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Original Research Article

Association of serum pregnancy associated plasma protein: a with gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes. GDM has many adverse consequences on the health of mother and fetus.
Methods: This cohort study was carried out involving 77 women of 11 to14-week pregnant attending in the Gynecology & Obstetrics and Fetomaternal Medicine OPD, BSMMU from September 2020 to August 2021.
Results: Respondents were divided into two groups. Low PAPP-A group (<0.5MoM) and normal PAPP-A group (>0.5MoM). In low PAPP-A group, out of 16 respondents, 8 (42.1%) developed GDM and remaining 8(13.8%) were euglycemic. Whereas, in normal PAPP-A group, out of 61 respondents, majority 50 (86.2%) were euglycemic and only 11 (57.9%) women developed GDM. A total 19 (24.68%) respondents developed GDM from both low and normal PAPP-A group. ROC analysis of PAPP-A level for detection of GDM, a AUC value of 0.889 (95% CI 0.818-0.960) found which was statistically significant. A cut off value of ≤16.80 showed the highest Youden index (0.652) with 89.4% sensitivity and 81% specificity, the accuracy was 83.35. Moreover, a cut off value ≤16.80 showed PPV and NPV of 62.1% and 95.9%, respectively. PAPP-A level of GDM detected (10.32±5.56) µg/ml was significantly lower from non GDM mothers (25.08 ±9.85) µg/ml, where p<0. 001.
Conclusions: Study finding revealed that maternal serum PAPP-A level was lower in 11-14 weeks of pregnancy who subsequently developed GDM. So, a low PAPP-A level (<0.5 MoM) in 11-14 weeks of pregnancy is associated for development of GDM.

Keywords: Gestational diabetes mellitus, Insulin like growth factor, Insulin like growth factor binding protein, Pregnancy associated plasma protein A

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common medical disorder in pregnancy. Some population-based studies conducted in Bangladesh at different time have revealed an increasing trend of GDM prevalence ranging from 9% to 10% based on using different diagnostic criteria.[1] Though there are different diagnostic criteria for diagnosis of GDM like WHO, ADA, NICE, O'Sullivan but we adopt WHO, 2013 criteria for diagnosis of GDM in this study. GDM is diagnosed when FBS is 5.1-6.9 mmol/L or 2

hour's plasma glucose is >8.5-11 mmol/L following 75 g oral glucose load.[2] During pregnancy the metabolic changes are essential to provide adequate nutrients to the growing fetus. As pregnancy progresses, increased level of somatotrophin, cortisol, prolactin, progesterone and estrogen lead to insulin resistance in peripheral tissues.[3] Insulin resistance is defined as condition in which physiologic insulin concentration elicit decreased biologic response in target tissues.[4] In case of normal pregnancy, the progressive insulin resistance causes increase insulin secretion by the pancreatic β-cells to maintain glucose homeostasis.[5]

Normally hypertrophy and hyperplasia occur in β-cell of pancreas to release more insulin in order to respond to the resultant increase in insulin resistance.[3] Though the cellular mechanism involved in development of GDM are not yet completely understood but maternal genetic predisposition coupled with environmental and fetoplacental factors play role in development of GDM.[6] The pathophysiology of GDM takes place weeks to months before clinical diagnosis.[7] Alteration of placental development and subsequent vascular dysfunction are present in diabetic patient. Villous immaturity, fibrinoid necrosis and increased angiogenesis occur in the placenta of diabetic patient. The type of dysfunction depends on how early in pregnancy glycaemia disorder occur.[8] It is reported that reduced number and diameter of villous capillaries lead to reduced PAPP-A production.[9] The Pregnancy Associated Plasma Protein -A (PAPP-A) is a zinc binding high molecular weight matrix metalloproteinase produced by trophoblast during pregnancy and can be identified from 28th day of fertilization. In non-pregnant women it is produced from corpus luteum and granulosa cells.[10] GDM is diagnosed after the onset of 2nd trimester, so fetus has exposed to high sugar level and associated with metabolic derangement of GDM throughout first trimester.[11] As per recommendation of WHO and International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnosis of GDM is performed with the use of 75gm 2-hour oral glucose tolerance test (OGTT) between 24 to 28 weeks.

However, earlier screening has the potential to either improve pregnancy outcome through life style modification and pharmacological intervention or even reduce the frequency of disease and the severity of the associated maternal and perinatal complication.[12] Screening for GDM after 24th gestational weeks and diagnosing GDM at the end of 2nd trimester cause possible delay in achieving the positive effects of pharmacological therapy, diet and exercise on placental vascularity, fetal development and maternal complications. So it has been necessary to find out an optimal biomarker to predict the development of GDM prior to its occurrence, ideally at the time of enrollment of prenatal care. PAPP-A binds to the surface of the cells, cleaves insulin like growth factor binding protein (IGFBP) and release bioactive insulin like growth factor (IGF) in the proximity to their receptor. The IGF-1 has significant structural homology with insulin.[13] IGF-1 improves insulin sensitivity and reduce blood glucose level by increase glucose uptake by peripheral tissues and suppress hepatic glucose production. Thus it produces hypoglycemic effect and reduce insulin production by negative feedback mechanism.[14] Reduced PAPP-A leads to decrease in IGF and increase in glucose and amino acid production is one of the possible mechanism for explaining the association between low PAPP-A and GDM.[10] Several studies have reported the association between low level of PAPP-A with GDM.[7] The paracrine/autocrine actions of trophoblastic IGF may be important in the invasion of trophoblast in endometrium.[15] Reduced serum level of PAPP-A could have an increased risk of spontaneous abortion, low birth weight, IUGR, pre-eclampsia, PROM and abruption placenta.[16] As only limited and conflicting data is available about the association of serum PAPP-A in 11-14 weeks of pregnancy with development of GDM, the aim of this prospective study was to investigate whether 1st trimester serum PAPP-A was associated in women who subsequently develop GDM and to evaluate its potential value and maternal factors as early pregnancy predictor for GDM.

The general objective of this study was to determine the association of pregnancy associated plasma protein -A with GDM. Specific objective of this study was to estimate the serum PAPP-A level at 11-14 weeks of pregnancy. Also, to perform OGTT by WHO criteria in 11-14 weeks and at 24-28weeks of pregnancy and to find out the association of PAPP-A with GDM.

METHODS

This cohort study was carried out involving 77 women of 11 to 14-week pregnant attending in the Gynecology and Obstetrics and Fetomaternal Medicine OPD, BSMMU from September 2020 to August 2021. At first OGTT was done to exclude diabetes. Blood sample was taken to measure serum PAPP-A level at 11-14 weeks. The respondents were divided into two groups-low PAPP-A group and normal PAPP-A group. Then both groups were invited to follow up at 24-28 weeks of gestation and OGTT was repeated to determine the percentage of patient developed GDM in low and normal PAPP-A group. Percentage of patient from two groups was compared. Difference between two groups was assessed by the Mann Whitney, Chi-square, T test and Fisher exact test. ROC was used to decide the best cut off point of PAPP-A level.

Inclusion criteria

Inclusion criteria were non diabetic (normal OGTT), pregnant women of 18 to 40 years of age in their 11 to 14 weeks of gestation and has given consent to participate.

Exclusion criteria

Exclusion criteria were diabetes diagnose at 11-14 week's gestation after doing OGTT, multiple pregnancy, pre-

existing diabetes mellitus, diagnosed case of chronic renal disease, diagnosed case of cardiovascular disease, chronic hypertension and previous history of pre-eclampsia, eclampsia or SLE.

After obtaining approval of Institutional review board, this cohort study was conducted among the respondent by face to face interview following the before mentioned criteria. Data regarding demographic profile, obstetric history, maternal medical history, past obstetric complication and family history were recorded. Height and pre-pregnancy weight or early pregnancy weight of each participant were recorded and BMI measured by using formula: weight in kilogram/height in $meter^2 (kg/m^2)$. For measuring the blood pressure, participants remained at rest for at least 15 minutes then measured on right arm at sitting position with appropriate size cuff. Period of gestation was confirmed by early USG. At first OGTT was done to exclude preexisting diabetes mellitus. Patient was advised to come for OGTT after an overnight fasting of 8-14 hours. During the previous 3 days, there must be an unrestricted diet and unlimited physical activity. While OGTT was done patient was advised to take rest. First of all, fasting plasma glucose was measured then again plasma glucose level was measured after 2 hour following consumption of 75 gm glucose diluted with 250 ml of water. For serum PAPP-A estimation at 11-14 weeks, with all aseptic precaution, 3 ml of venous blood was collected from the anti-cubital vein by trained blood collectors from each participants and taken in a sterile plain, dry test tube with proper labeling. The blood was allowed to clot at room temperature for 2 hours. The serum was separated by centrifugation at room temperature for 20 minutes at the speed of 2000-30000rpm. Then the serum was taken in an eppendorf and labeled as before. Specimen were stored at -20^{0}c until assayed in the lab of virology department of BSMMU. Serum PAPP-A was quantified by ELISA using DRG kit (Cat No EIA-2397) according to the manufacturer's instructions at the end of sample collection in the virology lab of BSMMU. The intensity of color reaction was quantified at a wave length of 450 nm in an automatic ELISA microplate reader (Multi scan FC Micro Plate Photometer). The concentration of serum PAPP-A were determined by interpolation from standard curve and the result were expressed as micro gram g/ml (microgram/ milliliter). The results were converted into multiple of median. These respondents were divided into two groups. Reduced concentration of serum PAPPA in group 1 and normal concentration of serum PAPPA in group ll. Then these patients were again invited to visit at 24-28 weeks and again OGTT was performed. The proportion of patient who developed GDM were noted. The association of low serum PAPP-A and GDM was determined.

Statistical analysis

Data were analized by using the SPSS version 22.0 software. The result was presented in tables in mean, standard deviation and percentage. Moreover, the categorical variables were presented in pie chart or bar diagram. Chi square test were adopted for identifying any association between categorical variables. Statistical analysis was done by using appropriate analytical tools like independent sample t-test for mean difference analysis. A ROC analysis was used to determine AUC and optimum cut-off PAPP-A level for best sensitivity, specificity and accuracy. Statistical significance was set at ≤ 0.05 level and confidence interval at 95% level.

The study was done in accordance with Helsinki Declaration for Research involving Human Subject, 1964, last amended in 2013. The study was approved by the Institutional Review Board in BSMMU.

RESULTS

In this study, the respondents were divided into low PAPP-A group and normal PAPP-A group. Out of 77 sample, 16 subjects had PAPP-A <0.5 MoM and considered as low PAPP-A. 61 sample had normal PAPP-A that was >0.5 MoM. The results of the study showed that the low PAPP-A and normal PAPP-A groups were statistically similar in terms of age and BMI and number of deliveries. The mean PAPP-A level in low PAPP-A group (7.42±3.57) was much lower than normal PAPP-A group (25.12±8.91) and the difference was statistically significant. Among 77 sample, 19 patient developed GDM and 58 patients were euglycemic. The PAPP-A level in GDM group (10.32±5.56) was significantly lower from non GDM group (25.08±9.58). The odds ratio of GDM in patients with reduced PAPP-A level was 4.55 times than that of non GDM pregnant women. The result of ROC showed the point 16.80 as the best cut off point for PAPP-A ng/ml, with a maximum sensitivity of 89.4% and a maximum specificity 81%. AUC of 0.889 shows that PAPP-A ug/ml is an acceptable index for predicting gestational diabetes (p=0.001). Among 77 study samples, a total 16(21%) patients had PAPP-A less than (0.5 MoM). Hence, they were considered as "Low PAPP-A".

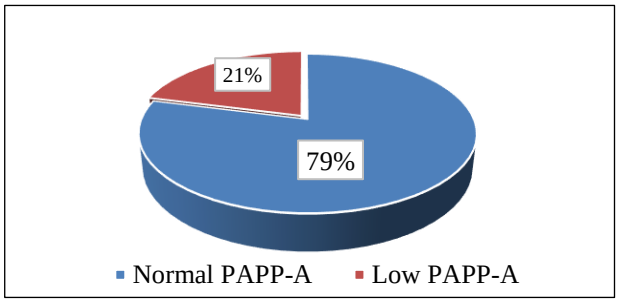

Figure 1: Low PAPP-A patients among the study sample (N=77).

Figure 1 showed Independent sample t test was used to compare the mean PAPP-A between low and normal PAPP-A group. The test was statistically significant. So it can be said that PAPP-A of low PAPP-A mothers (7.42±3.57) was significantly lower from normal PAPP-A mothers (25.12±8.91).

Table 1 showed most of the patients both in low (<0.5MOM) and normal PAPP-A (>0.5 MoM) were in the age group of 25 to 30 years of age. No significant difference was found for age between low and normal PAPP-A patients. Independent sample t test was used to compare the mean BMI between low and normal PAPP-A group. The test was not statistically significant. So it can be said that BMI of low PAPP-A mothers (25.28±4.02) was not significantly different from normal PAPP-A mothers (23.14±3.19). 68.7% pregnant women in low PAPP-A group had been pregnant more than once. In case of normal mother, the percentage was 54.1%. However, no significant association was found between gravidity and low PAPP-A).

Table 1: Demographic profile of the participants. (N=77).

Age (years)	Pregnant patient with Low PAPP-A		Pregnant patient with normal PAPP-A		P value
	Frequency (n=16)	Percentage (%)	Frequency (n=61)	Percentage (%)	
18-24 yrs.	3	18.8	23	37.7	
25-30 yrs.	11	68.8	29	47.5	
31-40 yrs.	2	12.4	9	14.8	
Mean ± SD	27.00±4.21		26.23±4.91		0.568
BMI	25.28±4.02		23.14±3.19		0.012
Gravida					
Primi	5	31.3	28	45.9	0.292
Multi	11	68.7	33	54.1	

Figure 2 showed independent sample t test was used to compare the mean PAPP-A between GDM and non GDM group. The test was statistically significant. So it can be said that PAPP-A of GDM group (10.32±5.56) was significantly lower from non GDM group (25.08±9.85).

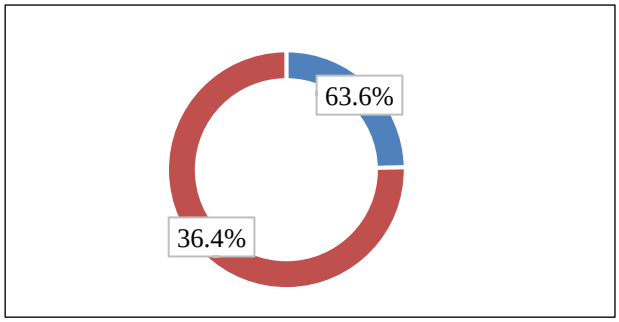

Figure 2: GDM development of the participants (N=77).

Table 2: Normality test of continuous variable (N=77).

Tests of normality	Kolmogorov-Smirnov		
	Statistic	df	Sig.
Age	0134	77	0.132
BMI	0.071	77	0.200
Fasting blood glucose	0.172	77	0.033
2 hours after 75 gm glucose	0.2.168	77	<0.001
PAPPA-A	0.110	77	0.082

Table 3 showed Mann-Whitney test was used to compare the mean fasting blood glucose as well as 2 hours after 75 g glucose intake between low and normal PAPP-A group. The test was statistically significant in each case. So it can be said that fasting blood glucose and 2 hours after 75 g glucose of low PAPP-A mothers (6.59±0.35; 8.89±0.74) were significantly greater from normal PAPP-A mothers (4.54±0.76;7.37±1.34) respectively.

Table 3: Comparison of mean blood glucose in Low and normal PAPP-A (MoM) group among study participants (N=77).

Parameter	Low PAPP-A (Mean±SD) (n=16)	Normal PAPP-A (Mean±SD) (n=61)	P value
FBS	6.59±0.35	4.54±0.76	<0.001
2 hours after 75 gm glucose	8.89±0.74	7.37±1.34	<0.001

Table 4 showed a significant association was found between development of GDM and PAPPA-A level (PO.05). The odds for developing GDM due to low PAPP-A is 4.55 [95% CI: 1.40-14.76]. About 50% low PAPP-A had GDM.

Table 5 showed a cut-off value of <16.80 showed the highest Youden index (0.757) with 89.4% sensitivity and 81% specificity. In addition, the accuracy was 83.0%. Moreover, a cut-off value of <16.80 showed, PPV and NPV of 62.1% and 95.9%.

ROC analysis of PAPP-A level for detection of GDM among pregnant women found an AUC value of 0.889 (95% CI 0.818-0.960) which was statistically significant (Table 6, Figure 3).

Table 4: Association of GDM with low PAPP-A (N=77).

PAPP-A	GDM		OR	95% CI	P value
	Yes (%)	No (%)			
Low (MOM <0.5)	8 (50)	8 (50)	4.55	1.40-14.76	0.008
Normal (MOM ≥0.5)	11 (18.0)	50 (82.0)			

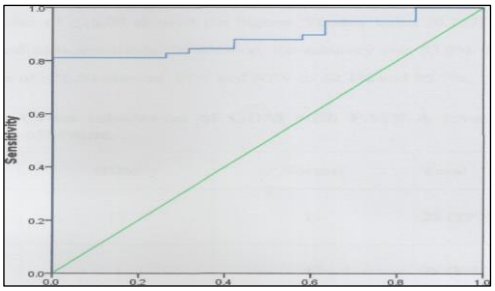

Figure 3: ROC analysis of PAPP-A level for detection of GDM among pregnant women (N=77).

Table 5: Determination of cut off value with Youden index. (N=77).

Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	Yourdon index (j=sen+spe-1)
16.76	0.894	0.793	0.586	0.958	0.818	0.652
16.80	0.894	0.810	0.621	0.959	0.833	0.757
17.20	0.842	0.810	0.593	0.940	0.818	0.705

Table 6: Cross tabulation of GDM with PAPP-A level based on derived cut-off value (N=77).

PAPP-A	GDM	Normal	Total
<16.80	17	11	28 (TP+FP)
>16.80	2	47	49 (FN+TN)
	All patients with GDM (TP+FN) 19	All patients without GDM (FP+TN)	77 (TP+FN+FP+TN)
		58	

DISCUSSION

The responders were divided into two groups. low PAPP-A group (<0.5 MoM) and normal PAPP-A group (>0.5 MoM). 16 women (21%) were in low PAPP-A group and 61(79%) women were in normal PAPP-A group. During follow up 19 (24.68%) women developed GDM and 58 (75.32%) were diagnosed as non GDM. Percentage of the patient developed GDM in these two groups were compared. In the present study, it was observed that in low PAPPA group 31.3% patients were primi gravida and 68.7% patients were multigravida. No significant difference was found between gravidity and low PAPP-A (p>0.05). Wright et al; 2015 illustrated in their study that serum PAPP-A was lower in parous women than nulliparous women.[17] The incidence of GDM increased from 3-5% in nulliparous women to 14.6% in women with parity ≥ 4. So, there may be a relationship with multiparity, low PAPP-A level and increased chance of development of GDM. In this current study it was observed that first trimester BMI among the pregnant women having low PAPP-A and normal PAPP-A had no significant difference. Among the study population, 1st trimester BMI were 25.72±3.46 kg/m^2 in the patient developed GDM and 21.42±3.35 kg/m^2 in non GDM ones. BMI was significantly higher in GDM patients. Wright et al (2015) stated in their study, that serum PAPP-A was decreased with maternal weight and increased with height.[17] But they didn't show any relation with BMI. In the study of Ledesma et al (2014), women over 70 kg weight and low level of PAPP-A was associated with higher risk of GDM. Martin et al (2015) stated that increasing maternal BMI is a significant risk factor for the development of GDM.[18] A higher BMI value was strongly associated with higher insulin level and insulin resistance in GDM.[19] Many study reported that pre pregnancy BMI and obesity were associated with higher prevalence of GDM and an independent risk factor for GDM.[20] Beneventi et al (2014) reported inverse association between low PAPP-A and BMI.[10] Overweight and obesity is associated with higher risk of GDM.[21] ROC analysis of PAPP-A level for detection of GDM among mothers found on AUC value of 0.889 (95% CI 0.818-0.960) which was statistically significant in this study. A cut off value of ≤16.80 showed the highest Youden index (0.757) with 89.45% sensitivity and 81% specificity. In addition, the accuracy was 83.3%. Moreover, a cut off value of ≤16.80 showed PPV and NPV of 62.1% and 95.9% respectively. The OGTT is currently the gold standard for the diagnosis of diabetes. Fasting plasma glucose and plasma glucose 2 hours after 75 gm oral glucose load is now a day routinely measured during early pregnancy to detect preexisting diabetes.[22] In this present study significant inverse correlation was observed between PAPPA and FBS (p=<0.001). There was also a significant correlation between PAPPA and 2 hours after 75 gm oral glucose. The PAPP-A level is gestational age dependent. PAPP-A levels in maternal blood become detectable soon after implantation and increase throughout

pregnancy. Therefore, the unit multiple of median (MoM) was used as it is gestational age independent.[23] In this study, 8 (42%) patients of low PAPPA group (<0.5 MoM) and 11 (57.9%) patients normal PAPP-A group (>0.5M0M) developed GDM. There was a significant difference between the two groups in terms of GDM (P-<0.008) and the risk of GDM was 4.55 fold higher in pregnant women with reduced PAPP-A than that of the normal PAPP-A (95% CI 1.40-14.76). In the study of Ramezani et al, (2019), 33.73% patient of low PAPP-A group developed GDM.[10] So, there was a correlation between low PAPP-A and GDM (P-0.001). Based on Beneventi et al 2014, a significant association was found between low PAPPA levels and GDM.[7] According to Inan et al, Sweeting et al, Donnovan et al and Shah et al, a significant association between low PAPPA levels and GDM exists.[24-27] Ramezani et al (2020) stated that low PAPPA was linked to an increased risk of GDM, implying that the protein may protect against the disease.[28] On the other hand, the results of Husllein et al (2012) did not show any difference between the amount of PAPP-A in the first trimester and GDM.[29] According to Wright et al (2015) PAPP-A level was different among different ethnicity.[17] It is higher in women of East Asian racial origin. The possible explanation of different result of their study was different ethnicity and different criteria for diagnosis of GDM. GDM has a relatively high prevalence. Women evaluated for GDM at 24-28 weeks of pregnancy. So, there is only a short window of time to intervene clinically. If there is an opportunity to intervene earlier during pregnancy, have a greater opportunity to improve outcome. Early diagnosis may reduce the adverse fetal and maternal complication of disease. Women at risk for GDM identified in 1st trimester of pregnancy could follow the lifestyle modification earlier than usual in pregnancy. Thereby, lifestyle modification can reduce the incidence of GDM; improve maternal health, pregnancy outcome and long term health of the offspring. Identification of new risk factor for GDM helps to early prediction of at risk pregnant women for developing GDM and by taking preventive measures, maternal and fetal complications could be prevented.[10] Low level of PAPP-A is associated with an increased risk of development of GDM. The current finding indicated that PAPP-A could be a biomarker to predict the risk of GDM. Further large scale studies involving diverse group of subjects are needed to explore /clarify the association between 1st trimester PAPP-A and other potential biomarker of GDM.

This study has some limitations. The respondents were relatively limited as recruited pregnant women from only one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country. In order to make the sample representation of the population, it will require such a study that would be conducted over a large population of vast area. But such an extensive study was not feasible during limited time period. Therefore, the outcome of this study cannot represent the entire population. The present study was conducted at a limited period of time. Prospective follow up study is needed to assess the association of PAPP-A level with development of GDM.

CONCLUSION

This study was undertaken to evaluate the association of maternal serum PAPP-A level at 11-14 weeks of pregnancy with GDM. This Study showed that the respondents in whom serum PAPP-A level is was decreased at 11-14 weeks had developed GDM. So, it can be concluded that the serum PAPP-A level can be used as a biomarker for prediction of GDM in early pregnancy.

Recommendations

Serum PAPP-A can be used as tool for prediction of GDM. A more extensive and advanced study should be carried out considering all the variables of the study. To overcome these limitations and thoroughly understand the role of PAPP-A in the progress of GDM, a well-designed population-based prospective studies should be conducted.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Mohiuddin AK. Diabetes fact: Bangladesh perspective. Inter j diab res. 2019;2(l):14-20.
2. Imoh LC, Asorose AS, Odo AI, Aina DO, Abu AO, Ocheke AN. Modification of WHO diagnostic criteria for gestational diabetes: implications for classification of hyperglycemia in pregnancy. Int J Reprod Contracept Obstet Gynecol. 2017;6:2716-23.
3. Carr DB, Gabbe S. Gestational diabetes: detection, management, and implications. Clin Diabet. 1998;16(1):4-12.
4. Creasy RK, Resnik R, Lams JD, Lockwood, Moore TR, Greene MF. Maternal-fetal medicine principle and practice. 7th ed. Philadelphia: Elsevier Saunders; 2014.
5. Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 world health organization laboratory methods for the examination of human semen. Eur Urol. 2016;70(4):635-645.
6. Berberoglu Z. Pathophysiology of gestational diabetes mellitus. EMJ Diabet. 2019;7(1):97-106.
7. Beneventi F, Simonetta M, Locatelli E, Cavagnoli C, Badulli C, Lovati E, et al. Temporal variation in soluble human leukocyte antigen-G (sHLA-G) and pregnancy-associated plasma protein A (PAPP-A) in pregnancies complicated by gestational diabetes mellitus and in controls. Ame J Reprod Immunol. 2014;72(4):413-21.
8. Jarmuzek P, Wielgos M, Bomba-Opon D. Placental pathologic changes in gestational diabetes mellitus. Neuroendocrinol Lett. 2015;36(2):101-5.

9. Huynh DT, Devitt AA, Paule CL, Reddy BR, Marathe P, Hegazi RA, et al. Effects of oral nutritional supplementation in the management of malnutrition in hospital and post-hospital discharged patients in India: a randomised, open-label, controlled trial. J Hum Nutr Diet. 2015;28(4):331-43.
10. Ramezani S, Doulabi MA, Saqhafi H, Alipoor M. Prediction of gestational diabetes by measuring the levels of pregnancy associated plasma protein-A (PAPP-A) during gestation weeks 11–14. J Reproduct Infertil. 2020;21(2):130.
11. Mansell W, McEvoy P, Tai S. What is good communication for people living with dementia? A mixed-methods systematic review. Int Psychogeriatr. 2017;29(11):1785-1800.
12. Lamain-de Ruiter M, Kwee A, Naaktgeboren C A, de Groot I, Evers I M, Groenendaal F, et al. External validation of prognostic models to predict risk of gestational diabetes mellitus in one Dutch cohort: prospective multicentre cohort study. BMJ. 2016;354:i4338.
13. Dudzińska M, Tarach JS, Matuszek B, Kowalczyk M, Wdowiak-Barton B, Kiszczak-Bochyńska E, et al. Evaluation of metabolic control in patients with type 2 diabetes depending on the type of hypoglycemic treatment. Experim Clin Diabetol/Diabetol Doswiadcz Klini. 2011;11(1).
14. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020;133(9):1015-24.
15. Fruscalzo A, Cividino A, Rossetti E, Maurigh A, Londero AP, Driul L. First trimester PAPP-A serum levels and long-term metabolic outcome of mothers and their offspring. Scientific Reports. 2020;10(1):5131.
16. Farina M, Rocha JB, Aschner M. Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. Life Sci. 2011;89(15-16):555-63.
17. Wright D, Silva M, Papadopoulos S, Wright A, Nicolaides KH. Serum pregnancy-associated plasma protein-A in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound Obst Gynecol. 2015;46(1):42-50.
18. Ledesma J. Conceptual frameworks and research models on resilience in leadership. Sage open. 2014;4(3):2158244014545464.
19. Martin S, Ferraz T, Pinto P, Guianas JT, Montenegro N, Ramalho C. Serum PAPPA as a predictor of gestational diabetes. Ame J Obstrt Gynecol. 2015;212(l):366-7.
20. Khalil S, Bardawil T, Stephan C, Darwiche N, Abbas O, Kibbi AG, et al. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. J Dermatolog Treat. 2017;28(8):684-696.
21. Yen I-W, Lee C-N, Lin M-W, Fan K-C, Wei J-N, Chen K-Y, et al. Overweight and obesity are associated with clustering of metabolic risk factors in early pregnancy and the risk of GDM. PLoS ONE 2019;14(12):e0225978.
22. Cosson A, Chapiro E, Bougacha N, Lambert J, Herbi L, Cung HA, et al. Gain in the short arm of chromosome 2 (2p+) induces gene overexpression and drug resistance in chronic lymphocytic leukemia: analysis of the central role of XPO1. Leukemia. 2017;31(7):1625-1629.
23. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjønneland A. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. BMJ. 2010;341:c5504.
24. Inan OT, Baran Pouyan M, Javaid AQ, Dowling S, Etemadi M, Dorier A, et al. Novel wearable seismocardiography and machine learning algorithms can assess clinical status of heart failure patients. Circ Heart Fail. 2018;11(1):e004313.
25. Sweeting AN, Wong J, Appelblom H, Ross GP, Kouru H, Williams PF, et al. A first trimester prediction model for gestational diabetes utilizing aneuploidy and pre-eclampsia screening markers. J Mater-Fet Neonat Medi. 2018;31(16):2122-30.
26. Donovan RJ, Rossiter JR, Marcoolyn G, Nesdale A. Store atmosphere and purchasing behavior. J Retaili. 1994;70(3):283-94.
27. Shah K, Sultana R, Bhat R, Bhat P, Bhat S. Impact of high levels of pregnancy associated plasma protein-a on pregnancy. J Clin Diagnos Res. 2018;12(9).
28. Ramezani S, Doulabi MA, Saqhafi H, Alipoor M. Prediction of gestational diabetes by measuring the levels of pregnancy associated plasma protein-a (papp-a) during gestation weeks 11-14. J Reprod Infertil. 2020;21(2):130-7.
29. Husslein H, Lausegger F, Leipold H, Worda C. Association between pregnancy-associated plasma protein-A and gestational diabetes requiring insulin treatment at 11–14 weeks of gestation. J Mat-Fetal Neonat Medi. 2012;25(11):2230-3.

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