

# Maternal serum pregnancy-associated plasma protein-A concentration at 11–14 weeks of gestation of women with common congenital anatomic uterine abnormalities

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**Objectives:** To evaluate maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels at 11–14 weeks of gestation in women with common congenital anatomic uterine abnormalities (AUAs). **Methods:** First trimester screening markers were compared between 12 AUA pregnancies and 60 age matched controls. **Results:** PAPP-A level and birth weight were significantly lower in AUA compared to control pregnancies ( $P < 0.001$ ). **Conclusion:** Our findings suggest that AUA pregnancies are associated with low first trimester maternal serum PAPP-A concentrations.

## Keywords

Pregnancy-associated plasma protein A; PAPP-A; Congenital anatomic uterine abnormalities; AUA

## 1. Introduction

Pregnancy-compatible and incompatible congenital uterine abnormalities (AUAs) are present in 4–7% of women worldwide [1]. The role of pregnancy-compatible AUAs in placental development, pregnancy outcome and susceptibility to preeclampsia remains unclear and is poorly documented.

The advent of first trimester screening, including ultrasonography and biochemical markers like pregnancy-associated plasma protein-A (PAPP-A) and free  $\beta$ -hCG, as a routine pregnancy chromosomal screening test, provides a direct mean to re-address the role of AUA in pregnancy at a finer level [2, 3].

Pregnancy-associated plasma protein-A (PAPP-A) is synthesized primarily by the syncytiotrophoblasts [4, 5] and increases in maternal serum throughout pregnancy [6]. Previous studies demonstrated positive association between low

maternal serum PAPP-A concentration and elevated risk of intrauterine growth restriction, extreme preterm delivery, preeclampsia and stillbirth [7–14].

To address the role of AUA's in pregnancy disorders, we compared first trimester PAPP-A concentrations, among women with common congenital AUA's and their age matched controls with normal uterus in the context of a retrospective study.

## 2. Materials and methods

Two groups of study participants ( $N = 72$ ) were recruited in the tertiary referral center of Central Greece (Thessalia University Hospital), during a period of three years. Cases ( $N = 12$ ) with known AUA and age matched women controls ( $N = 60$ ) with normal uteri were included in each group. No apparent deviations among first trimester nuchal translucency of study participants were detected in study groups. Measurements of nuchal translucency above 95<sup>th</sup> centile were not included. Table 1 compares common pregnancy characteristics between the two study groups. Clinical, demographic and first trimester ultrasonography data as well as blood samples and blood pressure measurements were obtained from all study participants. The study was approved by the Medical Ethics Committee of Thessalia University Hospital. Written informed consent was obtained from all study participants. The 12 cases of the 4 common types of congenital pregnancy-compatible AUA's studied included 4 didelphys, 4 unicornuates, 2 septated and 2 bicornuates [15]. Freshly drawn blood samples were analyzed for maternal serum levels of PAPP-A using a commercial kit (Hennigsdorf, Germany; <http://>

www.kryptor.net, Astraia software) during first trimester ultrasound examination for nuchal translucency of study participants and the values were expressed in multiples of median (MoM), using their clinical characteristics (age, maternal weight, smoking status, parity and method of conception) [16]. Placental weight was not recorded at delivery on these pregnancies and their placental size was visually assessed. All 72 study participants were Caucasians, inhabiting the area of central Greece (Thessalia).

**Table 1. Clinical pregnancy characteristics of study groups.**

	Control (N = 60) AUA (N = 12)		P
	N (%)	N (%)	
Parity			
1	48 (80)	12 (100)	0.826 <sup>q</sup>
2	10 (16,66)		
3	2 (3,33)		
Age (years), mean (SD)	31,8 (55,8)	31,8 (6,3)	0.941 <sup>+</sup>
Fetal sex			
Boys	31 (51,6)	7 (58,3)	0.661 <sup>*</sup>
Girls	29 (48,4)	3 (42,7)	
Week of gestation at delivery, median (IQR)	39 (38–40)	32 (31–34)	< 0.001 <sup>++</sup>
Preeclampsia development			
No	60 (100)	12 (100)	
Yes	0 (0)	0 (0)	
Preterm delivery			
No	56 (93,3)	2 (16,67)	
Yes	4 (6,7)	10 (83,33)	< 0.001 <sup>q</sup>
Birth weight (gr), median (IQR)	3300 (2840–3900)	1930 (1260–3030)	< 0.001 <sup>++</sup>

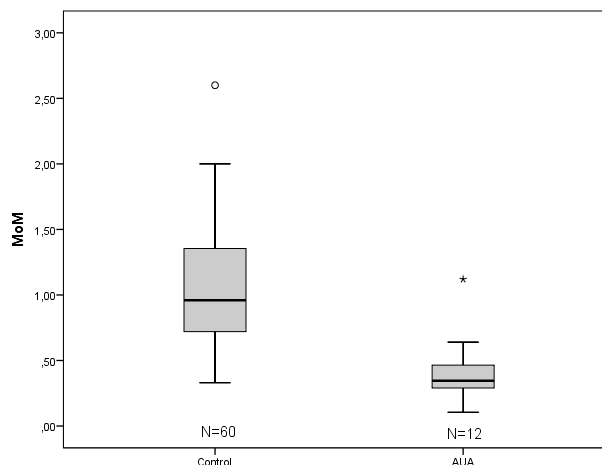
<sup>q</sup> chi-square test. <sup>\*</sup> Fisher's exact test. <sup>+</sup> Student's *t*-test. <sup>++</sup> Mann-Whitney test.

For the comparisons of proportions chi-square test, student's *t*-test, Mann-Whitney test and Fisher's exact tests were used. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 22.0).

### 3. Results

Seventy two subjects were studied during a three year period. Cases (N = 12) included the four of the most common types of congenital uterine malformations indicated in the material and methods section. The clinical and demographic data of known AUA carriers were compared with those of our age matched control group of women with anatomically normal uterus (N = 60) in Table 1. When we compared PAPP-A MoM values regarding preterm and term delivery in the two groups there was no significance difference (Table 2). No differences were recorded in ultrasonographic measurements and maternal demographics between the two groups. Doppler measurements were performed in both study groups without revealing any notable differences. The maternal serum PAPP-A MoM in the AUA group was lower than in controls ( $0.412 \pm 0.26$  vs  $1.07 \pm 0.47$ ;  $P < 0.001$ ) (Fig. 1).

Preterm labor occurred in 10 AUA's vs 4 in controls ( $P < 0.001$ ) and the mean birth weight was 1930 gm in AUA's and 3200 gm in controls (Table 1). There was no preeclampsia development in either group of study participants (Table 1). Placental size at delivery was evaluated by visual inspection. As expected, placental volumes of AUA's were significantly smaller consistent with premature age of delivery.



**Fig. 1. PAPP-A (MoM).** Box plots of maternal serum PAPP-A levels (MoM) in cases (N = 12) with common pregnancy-compatible congenital uterine abnormalities (AUA) and controls with normal uterus (N = 60); MoM of PAPP-A in AUA cases was significantly lower than in controls ( $0.412 \pm 0.26$  vs  $1.07 \pm 0.47$ ;  $P < 0.001$  by Mann Whitney test).

### 4. Discussion

We assessed the relative distribution of first trimester maternal serum PAPP-A in a Caucasian population of women with and without common pregnancy-compatible congenital anatomic uterine malformations from Central Greece. Our present study suggests that AUA is among the main influencers, like preeclampsia, chromosomal abnormalities, preterm labor that can influence PAPP-A concentration.

We observed that carriers of common congenital AUA's present significantly lower PAPP-A concentrations (Fig. 1) and considerably lower birth weight compared to their age matched controls with normal uterus (Table 1). When we divided the two groups regarding term and preterm delivery, results revealed no change regarding our previous observation for PAPP-A concentration (Table 2). To understand the biological significance of our observations and assess the relatively lower concentration of PAPP-A in AUA's, the central role of uterine anatomy in embryo development must be taken into account. If, according to popular acceptance, we view uterus as "home" of developing placenta implanted embryo-resident and PAPP-A concentration as an indicator of placental development, we can easily appreciate the critical role of uterine anatomy to support and maintain growing resident-embryo needs.

**Table 2. PAPP-A MoM values and Birth weight of study groups.**

	Control Term (N = 56)	Control Preterm (N = 4)	AUA Term (N = 2)	AUA Preterm (N = 10)
PAPP-A MoM values	1,08	0,95	0,415	0,411
Birth weight (g), median	3460	2880	3030	1260

All anatomical uterine deviations presently studied, were associated with reduced uterus size and dimension, leading to smaller placental volume. In this context, our findings of reduced first trimester PAPP-A concentration (Fig. 1) and increase in preterm labor of AUA carriers leading to reduced birth weight are in direct line with our working hypothesis of an existing association between uterus size and dimension and PAPP-A concentration as pregnancy marker. In addition the common trend of an association between low PAPP-A and poor placentation leading to preeclampsia [17] was not observed in our AUA study group (Table 1). In line to our working hypothesis, we propose that the low PAPP-A concentration of AUA cases recorded in Fig. 1 resulted from the small size and volume of placenta rather than from poor placentation.

Our AUA MoM PAPP-A values (Fig. 1) fall within the range of 0,412 adjusted Mom PAPP-A level used as predictor for preeclampsia risk, by RCOG, FMF, ACOG guidelines.

The eventual association of women with anatomical uterine deviations leading to increased uterus size and dimension and bigger placenta carrying multiple pregnancies with elevated PAPP-A concentrations at 11 to 14 weeks of gestation further supports and expands our hypothesis [18].

While clear differentiation between AUA and embryonic development as the causative cause of our findings cannot be made, placental size differences due to reduced available endometrial surface in congenital AUA's are likely to play a role. Finally at the clinical level, our findings suggest that a low first trimester PAPP-A concentration in AUA carriers is a valuable marker of pregnancy complications.

### Author contributions

SS conceived of the study, SS, MS, AG and AD collected the data and analyzed the results. SS, DNV and NVC wrote the initial manuscript draft. All authors edited the draft and approved the final version. All authors made substantive intellectual contributions, read and approved the final version of the manuscript.

### Ethics approval and consent to participate

The study was performed with respect to the ethical standards of the Declaration of Helsinki, as revised in 2008. Also, a written informed consent was obtained from the study participants.

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### Conflict of interest

The authors declare no conflict of interest.

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