

Role of pregnancy-associated plasma protein A (PAPP-A) and human-derived chorionic gonadotrophic hormone (free β -hCG) serum levels as a marker in predicting of Small for gestational age (SGA): A cohort study

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Background: Small-for-gestational-age (SGA) is one of the most important conditions, which is associated with the risk of perinatal mortality and morbidity. The levels of pregnancy-associated plasma protein A (PAPP-A) and β -human-derived chorionic gonadotrophic (β -hCG) in the first trimester can predict this adverse outcome, considering the controversial nature of studies in this area, this cohort study was conducted to investigate the role of PAPP-A and free β -hCG levels for predicting SGA. **Materials and Methods:** In this cohort study, from 16 randomly selected health centers in Isfahan, Iran, 4605 volunteer pregnant women who had performed first-trimester fetal anomalies screening tests were chosen based on the census, from July 2016 to June 2018. The multiples of the median (MoM) PAPP-A <0.4 and MoM β -hCG >3 were considered as abnormal; the samples were followed up after childbirth. The biomarkers' serum levels, relative risk, and odds ratio (OR) of SGA were compared in both SGA and appropriate for gestational age (AGA) groups. **Results:** In the SGA group, the mean of MOM PAPP-A was significantly lower (0.96 vs. 1.1 with $P = 0.001$) and MoM β hCG was significantly higher (1.24 vs. 1.15 with $P = 0.01$) than the AGA group. Odds for SGA in subjects with MoM PAPP-A <0.4 were 3.213; $P = 0.001$ and for subjects with MoM β hCG >3 reported as 0.683; $P = 0.111$. **Conclusion:** The results of the study showed that the low levels of PAPP-A would cause 3.213 times increase in the chance of developing SGA and no association between high level of β hCG >3 with SGA. Therefore, low level of the PAPP-A is a warning indicator for SGA.

Key words: Cohort study, Fetal anomalies screening, Free β -human-derived chorionic gonadotrophic, Pregnancy-associated plasma protein A, Small-for-gestational-age

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INTRODUCTION

Small-for-gestational-age (SGA) is associated with increased perinatal morbidity and mortality. This clinical condition increased the risk of long-term hospitalization of infants due to early termination of pregnancy, significant psychological consequences for

the family as well as increased cost of the health-care system.^[1-3]

Fetuses with SGA are at risk of perinatal mortality, birth hypoxia, neonatal complications, impaired neurodevelopment, metabolic syndromes in adulthood, such as Type 2 diabetes, coronary heart disease, and

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hypertension.^[4,5] Therefore, prenatal SGA identification enabled more appropriate surveillance, optimizing management for reducing the risk of adverse pregnancy outcomes.^[3]

Today, the combination of nuchal translucency (NT) and evaluation of serum levels of pregnancy-associated plasma protein A (PAPP-A) and free β -human-derived chorionic gonadotrophic (β -hCG) is one of the most effective methods for screening chromosomal anomalies during pregnancy, which are used during weeks 9–14 of the pregnancy.^[6] These screenings are used not only to diagnose the abnormalities, but all levels of these biomarkers can also help to predict adverse outcomes of the pregnancy.^[7]

PAPP-A is also a glycoprotein, which is mainly produced by syncytiotrophoblast^[8] and may affect placental function through insulin-like growth factors (IGFs) because PAPP-A is a protease for IGF binding protein (IGFBP) 4 and 5. The IGFBPs inhibit the action of IGFs. Lowered levels of PAPP-A would have less protease effect on IGFBPs, leading to higher levels of bound (biologically inactive) IGF-I and-II and it seems to play a key role in fetal growth regulation and trophoblastic invasion to decidua.^[9,10] So that the low level of PAPP-A increases the amount of bound state IGF and leads to decreased fetal growth.^[11]

PAPP-A is considered as an independent agent for adverse outcomes in pregnancy since its low level is associated with hypertension, spontaneous abortion, SGA, and preterm delivery.^[12] These associations have not been seen as consistently in other studies.^[13]

The receptor of hCG glycoprotein exists in the spiral arteries with the angiogenesis of the uterine vessels which facilitates the development of the fetus.^[14] Several studies reported a tendency for SGA infants to have low free β -hCG values, but this association was not confirmed when multivariable models were applied. There is contradictory evidence regarding the association of SGA with free β -hCG.^[15]

Detection of SGA is challenging, and the detection rates achieved in routine care settings are normally low. First-trimester fetal aneuploidy screening tests (serum level of PAPP-A and free β -hCG) may offer an early opportunity to find mothers who are at greater risk for low birth weight and follow them^[5] through close monitoring, timely delivery, and prompt neonatal care.^[11]

Therefore, this cohort study was conducted to investigate the role of PAPP-A and free β -hCG levels for predicting SGA.

MATERIALS AND METHODS

In this cohort study, by available sampling, 4605 eligible

pregnant women were selected from 16 health centers which randomly chosen among 52 health centers in Isfahan, Iran, from July 2016 to June 2018. These women came to health centers at the first trimester, with the results of 11 to 13 weeks and 6-day fetal anomalies screening tests. The study aims were described for them; the volunteers were given the written consent to participate in the study.

The Iranian pregnant volunteer women with single pregnancy, without fetal chromosomal abnormalities, absence of illness which affecting the on-placenta function like lupus, no tobacco use, no alcohol use, or no substance use in the first trimester were included in the study and were followed up after childbirth. Women with a diagnosis of fetal constructional abnormalities such as abdominal wall defects, neural tube defects, or fetal abnormalities which diagnosed during ultrasound anomaly scan at second trimester or after birth and delivery at home were excluded. The gestational age was calculated based on crown-rump length in the first-trimester ultrasound. Their obstetric and demographic characteristics including mother's age, spouse's age, mother's Body mass index (BMI), average number of previous pregnancies and deliveries, NT size, gestational age during the NT ultrasound, weight gain during pregnancy, age of the previous child (<18 months), the previous child's weight <2500 g, history of intrauterine fetal death, history of chronic hypertension, iron deficiency anemia in pregnancy, gestational diabetes, and exposure to smoking were collected and entered into SPSS software (version 16, Inc., Chicago, IL, USA).

Iranian national protocol, recommended combined screening of fetal anomalies in the first trimester, including the measurement of PAPP-A and free β -hCG levels in maternal serum combined with NT thickness in ultrasound, which is performed in the 11-13 weeks and 6 days of pregnancy. The serum levels were converted to multiples of the median (MoM) by adjusting the gestational age, ethnicity, BMI, diabetes, and smoking status based on local references. SGA was evaluated as birth weight <10th percentile for gestational age. Participants were followed up after childbirth. Information was obtained following the consent of pregnant women by a checklist which includes maternal characteristics, fetal/neonatal outcome, and serum levels of PAPP-A and β -hCG, its validity was approved by several experts. Checklist was completed four times (during sampling, 24–28 and 32–34 weeks of pregnancy and after childbirth) based on the clinical examinations, birth records, prenatal ultrasounds, and a computerized database and entered into SPSS software.

Then, the frequency of SGA was compared with the MoM of biomarkers. MoM PAPP-A and MoM β -hCG were classified into two groups of MoM PAPP-A ≥ 0.4 and MoM β -hCG ≤ 3

normal and MOM PAPP-A <0.4 and MOM β -hCG >3 were considered as abnormal.^[16]

In this study, descriptive statistics were used to describe the subjects of the study. Quantitative variables were expressed as mean and qualitative variables were expressed as a ratio. Independent *t*-test and Chi-square test were used to investigate the relationship between levels of β -hCG and PAPP-A biomarkers with the SGA.

To calculate the relative risk (RR) of abnormal PAPP-A and β -hCG biomarkers for SGA, the logistic regression method was used to adjust the results for the confounding variables including woman's age, spouse's age, age difference of previous children, birth weight of previous children, gestational diabetes, hypertension in pregnancy, urinary tract infections, and maternal weight gain during pregnancy. All women with consent entered the study voluntarily and were allowed to leave the study at any time. The study was approved by the Regional Medical and Bioethical Research Committee of Isfahan University of Medical Sciences (Grant no: 395391, ethical code no: IR.MUI.Rec. 1395.3.391.).

RESULTS

During the cohort study period, from July 2016 to June 2018, 4605 pregnant women who underwent first-trimester screening for aneuploidy met the inclusion criteria and were included in the study. Fifty-seven of them were excluded from the study due to intrauterine fetal death, and 10 persons were reluctant to continue their participation. The frequency of SGA was 11.8%. As a result, 538 people were included in SGA, and 4003 were included as appropriate

for gestational age (AGA) groups. Maternal's obstetric and demographic characteristics were compared in both groups [Table 1], then, variables which had a significant difference with $P<0.2$, would be considered as confounder and entered in logistic regression model.

The mean of MoM PAPP-A and MoM of β -hCG in the SGA group was compared with AGA group [Table 2]. The mean of MoM PAPP-A in the AGA group was 1.1 and in the SGA group, was 0.96, with a significant difference ($P = 0.001$) indicating that the lower PAPP-A was associated with an increase in SGA. The mean of MOM β -hCG in the AGA group was 1.15 and 1.24 in the SGA group ($P = 0.01$), representing that the higher β -hCG levels are related to SGA.

The values of MOM PAPP-A <0.4 and MOM β -hCG >3 were considered abnormal and the crude RR and crude SGA odds ratio (OR) were compared between the two groups. The crude RR of SGA was calculated for MoM PAPP-A <0.4 , RR = 2.42, with 95% confidence interval (1.93–3.02); $P = 0.001$, and for MoM β -hCG >3 , RR = 1.55 with 95% confidence interval (1.09–2.21); $P = 0.01$. The crude OR of SGA was calculated for MoM PAPP-A <0.4 , OR = 2.93, with 95% confidence interval (2.18–3.95); $P = 0.001$, and for MoM β -hCG >3 , OR = 1.61 with 95% confidence interval (1.09–2.57); $P = 0.013$ [Table 3].

Then, the effect of confounding variables including woman's age, spouse's age, age of previous children, birth weight of previous children, gestational diabetes, pregnancy induce hypertension, urinary tract infections, and maternal weight gain during pregnancy was controlled by logistic regression. The adjusted OR of SGA was calculated for MOM PAPP-A <0.4 , OR = 3.213, with 95% confidence interval (2.343–

Table 1: Comparison of maternal obstetric and demographic characteristics between appropriate for gestational age (AGA) and small for gestational (SGA) groups

Characteristics	Group		P value
	AGA (n=4003), n (%)	SGA (n=538), n (%)	
Mother's age (years)	28.35±4.95	29.05±5.40	0.002
Spouse's age (years)	32.54±4.87	33.38±5.4	0.001
Average number of previous pregnancies	1.85±0.91	1.81±1.00	0.35
Average number of previous deliveries	0.63±0.71	0.57±0.98	0.11
Mother's BMI (kg/m ²)	24.52±4.04	24.42±4.23	0.60
NT size (cm)	1.39±0.36	1.37±0.40	0.23
Gestational age during the NT ultrasound (day)	86.73±3.78	86.88±4.25	0.41
Weight gain during pregnancy (kg)	12.65±3.88	11.88±3.95	0.001
Age of the previous child (<18 months)	48 (1)	6 (1)	0.007
The previous child's weight (<2500 g)	188 (4)	31 (5)	0.001
History of Intrauterine fetal death	34 (0.8)	3 (0.5)	0.34
History of chronic hypertension	18 (0.4)	0	0.15
Iron deficiency anemia in current pregnancy	50 (1.2)	5 (0.9)	0.35
Gestational diabetes	343 (8.6)	25 (4.6)	0.01
Exposure to smoking	47 (1)	10 (1)	0.13

AGA=Appropriate for gestational age; SGA=Small for gestational age; BMI=Body mass index; NT=Nuchal translucency

4.406) and $P = 0.001$ for MOM β -hCG >3 , OR = 0.683, with 95% confidence interval (0.428–1.091) and $P = 0.111$ [Table 4].

DISCUSSION

The focus of the present study was to assess the role of PAPP-A and free β -hCG as a predictor for SGA, and MOM PAPP-A <0.4 and MOM β -hCG >3 were considered abnormal. The results showed that low level of PAPP-A <0.4 ; RR = 2.42 with 95% confidence interval (1.93 - 3.02) and $P = 0.001$ were related with SGA, while high serum levels of β -hCG > 3 , RR = 1.55 with 95% confidence interval (1.09 - 2.21) and $P = 0.01$, have no impressive risk for SGA. After controlling the confounding variables with logistic regression, we found that low quantile of PAPP-A <0.4 , OR = 3.213 with 95% confidence interval (2.343 - 4.406) and $P = 0.001$ were increased SGA, while MOM β -hCG > 3 , OR = 0.683 with 95% confidence interval (0.428 - 1.091) and $P = 0.111$ had no association with SGA.

Gundu *et al.* conducted a prospective study among women undergoing first-trimester screening in 2016. They found

an association between the lowest quintile of PAPP-A levels (<0.4 MoM) with SGA ($<10^{\text{th}}$ centile; 20.9% of cases in this PAPP-A quintile). Women in the lowest quintile of PAPP-A level had a significantly increased risk of SGA ($<10^{\text{th}}$ centile) than those with higher level (adjust OR 2.92, 95% confidence interval 2.00–4.27).^[17]

Kaijomaa *et al.* conducted a retrospective study in 2017 with the participation of 961 pregnant women. The MoM PAPP-A was <0.3 in the case group and MoM PAPP-A was (0.9–1.1) in the control group, the SGA was associated with low PAPP-A level with $P = 0.001$, CI (3.2–7.5), and OR = 4.9.^[12] In addition, PAPP-A levels with MoM <0.52 were related to SGA in pregnant women with no risk factors for SGA ($P = 0.002$ and OR = 3.3).^[13] Hansen *et al.* (2015) in a case–control study on 985 pregnant women showed that the MoM PAPP-A was lower in the pregnant women who deliver SGA neonates compared with the pregnant women who deliver normal-weighted neonates 1.03 (0.71–1.43) versus 0.87 (0.58–1.35), $P = 0.004$. In addition, they found no relationship between the β -hCG levels and SGA.^[18]

Ranganathan *et al.* (2017) showed that MoM PAPP-A ≤ 0.4 is associated with SGA $<10^{\text{th}}$ centile at $P = 0.04$ with a positive predictive value of 83.3% and negative predictive value of 79.3%.^[8]

Goetzinger *et al.* in a retrospective cohort study found that PAPP-A $<5^{\text{th}}$ with OR = 2.9 (1.6–5.2) and $P = 0.001$, and β -hCG $>90^{\text{th}}$ with OR = 1.6 (1.0–2.6) and $P = 0.045$ are associated with SGA.^[11]

Another study was conducted in 2015 to assess the correlation between PAPP-A and β -hCG in the first trimester with the birth weight, it was indicated that the incidence of SGA was higher in those with MoM β -hCG $>95^{\text{th}}$ ($P = 0.03$).^[19]

In the present study, PAPP-A low levels were associated with SGA which is consistent with previously published research but found no association between high levels of

Table 2: Comparison of the mean of MOM PAPP-A and MOM β -hCG in the SGA and AGA groups

Variables	Mean \pm SD		P
	AGA	SGA	
MoM PAPP-A	1.10 \pm 0.58	0.96 \pm 0.61	0.001
MoM β -hCG	1.15 \pm 0.77	1.24 \pm 0.89	0.01

AGA = Appropriate for gestational age; SGA = Small for gestational age; SD = Standard deviation; MoM = Multiples of the median; PAPP-A = Pregnancy-associated plasma Protein A; β -hCG= β -human-derived chorionic gonadotrophic

Table 3: The crude SGA relative risk and crude SGA odds ratio with PAPP-A and β -hCG values

Variables	RR and OR with 95% of CI		P
	Crude RR	Crude OR	
MoM PAPP-A < 0.4	Crude RR	2.42 (1.93–3.02)	0.001
	Crude OR	2.93 (2.18–3.95)	0.001
MoM β hCG > 3	Crude RR	1.55 (1.09–2.21)	0.01
	Crude OR	1.61 (1.09–2.57)	0.013

CI = Confidence interval; RR = Relative risk; OR = Odds ratio; MoM = Multiples of the median; PAPP-A = Pregnancy-associated plasma Protein A; β -hCG= β -human-derived chorionic gonadotrophic

Table 4: The SGA odds ratio after confounding variables adjusted with PAPP-A <0.4 and β -hCG >3

Variables	OR	SGA (birth weight $<10^{\text{th}}$ centile)	
		95% CI (lower–upper)	P
Pregnant woman’s age	1.003	0.791–1.036	0.875
Spouse’s age	0.953	0.923–0.948	0.003
Age difference between children	0.879	0.687–1.124	0.305
The birth weight of the previous child	0.679	0.488–0.944	0.021
Gestational diabetes	0.402	0.256–0.630	0.001
Pregnancy induce hypertension	0.891	0.805–0.896	0.026
urinary tract infections during pregnancy	0.312	0.075–1.291	1.108
Pregnancy weight gain	1.064	1.036–1.094	0.001
MoM PAPP-A <0.4	3.312	2.343–4.406	0.001
MoM β -hCG >3	0.683	0.428–1.091	0.111

CI=Confidence interval; OR=Odds ratio; MoM=Multiples of the median; PAPP-A=Pregnancy-associated plasma Protein A; β -hCG= β -human-derived chorionic gonadotrophic; SGA=Small for gestational age

β -hCG levels and SGA. Strengths of the present cohort study included the fact that this study was conducted for the first time in Iran with high sample size, on 4605 women. The inclusion and exclusion criteria were carefully considered and we tried to include pregnant women in the study without smoking and alcohol or drugs use, but maybe they not have answered us honestly. Moreover, confounding variables were also identified and controlled; mothers in SGA and AGA groups were similar in most of the characteristics and in cases of difference, the logistic regression was used to control the confounding factors.

Although screening the fetal anomalies of the volunteers in the current study was carried out in different laboratories which is a limitation of the present study, all the laboratories in Iran were required to standardize the MoM based on software approved by the Ministry of Health (BENETECH Canada and ALPHA of England). Furthermore, they use the DEMEDITEC kit for the ELISA methods and Cobas e 411 kit for the electro quantitative luminescent test.

CONCLUSION

SGA is correlated with MoM PAPP-A level so that the MOM PAPP-A <0.4 increases the SGA by 3.213 times, while the SGA is not related to the MoM β hCG >3 . Therefore, this study indicated that the PAPP-A low level is a warning indicator for SGA prediction and shows the need for beginning planned prenatal care for these mothers in early pregnancy. Additional studies are needed to explore the association between extremely increased β -hCG levels and the risk of developing SGA.

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Conflicts of interest

There are no conflicts of interest.

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