (CRL), nuchal translucency (NT), PAPP-A, beta-hCG, age group risk and Down syndrome risk values were calculated. Log10 transformation was applied to MoM values of NT, free Beta-hCG, and PAPP-A.

Statistical Aalysis

Statistical analysis was performed on a computer using statistical program for social sciences version 22.0 (IBM SPSS Statistics Base 22.0). 11,842 patients were divided into subgroups according to PAPP-A levels, diabetes status and race. Mean, median, minimum and maximum values were recalculated. Mann-Whitney U test was used to test whether the variables used in the study were significant. The significance level was set to 95%. Log-transformed data were also analyzed in this study to normalize the distribution of the residuals, as required for the linear regression and as it is a widely used method in this field. P-values less than 0.05 were considered statistically significant.

3. RESULTS

First, we analyzed the characteristics of 11,842 patients (Table I), and the characteristics of the subgroups that we created according to the pregnant women's diabetic status (Table II). As shown in Table II, there was a significant difference between PAPP-A MoM values of the diabetic and non-diabetic pregnant women (p = 0.0005). For diabetic pregnant women, mean of PAPP-A MoM was 1.03, while for non-diabetic pregnant women, this value was 1.18. Same statistical difference was also observed between PAPP-A log10MoM values of the diabetic and non-diabetic pregnant women (p=0.0005). For diabetic pregnant women, mean of PAPP-A log10MoM was – 0.06, while for non-diabetic pregnant women, this value was 0.002. Another statistically significant difference was found between the weights of pregnant and non-diabetic pregnant women (p <0.0001). For diabetic pregnant women, mean of weight was 89.4 kg, while for non-diabetic pregnant women, this value was 70.5 kg.

Table I. *Maternal and pregnancy characteristics of study population*

Characteristics	All patients		
	N	Mean (SD)	Median (min-max)
Age (years)	11842	31.76±5.46	32(14-53)
Weight (kg)	11842	70.87±17.1	66.6(36.5-182)
Gestational week	11842	11.5±0.82	12(10-14)
CRL (mm)	11842	61.3±8.5	61.3(36-79.3)
NT MoM	11842	1.04±0.3	1(0.3-6.28)
PAPP-A MoM	11842	1.1±0.7	1(0.06-12.4)
Beta-hCG MoM	11842	1.07±0.43	1.01(0.05-5.01)
PAPP-A (log10MoM)	11842	0.0016±0.24	0(-1.22-1.09)
Beta-hCG (log10MoM)	11842	-0.00056±0.17161	0.0043(-1.3-0.699)
Age group risk	11842	390.81±252.15	340(4-1200)
Ds_risk	11842	5023.38±5543.5	2800(2-20000)

CRL: Fetal crown-to-rump length, NT:Nuchal translucency, hCG: human chorionic gonadotropin, MoM: Multiples of median, Ds: Down syndrome.

Table II. *Maternal and pregnancy characteristics of diabetic status-based subgroups*

Characteristics	Diabetic			Non-Diabetic			p (Mann Whitney U test)
	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	Diabetic and non-diabetic
Age (years)	185	31.28±6.33	32(16-46)	11657	31.7±5.44	32(14-53)	0.385
Weight (kg)	185	89.4±24.5	85.3(47.9-182)	11657	70.5±16.7	66.6(36.5-172.4)	**<0.00001***
Gestational week	185	11.5±0.85	11(10-13)	11657	11.5±0.8	12(10-14)	0.543
CRL (mm)	185	60.42±9.22	60.8(38-79.3)	11657	61.3±8.5	61.3(36-79.3)	0.182
NT MoM	185	1.04±0.3	1.01 (0.55-2.51)	11657	1.04±0.3	1(0.3-6.28)	0.953
PAPP-A MoM	185	1.03±0.72	0.85 (0.16-5.67)	11657	1.18±0.7	1.01(0.06-12.4)	**0.00049***
Beta-hCG MoM	185	1.07±0.43	1.01 (0.16-2.86)	11657	1.07±0.43	1.01(0.05-5.01)	0.825
PAPP-A (log10MoM)	185	-0.06±0.26	-0.07 (-0.79-0.75)	11657	0.002±0.24	0.004(-1.22-1.09)	**0.00049***
Beta-hCG (log10MoM)	185	-0.006 ±0.18	0.004 (-0.79-0.45)	11657	-0.0004 ±0.17	0.0043(-1.3-0.69)	0.825
Age group risk	185	416.25±277.8	360(11-890)	11657	390.4±251.7	340(4-1200)	0.289
Ds_risk	185	4431.13±5219.5	240(8-20000)	11657	5032.78±5548	2800(2-20000)	0.055

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropin, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*

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We then divided our dataset into the following three subgroups according to the PAPP-A levels; low PAPP-A (PAPP-A level < 4), medium PAPP-A (4 < PAPP-A level < 5), and high PAPP-A (PAPP-A level > 5). Table III identifies the characteristics of these subgroups. Significant differences were observed between low PAPP-A level subgroup and medium PAPP-A level subgroup in terms of weight, CRL, Beta – hCG MoM, Beta-HCG log10MoM values (p values of Mann-Whitney U test<0.05). Similarly, significant differences were observed between low PAPP-A level subgroup and high PAPP-A level subgroup in terms of weight, Beta-hCG MoM, Beta-hCG log10MoM values (p values of Mann-Whitney U test<0.05). Mean of weight was 70.79 kg for low PAPP-A level subgroup, while this value was 91.84 kg for high PAPP-A level subgroup.

Table III. *Maternal and pregnancy characteristics of PAPP-A level-based subgroup*

	Subjects with PAPP-A level < 4 (Low)			4 < PAPP-A level < 5 (Medium)			PAPP-A level > 5 (High)			p (Mann-Whitney U test for PAPP-A levels)		
	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	Low-Medium	Low-High	Medium-High
Age (years)	11762	31.76±5.46	32(14-53)	52	31.7±5.43	32(21-40)	28	32.67±4.11	33.5(25-42)	0.905	0.479	0.606
Weight (kg)	11762	70.79±16.97	66.6(36.5-182)	52	77.9±19.2	71.4(48.8-135)	28	91.84±35.21	90.11(47.45-161.53)	**0.005***	**0.005***	0.217
Gestational week	11762	11.55±0.82	12(10-14)	52	11.25±0.7	11(10-13)	28	11.35±0.85	11(10-13)	0.006	0.144	0.722
CRL (mm)	11762	61.39±8.57	61.3(36-79.3)	52	57.07±8.53	57.3(41-79.3)	28	59.3±9.9	59.1(45.2-77.3)	**0.001***	0.224	0.356
NT MoM	11762	1.04±0.3	1(0.3-6.28)	52	1.1±0.34	1.05(0.5-2.39)	28	0.98±0.33	0.97(0.31-1.84)	0.222	0.327	0.162
Beta-hCG MoM	11762	1.07±0.42	1.01(0.07-5.01)	52	1.34±0.5	1.21(0.37-3.02)	28	1.46±0.73	1.37(0.05-3.41)	**<0.0001***	**0.001***	0.661
Beta-hCG (log10MoM)	11762	-0.001±0.17	0.0004 (-1.15-0.69)	52	0.09±0.17	0.08(-0.43-0.48)	28	0.08±0.32	0.13(-1.3-0.5)	**<0.0001***	**0.001***	0.661
Age group risk	11762	390.9±252.1	340(4-1200)	52	393.9±261.9	340(50-850)	28	341.6±210.3	265(35-760)	0.995	0.404	0.505
Ds_risk	11762	5011.6±5532.4	2800(2-20000)	52	6983±7096.1	3050(20-20000)	28	6321.78±6105.6	3100(310-20000)	0.081	0.146	0.972

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropin, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*

Table IV. *Maternal and pregnancy characteristics of racial origin based subgroups*

	Caucasian Patients (C)			Afro-Caribbean Patients (A)			Patients of Other Ethnicities (O)			P (Mann Whitney U test for diabetic yes and no)		
	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	C-A	C-O	A-O
Age (years)	8807	32.3±5.11	33(15-53)	1046	29.4±6.37	29(15-46)	1989	30.4±5.82	31(14-45)	**<0.0001***	**<0.0001***	**<0.0001***
Weight (kg)	8807	70.7±16.3	66.6(40.15-172.4)	1046	81.5±20.9	78.02 (45.17-182.06)	1989	65.7±15.6	62.05(36.5-161.5)	**<0.0001***	**<0.0001***	**<0.0001***
Gestational week	8807	11.5±0.8	11(10-14)	1046	11.7±0.86	12(10-13)	1989	11.6±0.8	12(10-14)	**<0.0001***	**<0.0001***	**0.002***
CRL (mm)	8807	61.2±8.49	61.1(36-79.3)	1046	62.16±8.87	62.1(36-79.3)	1989	61.5±8.7	61.5(36.1-79.3)	**0.001***	0.089	0.095
NT MoM	8807	1.04±0.32	1(0.3-6.28)	1046	0.98±0.25	0.95(0.31-2.78)	1989	1.06±0.32	1.02(0.41-4.74)	**<0.0001***	0.04	**<0.0001***
PAPP-A MoM	8807	1.14±0.66	0.98(0.06-8.32)	1046	1.45±1.01	1.21(0.16-12.4)	1989	1.18±0.73	1(0.08-6.24)	**<0.000001***	0.269	**<0.0001***
Beta – hCG MoM	8807	1.06±0.41	1(0.09-4.37)	1046	1.21±0.52	1.11(0.05-5.01)	1989	1.07±0.42	1.01(0.11-3.3)	**<0.0001***	0.170	**<0.0001***
PAPP-A (log10MoM)	8807	-0.006±0.23	-0.0087(-1.22-0.92)	1046	0.075±0.27	0.08(-0.79-1.09)	1989	0.00038±0.25	0(-1.09-0.79)	**<0.0001***	0.269	**<0.0001***
Beta – hCG (log10MoM)	8807	-0.006±0.16	0(-1.04-0.64)	1046	0.04±0.18	0.04(-1.3-0.69)	1989	0.00043±0.16	0.004(-0.95-0.51)	**<0.0001***	0.170	**<0.0001***
Age group risk	8807	365.09±240.05	310(4-900)	1046	494.17±282.6	525(11-900)	1989	450.36±263.25	430(14-1200)	**<0.0001***	**<0.0001***	**<0.0001***
Ds_risk	8807	4679.9±5271.3	2600(2-20000)	1046	6660.5±6405.7	4300(11-20000)	1989	5683.2±5998.2	3200(2-20000)	**<0.0001***	**<0.0001***	**<0.0001***

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropiN, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*

We also divided our dataset into the following three subgroups according to the racial origin. 74.3%, 8.8%, 16.8 % of the 11,842 subjects were Caucasian, Afro-Caribbean, other, respectively. Table IV summarizes the characteristics of these subgroups. Significant differences were observed between all pairs in terms of weight, gestational week, NT MoM, PAPP-A MoM, Beta-hCG MoM, PAPP-A log10 MoM, Beta-hCG MoM, age group risk, Down syndrome risk values. There was a significant difference in CRL between the Caucasian and Afro-Caribbean subgroups ($p < 0.05$). While the mean of CRL was 61.1 for Caucasian subgroup, this value was 62.16 for Afro-Caribbean subgroup.

We looked at the correlation between fetus NT values and PAPP-A MoM values of pregnant women whose PAPP-A MoM values were grouped as low-normal (less than 4), high (between 4 and 5) and very high (greater than 5) (Figure 1). There was no significant correlation between PAPP-A MoM and fetus NT measurement in these groups (r=0.04, 0.4, 0.1 for PAPP-A low-normal, high, very high subgroups, respectively).

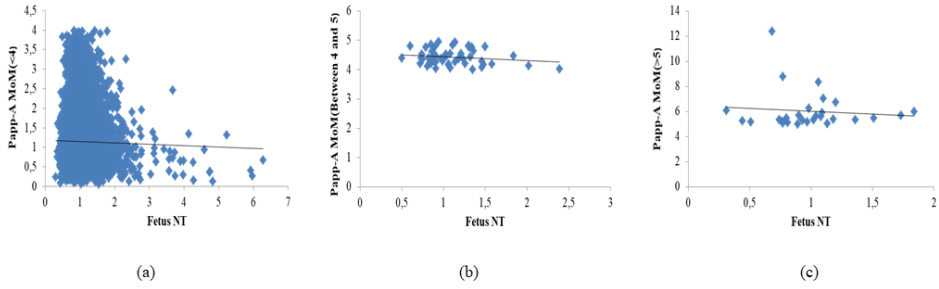

Figure 1. *Correlation between fetus nuchal translucency (NT) values and PAPP-A MoM (multiples of median) values of pregnant women. PAPP-A MoM values were grouped as (a) low-normal (less than 4), (b) high (between 4 and 5) and (c) very high (greater than 5).*

In addition no correlation was observed between PAPP-A MoM and NT values for racial origin groups (r= 0.009, 0.029, 0.029, for Caucasians , Afro-Caribbean's,other ethnicities, respectively) (Figure 2). There was no correlation between PAPP-A MoM and CRL values for racial origin groups (r= 0.04, 0.06, 0.03 for Caucasians, Afro-Caribbeans, other ethnicities, respectively) (Figure 3).

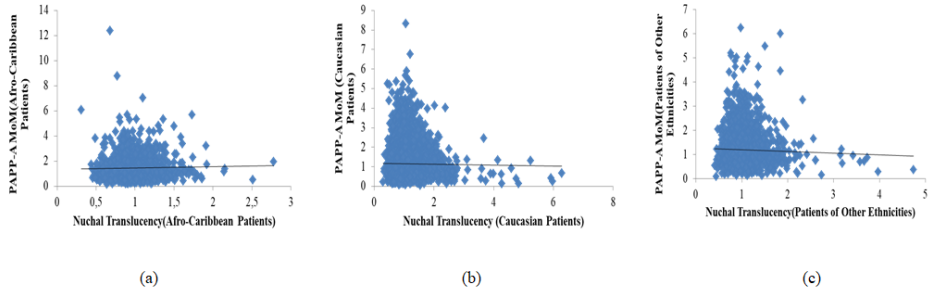

Figure 2. *Correlation between PAPP-A MoM (multiples of median) values and nuchal translucency (NT) values for different racial origin groups, i.e. (a) Afro-Caribbean Patients, b) Caucasian Patients, c) Other Patients*

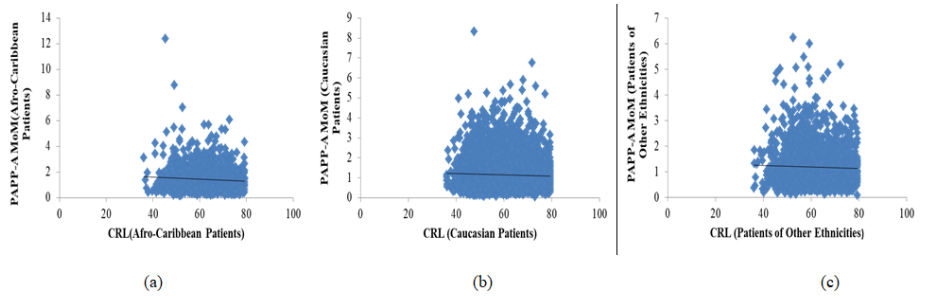

Figure 3. *Correlation between PAPP-A MoM (multiples of median) values and fetal crown-to-rump length (CRL) values for different racial origin groups, i.e., (a) Afro-Caribbean Patients, b) Caucasian Patients, c) Other Patients*

4. DISCUSSION

Pregnancy-associated plasma protein A values are used in predicting pregnancy outcomes, so using accurate cut-off values according to patient's characteristics is important to avoid misinterpretation of results. We found similar results with the previous studies [5-7], that there was a racial difference; Caucasians had lower PAPP-A values than Afro-Caribbeans and other racial groups. In aneuploidy screening one does not fit all, and more studies are needed to make specific charts for different ethnic groups.

Gestational diabetes is another factor that affects PAPP-A levels. Again in line with previous studies [8,9], we also found that PAPP-A levels were significantly lower in pregnant women with diabetes. As expected, the weights of the women in the diabetes group were higher than the non-diabetics regardless of ethnic background. Pregnant women must be counseled about healthy diet.

Pregnancy-associated plasma protein A is a protease for insulin like growth factors (IGF) and acts as an important regulator in their function [10]. IGFs stimulate growth and decrease glucose levels. It is therefore reasonable to observe low PAPP-A levels in diabetic pregnant women.

When we looked at correlations between CRL, NT and ethnic differences, we found that there was a small but significant difference in NT and CRL measurements between fetuses of different ethnic origin. Intrauterine fetal growth charts developed by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) [12], INTERGROWTH [13] and WHO [14] also showed that the percentile cut-points for SGA and LGA varied among the studies. Both environmental and genetic factors are hypothesized to cause differences in body size and proportion [15] , but still determinants of fetal growth are not fully understood [16,17].

Our study with its large cohort of pregnant women coming from different ethnic origins provides useful data for examining the relationship between certain demographic factors, diabetes, CRL, NT and PAPP-A levels. Adjusting the normal values for different backgrounds is important to make accurate patient specific risk predictions [18]. Understanding its interaction with other pregnancy markers and demographics may help us better understand PAPP-A physiology and function in pregnancy.

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Compliance with Ethical Standards

Ethical Approval: The study was approved by Yale University, School of Medicine Ethics Committee (September 23, 2008, protocol number HIC 080.900.4229).

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Author contributions: Research idea, data collection, literature search, reviewing of analysis results, writing: H.K.,

Data mining, statistical analysis, drawing the tables and figures, writing, literature search: O.G.U.,

Statistical analysis, literature search: J.H.,

Data mining, statistical analysis, reviewing and editing of the manuscript, literature search: B.B.G. We confirm that the final version of the article has been read and approved by all named authors.

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