Prediction of Prevalence Preeclamptic Women by the Screening of First-Trimester Biochemical Indices (PAPP-A & Free B-HCG) and Third-Trimester Uterine Artery Doppler using ARC GIS in Khuzestan Province/Iran

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ABSTRACT

Background & Objective: The objective of this study was to determine the association between the maternal serum concentration of PAPP-A and free B-HCG at 11-13(+6) weeks and the uterine artery pulsatility index (PI) at 30-34 weeks with the prediction of preeclampsia.

Materials & Methods: This cohort study was performed on 882 women with singleton pregnancies from March 2018 to November 2020 at the university hospital (referred center) in Ahvaz/Khuzestan. Maternal serum PAPP-A and free B-HCG at 11-13(+6) weeks and uterine artery PI at 30-34 weeks were measured and compared between women with and without PE. MOM PAPP-A<0.4, MOM-free B-HCG>3, and uterine artery pulsatility index >1 (>95%) were considered abnormal. Then The effect of each of the indicators on preeclampsia was determined by overlaying the layers and performing logical calculations in ARC GIS software. The distribution of PE in different cities of Khuzestan province was investigated.

Results: The mean MOM PAPP-A was significantly lower (1.05 vs. 1.21 *P*=0.03), and uterine artery PI was significantly upper (0.93 vs. 0.88 *P*<0.01) in preeclamptic women compared to women without PE. No significant differences were observed in the mean MOM-free B-HCG between women with and without PE (1.33 vs. 1.2 *P*=0.667). The highest percentage of PE was in two regions of Ahvaz (80%), but concerning women referred from different cities was in Andimeshk (75%).

Conclusion: A low level of maternal serum PAPP-A and increased uterine artery PI promoted the chance of developing PE. The highest prevalence of PE was in two regions of the center of Khuzestan province, and the most preferred due to PE in different cities was in Andimeshk.

Keywords: ARC GIS, Free B-HCG, PAPP-A, Preeclampsia, Uterine artery PI

Introduction

The preeclampsia (PE) syndrome is the most dangerous in pregnancy, either alone or superimposed on chronic hypertension (1, 2). In angiogenesis, human chorionic gonadotropin (HCG) is one of the most effective hormones (3). Placental dysfunction may lead to pregnancy problems like intrauterine growth restriction (IUGR) or PE (4). It can also be caused by the increase in HCG (5). The peptidase enzyme secreted by placental trophoblastic cells is Pregnancy-associated plasma protein-A (PAPP-A) (6).

A decrease in PAPP-A predicts outcomes and pregnancy complications, and PE has been shown in studies (7). Evaluation of uterine artery pulsatility index is another test that has been suggested as a screening for pregnant women (8). The uterine artery blood flow increases uterine artery PI, increasing the risk of PE and representing the maternal hemodynamic status (9). In addition, numerous pieces of literature have proved that the presence of an early diastolic notch in the waveform can be related to adverse outcomes (10, 11).

Serum hormone levels of free B-HCG and PAPP-A are measured at the first-trimester screening in pregnant women (12, 13). Several studies emphasized the effectiveness of two biochemical indices in predicting the occurrence of PE (14, 15). Also, a relation can be seen between the increase of uterine artery PI with the risk of PE (16, 17). The evaluation of

the predictive value of the level of biochemical indices and uterine artery Doppler in the occurrence of PE among Iranian women and the distribution of PE in different cities of the Khuzestan province using ARC GIS was decided.

Methods

This cohort study was performed on 882 women with singleton pregnancies in Ahvaz from March 2018 to November 2020. The samples related to the mother's serum for PAPP-A and free B-HCG were taken at 11-13 weak (+ 6 days) of gestational age, and the findings were translated as multiples of the median (MOM) through employing fetal medicine foundation software. Uterine artery PI at 30-34 weeks was measured in singleton pregnant women. In addition to the uterine artery Doppler, an early diastolic notch was evaluated in pregnant women. The inclusion criteria included singleton pregnancy, no fetal abnormality, no drug use, and no history of disease that affects pregnancy, such as APS or SLE. The demographic characteristics of pregnant women (age, gravida, para, history of abortion, history of DM and HTN, BMI) were recorded in the information forms. In this research, PE can be described as Increased BP in the gestational period after twenty weeks of gestation ≥140/90 mmHg on 2 measurements 6 h apart and proteinuria 300 mg in 24h) (or ≥ 1 protein on dipstick analysis) or SBP ≥160 mm Hg or DBP ≥110 mm Hg on 1 occasion (18). The mean of MOM PAPP-A, MOM-free B-HCG, and uterine artery PI was compared in women who have PE plus without PE.

The SPSS software (version 16, SPSS, Inc, Chicago, IL, USA) was employed for statistical analysis. To determine the relationship between the levels of free B-HCG, PAPP-A biomarker indices, uterine artery PI in PE, independent samples t-test and Chi-Square test were used.

Also, using ARC GIS software (version 10.7) the required types of files were digitized

And required Shape-files (such as patient-shape-file) with their descriptive information were created. Then, Raster files (with standard pixel size and high accuracy) were created for each of the studied indicators. For the production of some layers, internal components (Analyst tools) in GIS software, as well as interpolation methods (such as IDW, etc.), were used.

The effect of each of the indicators on the preeclampsia was determined by Overlaying the layers and performing logical calculations in ARC GIS software,

Also, using this software, the spatial distribution and frequency of PE in the province, city, and region were determined. This method determines the treatment priorities in each region, the necessary warnings, and actions for the awareness of health care managers.

Results

135 (15.3%) women had developed preeclampsia, and 747 (84.6%) women were without preeclampsia out of the 882 females that were part of this study. No substantial differences were seen in the number of pregnancies amongst the preeclampsia and those without preeclampsia groups, age, and BMI. The other demographic and obstetric features between the 2 groups are listed (Table 1).

The mean of MOM PAPP-A in the PE group was equal to 1.05±0.048 and in the non-PE group was equivalent to 1.21±0.026. The mean of MOM-free B-HCG in the PE group was equivalent to 1.33±0.065 and in the non-PE group was equivalent to 1.2±0.026. The mean uterine artery PI of pregnant women without PE was 0.88±0.11, and that in women with PE was 0.93±0.02.

Lower serum PAPP-A (*P*= 0.03) and increased uterine artery PI (*P*<0.01) had a significant relation with developing PE, but serum-free B-HCG hadn't significantly relation with developing PE (*P*=0.66).

The Eleventh percent of pregnant women with PE (vs. 2% without PE) had bilateral uterine artery nothing (*P*=0.00), and 48% (vs. 2% without PE) of them had unilateral uterine artery nothing (*P*=0.00). Also, 10.37% of PE women had increased uterine artery PI, decreased PAPP-A, and uterine artery notch.

Table 1. Comparison of maternal obstetric and demographic features of the group with PE and the group without PE

Variables	Groups		p value
	without PE (n:745)	with PE (n:135)	
Mothers age (year) (Mean ± SD)	31.071 ± 0.17	31.222 ± 0.42	0.918
BMI (Mean ± SD)	26.558 ± 0.16	27.963 ± 0.39	0.844
number of pregnancies (Mean ± SD)	2.022 ± 0.08	2.162 ± 0.47	0.042
number of deliveries (Mean ± SD)	1.753 ± 0.03	2.022 ± 0.86	0.188
History of overt DM	283 (38%)	53 (39%)	0.023
Gestational diabetes	16 (2%)	14 (10.29%)	0.00

Variables	Groups		p value
	without PE (n:745)	with PE (n:135)	
Chronic hypertension	5 (67%)	49 (36%)	0.04
Abortion history	202 (27%)	38 (28%)	0.055
Gestational hypertention	3 (0.4%)	30 (22%)	0.04
Unilateral uterine artery notch	42 (5.6%)	65 (48%)	0.00
Bilateral uterine artery notch	15 (2%)	15 (11%)	0.00

The distribution of those females with PE plus non-PE in different cities of the Khuzestan province was investigated using ARC GIS (Figure 1). It showed that the highest percentage of PE among the cities of Khuzestan of the total population was in Ahvaz (80%) (Figure 2). Regarding people who were referred from different cities, the highest percentage of PE was in Andimeshk (75%) (Figure 3). Due to the prevalence of PE in Ahvaz, most cases of PE were in regions 2 (30%) and 6 (28%), which included North and South Kamplo, Alavi, Salim Abad, and Sayahi (Figure 4)
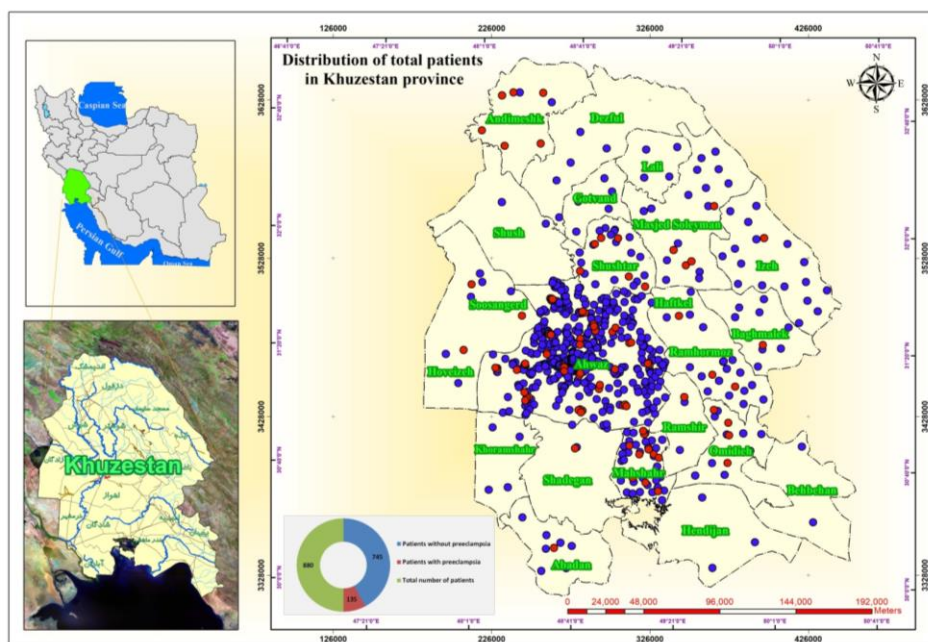

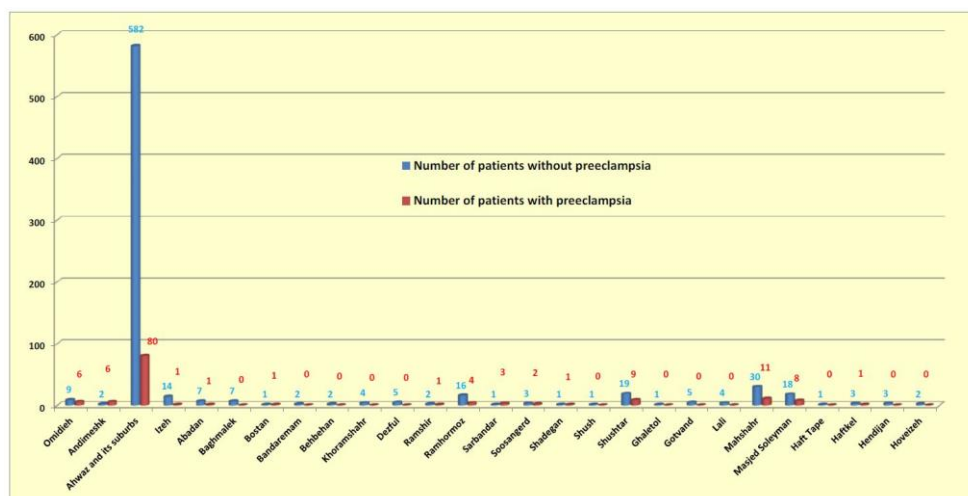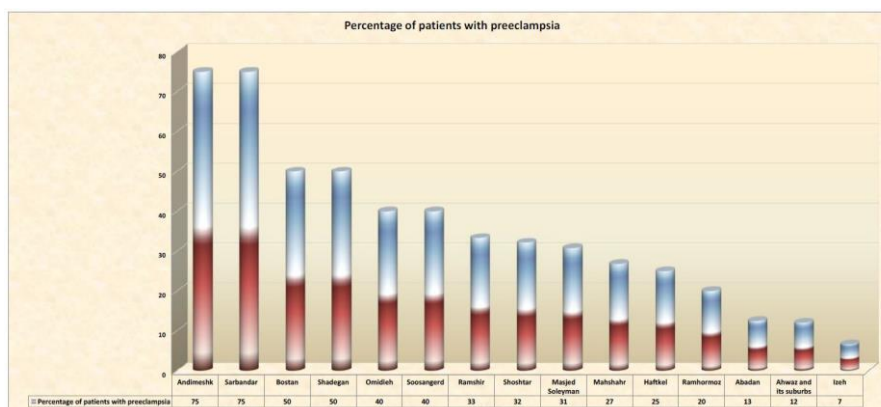**Figure 1. Distribution of total patients in Khuzestan province.**
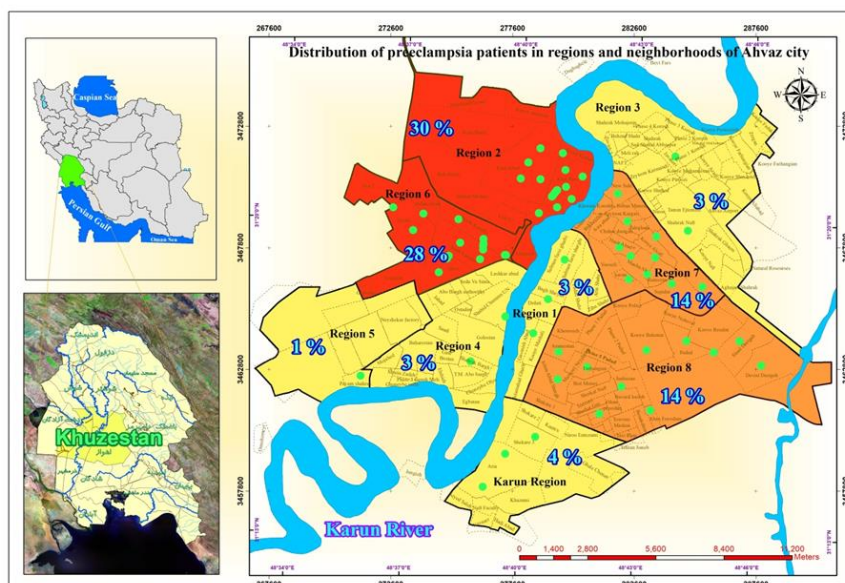

Figure 2. Number of PE among the cities of Khuzestan province about the total population

Figure 3. Percentage of PE among the cities of Khuzestan province concerning people referred from different cities

Figure 4. Distribution of PE in regions of Ahvaz city

Overlaying the layers and performing logical calculations in ARC GIS software showed that the increase of uterine artery PI, the decrease of PAPP-A, and uterine artery notching are shown to be associated with possibilities PE. There was no relationship between free B-HCG and PE. However, data analysis in SPSS software showed similar results. Still, it is impossible to display the spatial distribution of patients and identify the affected cities with PE and the frequency of patients. Therefore, preventive actions can not be prioritized based on location.

Discussion

This cohort study was done among 882 singleton pregnant women in Khuzestan/Iran to evaluate the association between uterine artery PI together free B-HCG and PAPP-A with PE. The result of the present research revealed that decreased amount of PAPP-A, an increase of uterine artery PI together with a notch of the uterine artery were significantly related to PE but levels of free B_HCG had no significant relation with PE. The center of Khuzestan province and especially in

two regions had the highest prevalence of PE. This distribution may be because of nutritional, racial, and socio-economic, differences. The most refer due to PE in different cities was in Andimeshk and it seems to need more information and education about PE and disease diagnosis in health centers and maternity care centers in Andimeshk city.

Adekanmi *et al.* showed that the mean uterine artery PI of those females with PE (median = 1.38, SD = 0.67) was definitely higher than the mean uterine artery PI of those females without established PE (median = 0.75, SD = 0.28) (*P*<0.001), which was compatible with our study. Also, they found that the mean umbilical PI of pregnant women who do not have preeclampsia (median = 0.88, SD = 0.20) was lesser as compared to the mean umbilical PI of women with preeclampsia (median = 1.14, SD = 0.48) (*P*=0.001) **(19)**.

Compatible with our study, Khanam *et al.* (2021) showed that The best test for predicting preeclampsia and gestational hypertension was uterine artery PI with ROC AUC (± standard error) = 0.934 ± 0.028, *P*<

0.0001. They combined uterine artery PI with PAPP-A and free B-HCG to predict PE. They found that uterine artery PI (95th percentile) along with PAPP-A at a cutoff value of ≤ 0.27 with a sensitivity and specificity of 44% and 100% had an association with PE, but with free B-HCG at a cutoff value of ≤ 0.5 did not reveal the sensitivity related to identifying preeclampsia but had hundred percent specificity **(20)**. Moreover, Obican *et al.* revealed that unusual uterine artery doppler indices in the final 3 months of pregnancy, especially left uterine artery notching and pulsatile index (PI) greater than 95th percentile, were considerably interrelated with SGA, RR 1.76 (1.03–3.04) and PE, RR 2.53 (1.47–4.37). The mean uterine artery PI greater than the 95th percentile consists of a better sensitivity for SGA and left uterine artery notching, and uterine artery PI >95th percentile had a predictive value for PE **(21)**.

Liu *et al.* found that in pregnant women with PE, the serum level of free B-HCG was higher than normal pregnant women, which was Contrary to our study. They also revealed in the study that the serum level of free B-HCG in Caucasians and Asians with PE was higher than in the other ethnicity **(22)**.

Similar to our study, Belovic *et al.* reported that serum levels of PAPP-A in the initial 3 months of the pregnancy positively correlated to the occurrence of both early and late gestational hypertension (p=0.016). Also, they found in PE women, most changes in serum levels occur for B-HCG (Contrary to our study), PAPP-A, AFP, Estriol, and Inhibin (15–17w) **(23)**.

Analogous to this literature, Honarjoo *et al.* showed that the lesser level of PAPP-A was associated with possibilities of preeclampsia (*P*=0.006). In contrast

with our study, the higher levels of free B-HCG were related to the chance of developing PE (*P*=0.001). They concluded that MOM PAPP-A < 0.4 and MOM-free B-HCG > 3 cause a higher possibility of developing PE **(13)**.

The strength related to this literature was to assess the prediction of PE based on the initial 3 months of pregnancy screening and uterine artery Doppler at 30-34 weeks of pregnancy with the ARC GIS software. The limitation of this study was that the research was performed in one province of the country, and it should be done in several centers.

Conclusion

Uterine artery PI>95% at 30-34 weeks and lower maternal serum PAPP-A at 11-13(+6) weeks was correlated with PE. Therefore, the uterine artery PI and serum level of PAPP-A can be reflected as one of the methods for ruling out PE; but serum-free B-HCG does not help predict PE. The highest prevalence of PE was in the center of Khuzestan province, especially in two regions where the most preeclamptic women referred from different cities was in Andimeshk.

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Conflict of Interest

The author declared no conflict of interests.

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