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Maternal PAPP-A Levels at 11 - 13 Weeks of Gestation Predict Foetal and Neonatal Growth

—PAPP-A Growth Predictor

M. Gentile[1], M. Schifano[2], S. Lunardi[1], C. Nanini[2], F. Moscuzza[1], C. Sergiampietri[2], M. Ciantelli[1], F. Monacci[2], A. Boldrini[1], C. Luchi[2], P. Ghirri[1*]

[1]Department of Clinical and Experimental Medicine, Neonatal Intensive Care and Neonatology Unit, University Hospital of Pisa, Pisa, Italy
[2]Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynaecology, University Hospital of Pisa, Pisa, Italy
Email: [*]pghirri@med.unipi.it

Abstract

Recent reports suggest that maternal serum levels of pregnancy-associated plasma protein A (PAPP-A) may predict perinatal outcome. PAPP-A is a syncytiotrophoblast derived protease for insulin-like growth factor binding protein (IGFBP4); its protease activity cleaves complexed growth factor binding protein increasing insulin-like growth factor I (IGF-I) bioavailability. The aim of our study was to evaluate the correlation between maternal PAPP-A serum levels and neonatal growth. We analysed 100 full term and preterm (30 - 36 weeks) small for gestational age (SGA) and adequate for gestational age (AGA) babies whose mothers had been tested for serum PAPP-A at 11 - 13 weeks of gestation. We found a significant positive correlation between maternal PAPP-A and neonatal weight, length, and head circumference at birth in both term and preterm infants. Low maternal PAPP-A serum levels (maternal PAPP-A < 0.5) were associated with small for gestational age neonates. A significant positive correlation was also evident between maternal PAPP-A and babies' growth parameters at 6 months of age. Our results suggest that maternal levels of PAPP-A in early pregnancy affect growth during both foetal and early postnatal life.

Keywords

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[*]Corresponding author.

1. Introduction

Recent reports suggest that maternal serum levels of pregnancy-associated plasma protein A (PAPP-A) at 9 - 14 weeks of gestation may predict foetal and neonatal outcome. Several studies reported a correlation between maternal PAPP-A levels during pregnancy and baby's birth weight [1]-[3]. Lower maternal serum PAPP-A levels were, according to a few studies, associated with maternal hypertension during pregnancy [1] [4]-[13]. Large population-based screening studies demonstrated that low levels of PAPP-A were associated with reduced foetal growth [4]-[6] [8]-[10] [12] [14]-[22].

PAPP-A's role in foetal growth is due to its interaction with the insulin-like growth factor (IGF-1) system. Insulin like growth factor seems to play a significant role in trophoblastic invasion [23]-[26], affecting early development and vascularisation of the placenta and the placental bed and activating downstream signaling pathways. IGF-1 is usually bound to circulating proteins that make it more stable. PAPP-A is a syncytiotrophoblast-derived protease for insulin-like growth factor binding protein [27]; its protease activity cleaves complexed growth factor enhancing its bioavailability [28] [29]. Thus high PAPP-A concentrations lead to enhanced growth factor bioactivity which leads to enhanced growth [27] [30].

Our objective was to confirm the relationship between first-trimester PAPP-A levels and birth weight hypothesizing that, at a certain point in the first trimester, PAPP-A predicted subsequent placental function and neonatal growth outcome.

2. Materials and Methods

We analysed 100 babies born in our Neonatology Unit whose mothers had been tested for serum PAPP-A at 11 - 13 weeks of gestation. Our sample collected babies from 30 weeks of gestational age both Small for Gestational Age (SGA) and Adequate for Gestational Age (AGA). Neonates with congenital malformations were excluded from our study.

Neonates were divided in 4 groups of 25 babies each according to their gestational age and weight at birth: term SGA babies, term AGA babies, preterm SGA babies, preterm AGA babies. AGA and SGA definition was based on the Bertino's Italian population based growth charts [31]. SGA infants were defined by a birth weight below the 10th percentile for their gestational age (GA), whereas AGA infants were those with a birth weight between the 25th and the 75th percentile.

The following variables were studied: neonatal weight, length and head circumference, placenta's weight, maternal age, neonatal Red Blood Cells (RCB) count and haemoglobin levels at birth. Other neonatal outcomes such as presence of respiratory distress and length of hospitalization were considered as well.

These variables were compared to maternal PAPP-A serum levels at 11 - 13 weeks of gestation by means of a statistical study of linear regression and correlation.

PAPP-A levels were adjusted for other parameters while calculating (first trimester screening program) the risk in each pregnancy: each measured value was converted to a multiple of the median (MoM) specific parameter for GA, maternal weight, ethnic origin, smoking status and method of conception. The biochemical calculation considers various parameters which are, in addition to gestational age derived from the measurement of CRL, mother's weight, ethnic group, smoke of cigarettes, IVF, parity, numbers of foetuses and chorionicity in case of twin pregnancy.

We also studied in preterm infants (both SGA and AGA at birth) auxological outcome at 6 months of corrected age. Weight, length and head circumference at 6 months were defined according to the World Health Organization Child Growth Charts and then compared to maternal PAPP-A levels.

Statistical study was performed by SPSS 16.0.

3. Results

The 100 babies we analysed in our study were divided in 4 groups of 25 babies each according to their gestational age and weight at birth: term SGA babies, term AGA babies, preterm SGA babies, preterm AGA babies. Comparing the studied neonatal variables to maternal PAPP-A serum levels at 11 - 13 weeks of gestation we observed a statistically significant positive correlation between maternal PAPP-A MoM levels and neonatal weight (W), length (L) and head circumference (HC) at birth both in term and preterm newborns (**Figure 1** and **Figure 2**).

We were able to highlight as well a significant positive correlation between PAPP-A MoM levels and placental weight both in term and preterm babies (**Figure 1** and **Figure 2**).
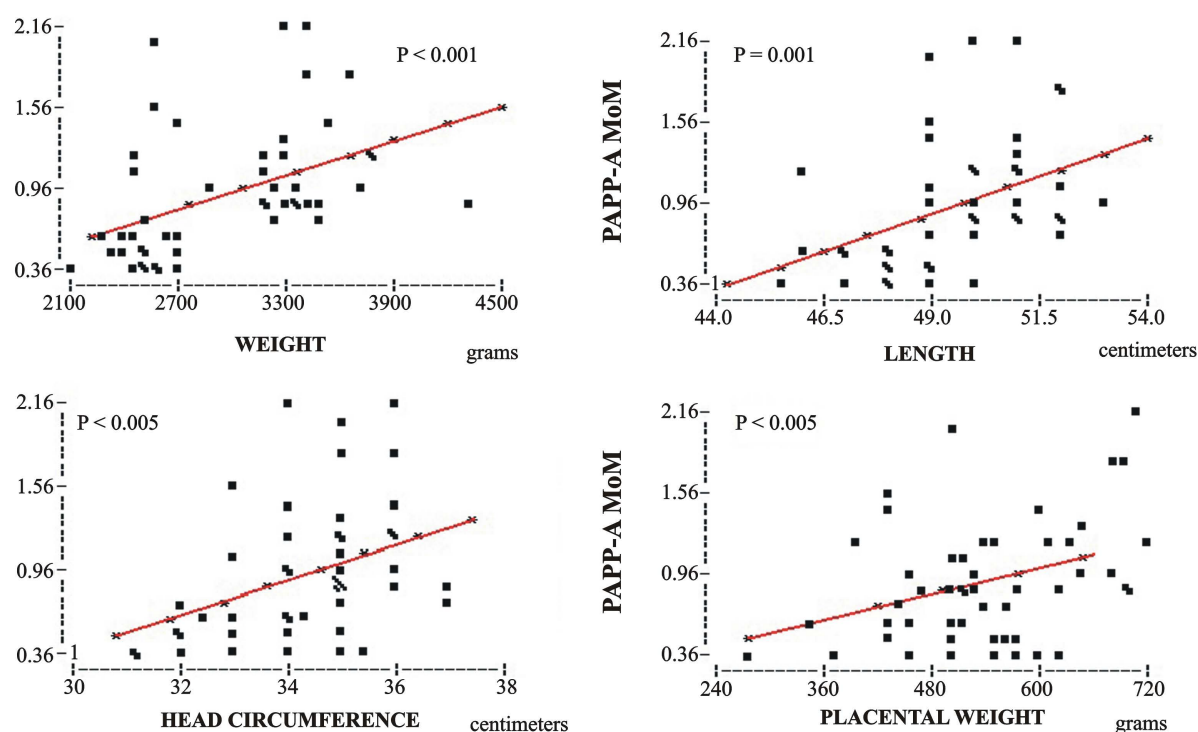

Figure 1. Maternal PAPP-A MoM levels at 11 - 13 weeks of gestation compared to neonatal weight (grams), length (centimeters) and head circumference (centimeters) at birth and placental weight (grams), in term pregnancies.
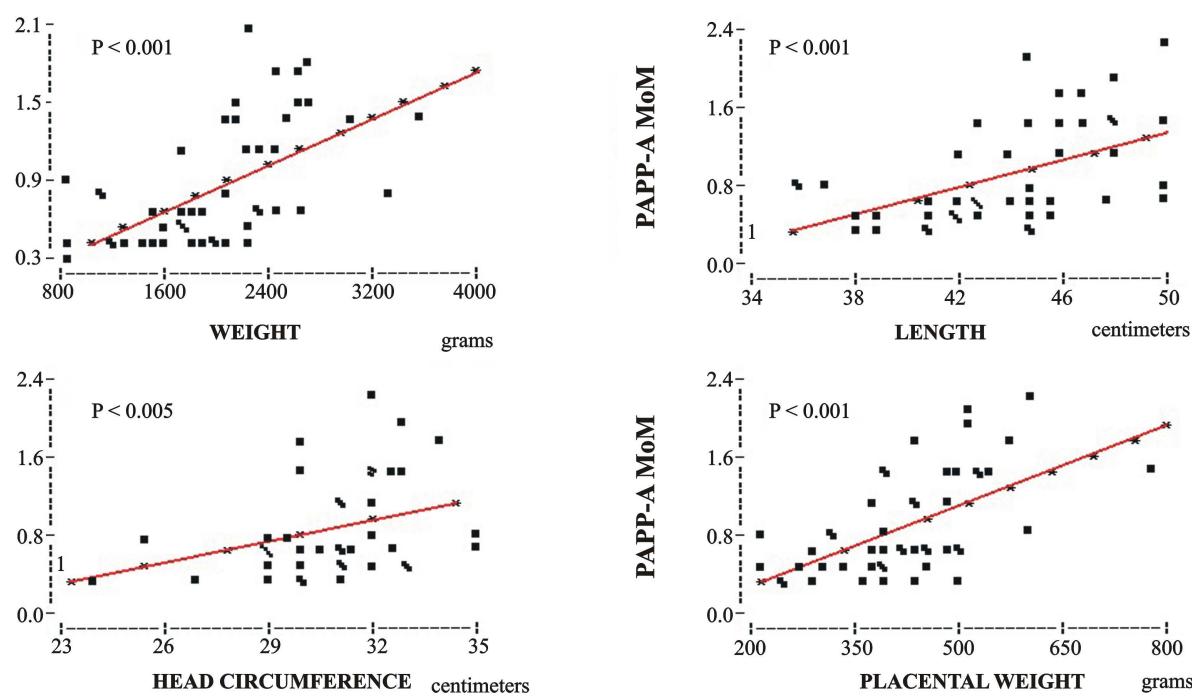

Figure 2. Maternal PAPP-A MoM levels at 11 - 13 weeks of gestation compared to neonatal weight (grams), length (centimeters) and head circumference (centimeters) at birth and placental weight (grams) in preterm pregnancies.

Table 1. Distribution of SGA babies after grouping them according to MoM values.

	Distribution of SGA[a] babies after grouping them according to MoM values		
	MoM < 0.5	MoM 0.5 - 1	MoM 1 - 1.5
SGA preterm babies (25 cases)	11 SGA for W[b], L[c], HC[d] 2 SGA for W, L 3 SGA for W, HC	4 SGA for W, L 4 SGA for W, HC	1 SGA for W
SGA full term babies (25 cases)	10 SGA for W, L, HC 4 SGA for W, L	2 SGA for W, L 3 SGA for W, HC	6 SGA for W

[a]Small for gestational age babies; [b]Weight; [c]Length; [d]Head circumference.

No statistically significant correlation was found instead between PAPP-A MoM levels and maternal age, neonatal red blood cells count and haemoglobin levels at birth, incidence of persistent periventricular hyperechogenicity (lasting more than 14 days) and length of stay in hospital in preterm AGA and SGA babies.

Moreover, analysing all babies whose mother had a PAPP-A MoM < 0.5, it was shown that both full term and preterm neonates were SGA for weight and at least another anthropometric parameter (2/3 of neonates were SGA for weight, height and head circumference) (**Table 1**) [32].

Levels of PAPP-A MoM between 0.5 and 1 were associated with infants SGA for two anthropometric parameters (weight and height/or weight and head circumference). PAPP-A > 1.5 was associated instead in all cases to the birth of an AGA newborn (no matter what the gestational age was).

We also examined whether in case of SGA infant with PAPP-A MoM < 0.5 the mother had suffered from any kind of disease during pregnancy. Maternal gestosis or diabetes had occured in 15 preterm SGA babies and in 8 term SGA newborns.

The evaluation of correlation between the placental weight and the neonatal parameters showed that in both AGA and SGA preterm babies there was a significant positive correlation between birth weight, length, head circumference and placental weight.

4. Follow-Up

We evaluated the growth of our SGA and AGA premature babies at 6 months of corrected age. A linear, positive and significant correlation between weight (p 0.029), length (p 0.036), cranial circumference (p 0.016) and PAPP-A maternal levels was still detectable at 6 months of age (**Figure 3**).

At 6 months of corrected age weight, length and head circumference of SGA preterm babies were still below the 10th centile respectively in 80%, 76% and 60% of them.

5. Discussion

Our study supports the idea that the majority of pregnancies leading to SGA infants are complicated by gestosis or diabetes (in our study 15 out of 25 premature SGA babies and 8 out of 25 full term SGA babies were born to mothers with gestosis or diabetes). The levels of PAPP-A MoM were ≤0.5 in these pregnancies. This confirms that low levels of PAPP-A are not associated with a positive outcome of pregnancy.

Recent multicenter studies showed that levels of PAPP-A below the 5th centile in the first trimester of pregnancy are more frequently associated with intrauterine death, premature birth, preeclampsia and low birth weight [4]-[6] [8] [9] [12] [14]-[16] [33] [34].

In our study we demonstrated that there is a significant, positive correlation between PAPP-A plasma levels and birth weight, length, head circumference and placenta's weight.

PAPP-A is a protease of IGFBP4 which acts as a binding protein for IGF-1 and a powerful inhibitor for IGF-1. Therefore, low levels of PAPP-A are associated with high levels of IGFPB4 and consequently with reduced levels of free circulating IGF-1. IGF-1 plays an important role in regulating foetal growth by controlling glucose and amino acids absorption in trophoblastic cells.

We think that PAPP-A plays as well a significant role in controlling autocrine and paracrine trophoblastic invasion. Thus low levels of PAPP-A could cause an inadequate trophoblastic invasion and consequently an higher incidences of abortions, premature labours, low birth weight and preeclampsia [27] [28].

Instead, high PAPP-A levels cause more IGFBP4 proteolysis increasing free IGF-1 circulating levels. Thus,
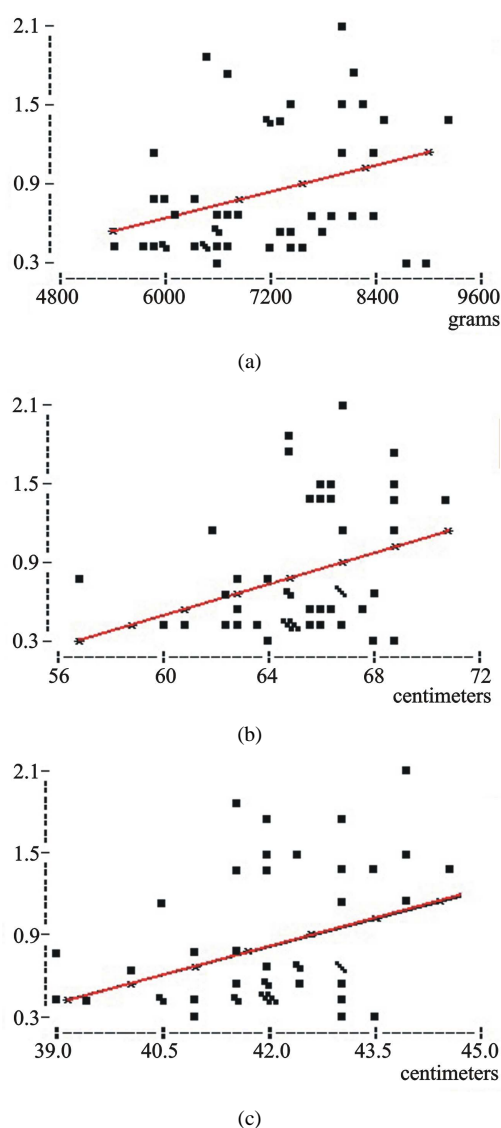
(a)

(b)

(c)

Figure 3. 6 months follow-up: correlation between (a) weight (grams); (b) length (centimeters); (c) head circumference (centimeters) and maternal PAPP-A MoM.

we could expect a positive correlation between high levels of PAPP-A (>90th percentile) and foetal macrosomia. In our study we analysed only 3 infants with high levels of PAPP-A (PAPP-A MoM > 2) and only one of them had a birth weight > 97th percentile (the other two cases weighed between the 75th and the 90th percentile). More studies will be necessary to verify the correlation between high levels of PAPP-A and macrosomia.

As far as preterm and term SGA infants are concerned, PAPP-A MoM levels < 0.5 are associated with 70% of babies SGA for three anthropometric parameters (W, L and HC). Levels of PAPP-A MoM between 0.5 and 1 were associated with infants SGA for two anthropometric parameters (weight and height/or weight and head circumference). Levels of PAPP-A MoM > 1.5 were all associated with the birth of AGA infants.

Furthermore in our study PAPP-A levels correlate with weight, height and head circumference at 6 months suggesting that higher levels of free IGF1 during foetal life due to higher levels of maternal PAPP-A may affect foetal and early postnatal growth.

Moreover the correlation between PAPP-A levels and head circumference at 6 months suggests that probably low levels of circulating IGF1 are associated to smaller head circumferences.

IGF1 is important for foetal and early infantile neurological development. In particular, it plays an important role in neuroprotection by reducing neuronal death caused by different types of injuries [35].

Further studies should be carried out in order to evaluate the relationship between PAPP-A levels, IGF1 and neurological development in the first years of life.

6. Conclusions

In conclusion, values of PAPP-A MoM < 0.5 at 11 - 13 weeks of gestational age are predictive for unfavourable outcome of pregnancy and birth of infants SGA for weight, length and/or cranial circumference.

Even if further and wider studies on the topic would be useful to confirm our hypothesis, we can conclude that in case of MoM < 0.5 - 1 a closer monitoring of pregnancy, a labour planning in a II-III level centre and a careful auxological follow-up in the first years of life are recommended.

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