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Review Article

First trimesters Pregnancy-Associated Plasma Protein-A levels value to Predict Gestational diabetes Mellitus: A systematic review and meta-analysis of the literature

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ABSTRACT

Detecting pregnant women at risk of diabetes in first months can help them by early intervention for delaying or preventing onset of GDM. In this study, we aimed to assess the Predictive value of first trimester Pregnancy related plasma protein-A (PAPP-A) levels for detecting Gestational diabetes Mellitus (GDM). This systematic review and meta-analysis was conducted through probing in databases. PubMed, Scopus, Medline and Google scholar citations were searched to find the published papers from 1974 to 2017. Studies were considered eligible if they were cohorts, case–control studies, reported GDM result, not other types, conducted on singleton pregnancy, measured Serum pregnancy associated plasma protein A in the first trimester and evaluated the relation of first trimester pregnancy associated plasma protein–A and GDM. Two reviewers independently assessed the quality with Newcastle–Ottawa and extracted data in the Pre-defined checklist. Analysis of the data was carried out by "Comprehensive Meta-analysis Version 2 (CAM)" and Metadisc software. 17 articles have our inclusion criteria and were considered in our systematic review, 5 studies included in Meta-analysis. Meta-analysis of these articles showed that the predictive value of PAPP-A for GDM has 55% sensitivity (53–58), 90% (89–90) specificity, LR + 2.48 (0.83–7.36) and LR − 0.70 (0.45–1.09) with 95% confidence intervals. In our study PAPP-A has low predictive accuracy overall, but it may be useful when combined with other tests, and this is an active part for future research. One limitation of our study is significant heterogeneity because of different adjusted variables and varied diagnostic criteria.

Introduction

Gestational diabetes Mellitus (GDM) is one of the most prevalent disorders in pregnancy [1]. GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes [2]. It can increase many complications of pregnancy such as preeclampsia, macrosomia, polyhydramnios, dystocia and cesarean section rate [1]. Early distinction and treatment can prevent these complications [3]. World Health Organization demonstrated an increase in the prevalence of GDM [4]. This enhancement is due to the increased prevalence of obesity, mean age of the population and also changing in GDM screening methods [5]. Now based on the guidelines of the International Association of diabetes, gestational diabetes screening has done for all women at 24–28 weeks gestation with 75 g oral glucose [2]. But in these cases, however, it seems that selective screening is economically more affordable [6]. This method doesn't have optimal sensitivity and specificity for risk assessment, and further research is needed to determine the best screening test [7]. Studies have shown that in women with GDM, blood glucose increases in the first trimester due to changes in their body metabolism. So the use of screening tests in the first trimester can reduce complications associated with GDM through early detection and appropriate intervention to high risk patients [8].

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PAPP-A is a high-molecular-weight metalloproteinase with lower level in pregnancies showing fetal Down syndrome. Pregnancy related plasma protein-A (PAPP-A) performance as a screening marker, and decrease with increasing gestational age between 9 and 13 weeks [9]. Measuring PAPP-A, routinely used to screen Down syndrome in 11–13 weeks of gestation [7,10].

In some articles, it is said that reduced serum levels of PAPP-A could have an increased risk of spontaneous abortion, low birth weight, IUGR, preeclampsia, PROM and abruptio placenta [11,12]. Recent studies have shown that low levels of PAPP-A in the first trimester associated with GDM in later stage of pregnancy [13]. Thus, the measurement of PAPP-A, can help assess the risk of GDM in pregnant women [14]. Early prediction and intervention could possibly elude the progress of GDM or avoid harmful maternal and fetal outcomes [15]. Systematic review and meta-analysis were essential tools for accurate and reliable summarizing of evidences [16]. Researchers feel the necessity of having a systematic review and meta-analysis study to give clear and uniform results and Comprehensive guides applicable for clinical areas. The aim of this systematic review and meta-analysis was to assess the Predictive value of first trimester PAPP-A levels for detecting GDM in pregnant women.

Methods

Identification of studies

We searched PubMed, Scopus, Medline and Google scholar citations to explore papers about the relationship between plasma protein-A and gestational diabetes mellitus. Search keywords which selected from MeSH terms were Pregnancy-Associated Plasma Protein A OR PAPP-A AND Gestational diabetes mellitus OR GDM. There was no limitation on the location of the study and its language. But we had a time limitation and articles should have been published between 1974 and 2017. The year 1974 was chosen because Lin et al. in that year for the first time described plasma protein-A in the blood of pregnant women [17].

Study selection

The search strategy was guided based on PRISMA guidelines. Four step search tactic as described below was used to select papers: The first step for selecting relevant papers was observing and checking the databases by researchers to find original papers through electronic search with using MeSH terms. The second step was screening by title and abstract. In third step, full papers scrutinized to recognize articles which met our inclusion criteria and then opinion of experts were asked. Furthermore manual searching of articles' references and forward searching of eligible articles citations was done to find articles not obtained by electronic probes. In the last step we determined articles which can include in meta-analysis and systematic review. All papers were downloaded to EndNote software to be stored and organized.

Inclusion criteria

Articles were entered in our systematic review if they had the following criteria: 1- reported GDM result, not other types of diabetes. 2-research conducted on singleton pregnancy 3- measured Serum pregnancy associated plasma protein A in the first trimester 4-evaluated the relation of first trimester pregnancy associated plasma protein–A and GDM 5- Study design: cohorts, case–control 6-published after 1974.

Data extraction and quality assessment

Two researchers independently extracted data and entered into an Excel spread sheet and differences were resolved by discussion with a third one. Following data were extracted in the pre-defined form: first author, study design, country of origin, publication year, sample size, maternal age, BMI, GDM diagnosis test, Time of taking Test, Result, Median or mean ± SD of PAPP-A for GDM and non GDM groups, adjusted variables and quality of studies.

Quality of our selected articles was evaluated with eight-item Newcastle–Ottawa (NOS) checklist for case–control and cohort studies. This instrument has three domains: 1.selection of participants, 2.comparability, and 3.outcome ascertainment. NOS judge the studies by implementing a 'star system'. Each study can get ranges between zero up to nine stars. Stars on questions related to the selection of groups are "four stars", the comparability of the groups "two stars" and of outcome "three stars" [18]. The face/content validity and inter-rater reliability of the NOS has been established based on a critical review of the items by several experts [19]. Scores of 9, 8, and 7 assigned to high quality labels, 6, 5 considered moderate, and below 4 were assigned to low quality group.

Statistical analysis

CMA version 2 and MetaDisc were used for statistical analyses. Sensitivity and specificity of pregnancy associated plasma protein–A for predicting GDM were calculated and used for meta-analysis. Sensitivity, specificity and the likelihood ratios (LR) were calculated based on the reported cut offs in the included studies. False negative, true negative, false positive and true positive values were used in the statistical software accordingly.

We used random effects model for pooling data across studies. Results were displayed as forest plots. For heterogeneity evaluation Cochrane Q test ($p < 0.05$ as statistically significant) and I^2 index were used. To explore potential publication bias, funnel plots and Egger's regression intercept were used.

In order to evaluate the threshold effect of the diagnostic value of PAPP-A, correlation between Logit false positive and Logit true positive rates was used. In order to show the overall accuracy of the test, SROC curve, diagnostic odds ratio (DOR), area under the curve (AUC) and Q* were used.

Results

The PRISMA process of searching and literature selection is summarized in Fig. 1. In first search 385 articles were found by using internet search, then articles were excluded by screening titles and abstracts, then Full-text articles assessed for eligibility and 23 articles excluded due to not having inclusion criteria, and not having enough information, so 14 studies remain. 3 new studies were found in searching references lists and citations of selected full text studies. The remaining articles were assessed in depth ($n = 17$).

The characteristics of included studies were summarized in Table 1. All included studies were case-control and cohort and one of them was case series. In all articles the mean age and BMI of women with GDM was higher. PAPP-A screening was performed between 10 and 14W. Median or mean values for PAPP-A were lower in GDM group versus non GDMs.

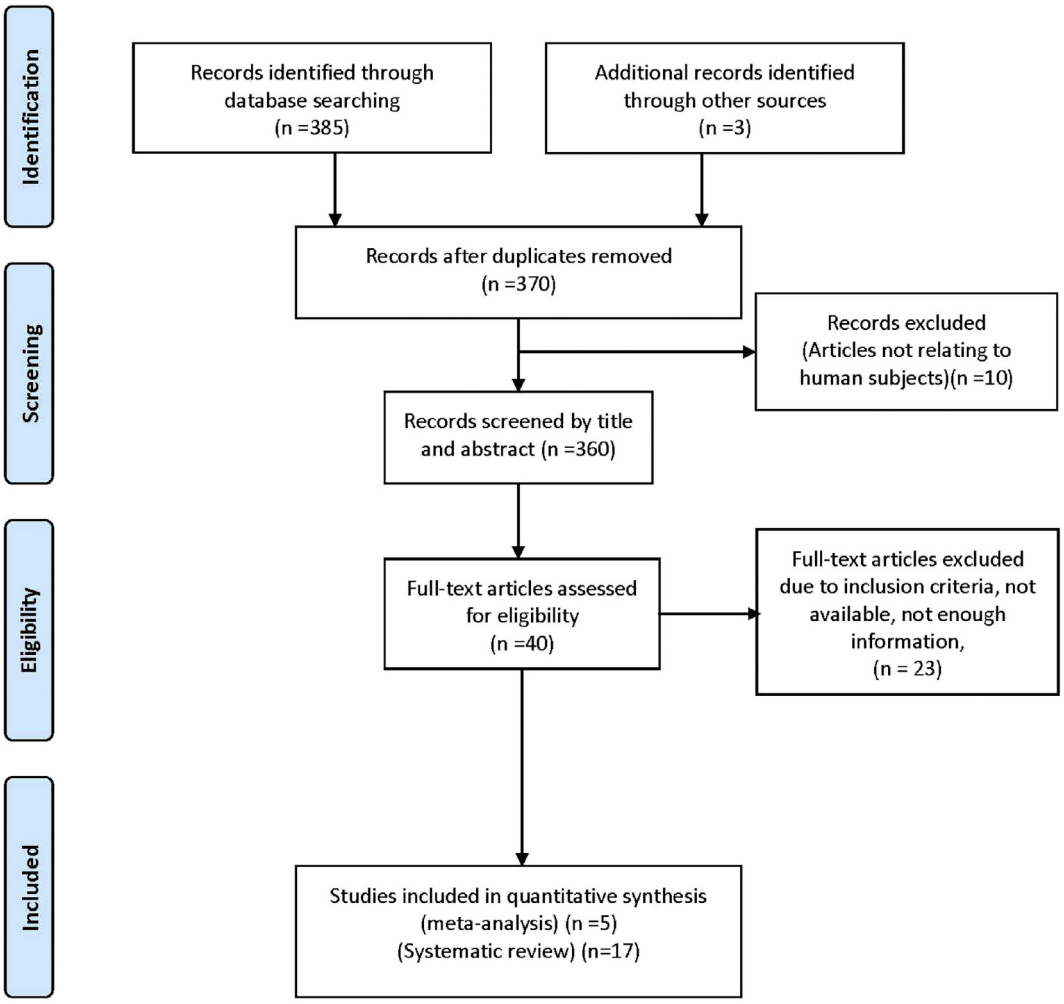

Fig. 1. PRISMA flow diagram of selection of studies process.

Various studies showed contradictory results. Some of them have shown significant correlation between PAPP-A and GDM, but some studies did not report any association between these two variables. More accurate details of selected studies have shown in Table 1. Also the evaluation of quality assessment of each article with NOS was presented in this table. Total quality ratings indicated 9 average quality studies, and 8 high quality studies. No study was excluded due to methodological limitations.

The results for PAPPA as biochemical markers to predict Gestational diabetes mellitus are summarized in Figs. 2–4. The pooled diagnostic indices from five papers [7,15,20–22] for GDM was 55% sensitivity (53–58) and from four papers [7,15,20,21] 90% (89–90) specificity, LR + 2.48 (95% CI: 0.83–7.36), LR − 0.70 (95% CI: 0.45–1.09) and DOR was 3.61 (95% CI: 0.98–13.33). Funnel plots of sensitivity and specificity pooling are shown in Figs. 5 and 6. The asymmetrical distribution of the points for sensitivity suggests possible publication bias that was confirmed by Egger's test intercept 3.3385 ($p = 0.3428$) and for specificity Egger's test intercept 6.1402 ($p = 0.4945$). To assess the sources of heterogeneity we should run the meta-regression analysis. However, with these number of studies which enter in our meta-analysis was not suitable to perform statistical subgroup analysis.

Correlation between true positive and false positive rates was 0.98 ($p < 0.00001$) which shows the potential threshold effect. Pooled DOR was 3.61 [0.98–13.33] (see Fig. 7). Because of low number of studies included in meta-analysis, bivariate model could not be performed so we used SROC. The SROC curve presents a global summary of test performance, and shows the tradeoff between sensitivity and specificity. The area under the curve (AUC) and an index Q value are discussed as useful summaries of the curve. SROC curve is shown in Fig. 8, our data showed AUC = 0.7, and $Q^* = 0.65$.

Discussion

One of the most important goals of systematic and meta-analysis studies, is providing a credible result, due to the increased sample size and combination of different studies and thus reduces confidence interval of this size and solving the problems caused by controversial results of previous studies [23]. Several studies investigated the relation between PAPP-A and GDM; however meta-analysis in this area has not been done so far. Prognostic factor studies are so important because they help us to improve consequence for patients by identifying modifiable factors by either intervention or other different managements such as surveillance. Identification of any early changes in biochemical markers in the first trimester can lead to detecting pregnant women at risk earlier [24]. The pathophysiology of gestational

Table 1
Characteristics of 15 studies included in our systematic review.

Authors [reference]	Publication year	Country	Type of Study	Age of sample (cases/ controls)	BMI(cases/ controls)	Sample size (cases)	Sample size (controls)	GDM diagnosis	Prediction test	Time of prediction test	Result	Adjusted variables	Total NOS star rating	Median (Iqr) or mean ± SD (Cases)	Median (Iqr) or mean ± SD (Controls)	area under the curve
Ong et al. [22]	2000	UK (London)	Cohort	_	_	49	4297	OGTT-75	PAPPA, β-hCG	10–14W	Significant	Gestational age,smoking	6	0.848 (0.691, 1.006)	1.049 (1.028, 1.070)	–
Tul et al. [37]	2003	Slovenia	Retrospective Cohort	_	_	27	1109	OGTT-100	PAPP-A, βhCG, NT, inhibin-A	10–14W	NS	Maternal age, weight, smoking, parity and gravidity	7	–	–	–
Savvidou et al. [36]	2011	UK (London)	Case–control	33.7/32.1	28.3/24.2	779	41,007	OGTT-75	PAPPA, β-hCG	11 + 0_13 + 6	NS	Maternal weight, smoking, parity, racial origin, fetal CRL	6	0.94 (0.65–1.39)	1.00 (0.68–1.42)	
Beneventi et al. [13]	2011	Italy	Case–control	34/33	23.2/22.1	228	228	GCT-50 & OGTT-100	PAPPA, β-hCG	11 + 0_13 + 6	Significant	Maternal weight, days of gestation,smoking	6	0.7 (0.5–1.2)	1.2 (0.8–1.6)	
Husslein et al. [34]	2012	Austria	Case–control	34.2/32.3	27.9/26.7	72	216	OGTT-75	PAPPA, β-hCG	11–14W	NS	Gestational age,BMI	6	1.17 ± 0.71	1.13 ± 0.58	–
Lovati et al. [7]	2013	Italy	Case–control	33.58/32.33	24.7/22.6	307	366	OGTT-75	PAPPA	11–14W	Significant	Maternal weight, days of gestation and smoking habit	6	0.76 (0.52–1.32)	1.21 (0.83–1.56)	0.6
Spencer and Cowans [29].	2013	UK	Cohort	32/29	28.4/27.5	870	6559	OGTT-75	PAPPA, β-hCG, NT	11 + 0_13 + 6	Significant	Gestational age, maternal weight, smoking status, ethnic origin, parity	6	0.91	1	0.55
Kulaksizoglu et al. [24]	2013	Turkey	Case -control	31.48/30.05	23.2/22.1	60	60	GCT-50 & OGTT-100	PAPPA	10–14 W	Significant	Maternal age	7	0.77 ± 0.42	0.97 ± 0.4	–
Beneventi et al. [20]	2014	Italy	Retrospective and prospective case–control	retro: 34.5/32.4 pros: 35.2/33.5	23.46/22.14	retro:112 pros:18	retro:112 pros:105	OGTT-75	PAPPA, sHLA-G	11–14W	significant	Gestational age, maternal weight, smoking status, ethnic origin, parity	9	1.06 ± 0.59	1.22 ± 0.64	0.636
Syngelaki et al. [21]	2015	UK (London)	Case–control	33.2/30.6	77.2/66.8	787	30,438	OGTT-75	PAPPA, PLGF	11 + 0_13 + 6	Significant	Gestational age at sampling, maternal racial origin, weight, smoking status, method of conception	7	0.949 (0.913, 0.987)	1.000 (0.994, 1.006)	0.8409
Wells et al. [18]	2015	Australia	Case–control	34.7/33.56	25.8/22.8	274	1664	GCT-50 & OGTT-75	PAPPA	10–14W	Significant	Gestational age, maternal weight, ethnicity and smoking status	8	0.79 (0.51–1.28)	1.00 (0.68–1.40)	–
Ferraz T et al. [28]	2015	Portugal	Retrospective cohort	32.3/30.5	27.6/24.8	205	1853	OGTT-75	PAPPA	11-13W	Significant	Maternal age, parity,BMI	6	2.3 ± 1.7	2.9 ± 1.9	–
Farina et al. [15]	2016	Italy	Case–control	33.5/32	24.95/22.40	12	60	OGTT-75	PAPPA, PP13	11–14W	Significant	Maternal weight, gestational age,BMI	6	0.7 (0.55–1.04)	1.10 (0.72–1.44)	0.685
Sert et al. [25]	2016	USA	Retrospective cohort	32.4/29.5	_	95	1156	GCT-50 & OGTT-100	PAPPA	11–14W	Significant	Gestational age, maternal weight and race/ethnicity.	6	0.7 (0.5–1.0)	0.9 (0.6–1.3)	–
Cheuk et al. [35]	2016	Hong Kong	Prospective case series	34/32	22.5/21.3	169	351	OGTT-75	PAPPA, β-hCG	Before14W	NS	Maternal weight,ethnicity	7	0.97 (0.65–1.32)	0.99 (0.67–1.44)	–
Xiao et al. [31]	2017	china	Case–control	32/29	20.83/19.72	599	986	OGTT-75	fβ-hCG, PAPP-A	10–14W	Significant	Maternal age,Parity,BMI, nationality, talassemia, method of conception	8	0.88 (0.60–1.28)	0.97 (0.67–1.37)	0.53
Ramezani et al. [30]	2017	Iran	Cohort	25.42/25.37	26.26/24.26	172	78	OGTT-75	PAPP-A	11–14W	Significant	Maternal age, parity, BMI	9	–	–	–

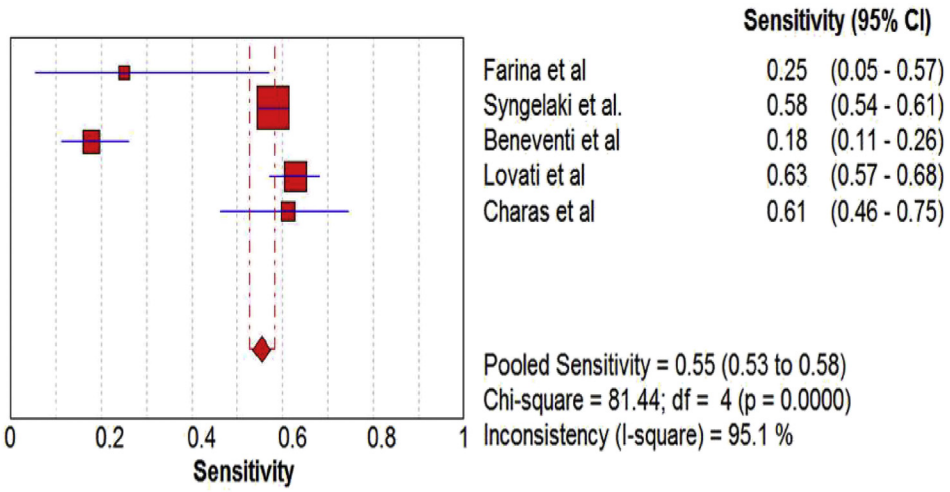

Fig. 2. Forest plot of PAPP-A as biochemical markers for prediction of GDM.

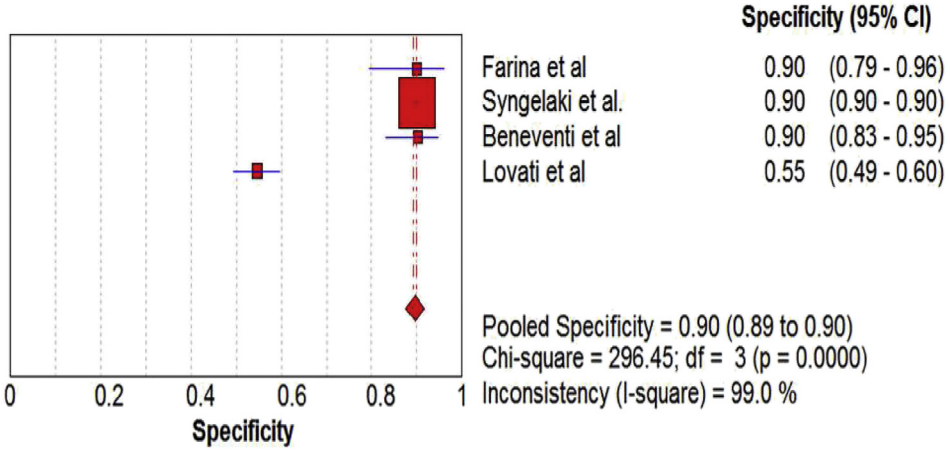

Fig. 3. Forest plot of PAPP-A as biochemical markers for prediction of GDM.

diabetes occurs weeks or months before the diagnosis, so the factors related to the pathogenesis can be present in the blood before clinical diagnosis of gestational diabetes [13].

In our study we evaluated the predictive accuracy of PAPP-A for GDM which is a marker commonly used in first trimester of pregnancy screening. Overally the findings demonstrate low predictive accuracy. This meta-analysis showed the predictive value of PAPP-A for GDM has 55% sensitivity (53–58), 90% (89–90) specificity. Respectively these indicators reflect the number of patients who have the positive disease test and measure of false positive rate. The SROC curve summarizes the potential capacity to discriminate the samples with disease from those without disease. It shows, that is a good test if AUC close to 1. In the present study AUC was 0.7 indicating a low level of accuracy. The DOR indicates a single number which is combination of the data from sensitivity and specificity. The range of a DOR can be from 0 to infinity. Higher values show the higher accuracy. In our study DOR was 3.6 which also indicating a low level of accuracy. Likelihood ratios in comparison with the DOR and the SROC curve are more useful in clinical situation. They are the most important indicators of functional diagnostic tests. With likelihood ratios we can explain how many times samples with disease are more likely to receive a special test result than samples without disease. A PLR of 2.48 in our meta-analysis shows that patients with low maternal serum PAPP-A have about 2.48-fold higher chance to detect GDM for them. A NLR of 0.70 suggests that PAPP-A alone isn't a sensitive test to detect GDM patients.

According to Table 1 results of some studies [7,13,15,21,22,24–31] demonstrate somehow association between low maternal serum PAPP-A in the first trimester and gestational diabetes but the results showed medium predictive accuracy overall. PAPP-A is produced in the placenta and decidua. It acts in trophoblast as a protease for controlling the insulin growth factor (IGF) in binding protein (IGFBP)-4. Because IGFBP is decomposed by PAPP-A, Low levels of PAPP-A cause high levels of IGFBP and low levels of IGF. IGFs control uptake of amino acids and glucose in trophoblast and act as paracrine and autocrine regulator of trophoblast invasion of the decidua. Therefore decreased PAPP-A can worse placental condition and as a result adverse obstetric outcomes occur [32,33]. Also Low levels of IGF lead to an increase in insulin, insulin resistance and abnormal glucose clearance [7]. These descriptions may be an acceptable reason for association. In Pellitero et al. (2007) article, the relationship between PAPP-A and glucose control evaluate in non-pregnant diabetic patients, and

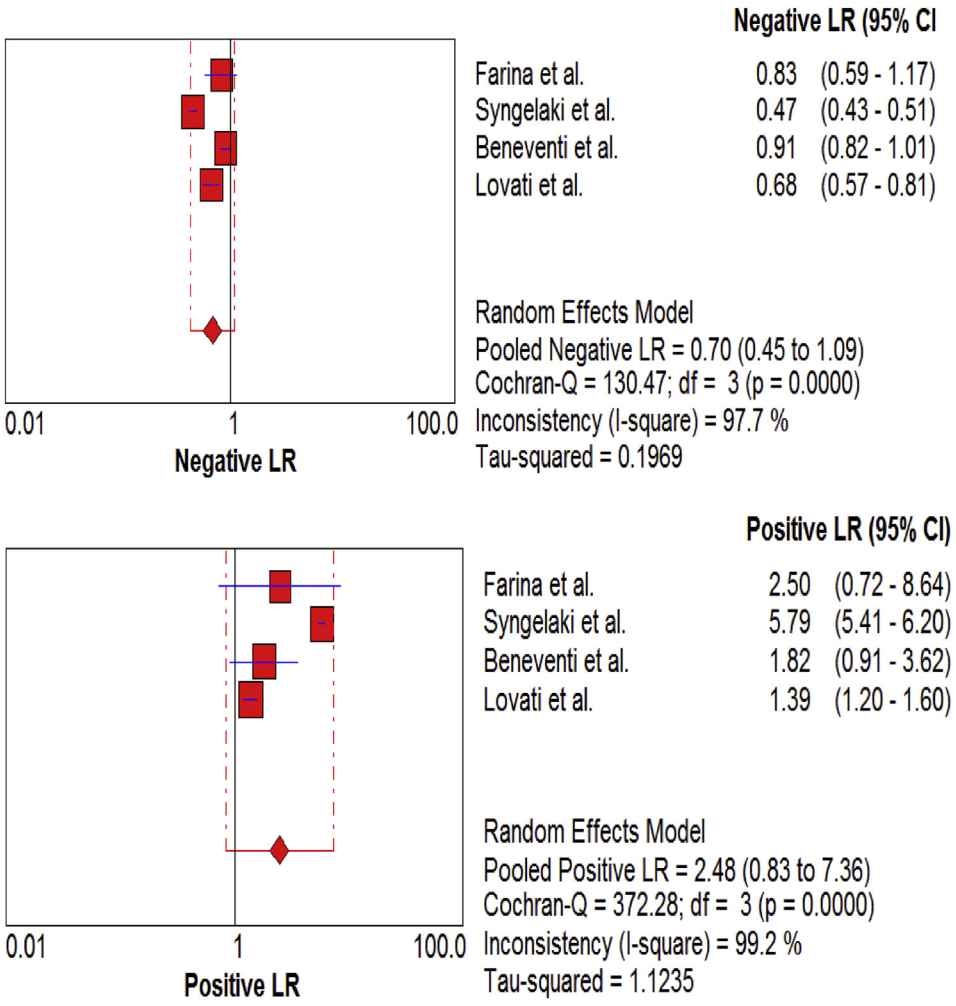

Fig. 4. Forest plot for PAPP-A to predict GDM: forest plot showing likelihood ratio of a positive and negative test result with 95% confidence intervals (95% CI).

opposite relationship was found among hemoglobin A1C and PAPP-A level. This means the effect of glycemic control on the expression of PAPP-A in serum [14].

In contrast, some articles [34–37] didn't show any association. There are some reasons behind these differences as we described below. One explanation is the differences in severity of gestational diabetes as Savvidou et al. (2011) declared that there is a significant PAPP-A level differences in women who need diet therapy with women who need more serious intervention [34]. Also Lovati et al. (2013) showed that lower level of PAPP-A in the first trimester of pregnancy associated with risk of insulin therapy in diabetic pregnant women [7]. Another explanation of different results can be related to different adjusted variables. The next reason of diversity happened due to the usage of different method for detecting GDM such as (Table 1): GCT-50 g, OGTT-75 g 2 h, OGTT-100 g 2 h, OGTT-100 g 3 h or mix of two of them. Shirazian et al. (2008) in their study about varied diagnostic criteria noted that different criteria detect different rate of GDM in the same population: (6.1%, 12.1%, 18.8% in ADA, WHO, and ADIPS) [38]. Somani et al. (2012) showed different Prevalence of GDM by WHO criteria (4.8%), by Carpenter and Coustan's criteria (6.36%), by O'Sullivan's criteria (3.5%) [39]. Also other reason can be pointed out for differences in results is that in each study OGTT was done based on different reason, for example: abnormal random blood glucose level, based on risk factors for GDM, 50-g glucose challenge test and universal screening test.

There are several limitations in our study that must be considered. One main limitation of our study was significant heterogeneity. Presence of heterogeneity might be because of different adjusted variables and varied diagnostic criteria. Another limitation was that, all studies we selected were from low risk population, since few studies has been done on high risk ones. One another restriction was that this study conducted based on databases and published studies and unpublished studies didn't use. Funnel plot showed an asymmetric distribution which shows that publication bias (if present) can be affect the results of the current study. It can be a concern in our study which our results should be interpreted with caution. Another important limitation of the current systematic review is the threshold effect which is a major source of heterogeneity in the diagnostic studies. The correlation between sensitivity and specificity was high and showed the possibility of important threshold effect. Curvilinear SROC curve also corroborate this notion. AUC, DOR, and Q* were moderately high which showed that overall diagnostic accuracy of PAPP-A for screening of gestational diabetes is not very high.

Implications for practice and research

Because PAPP-A routinely assessed in screening for abnormalities, it is cost-effective for pregnant women. The worthiness of first-trimester screening for detecting GDM women may give them chance for early intervention. Lifestyle interventions such as

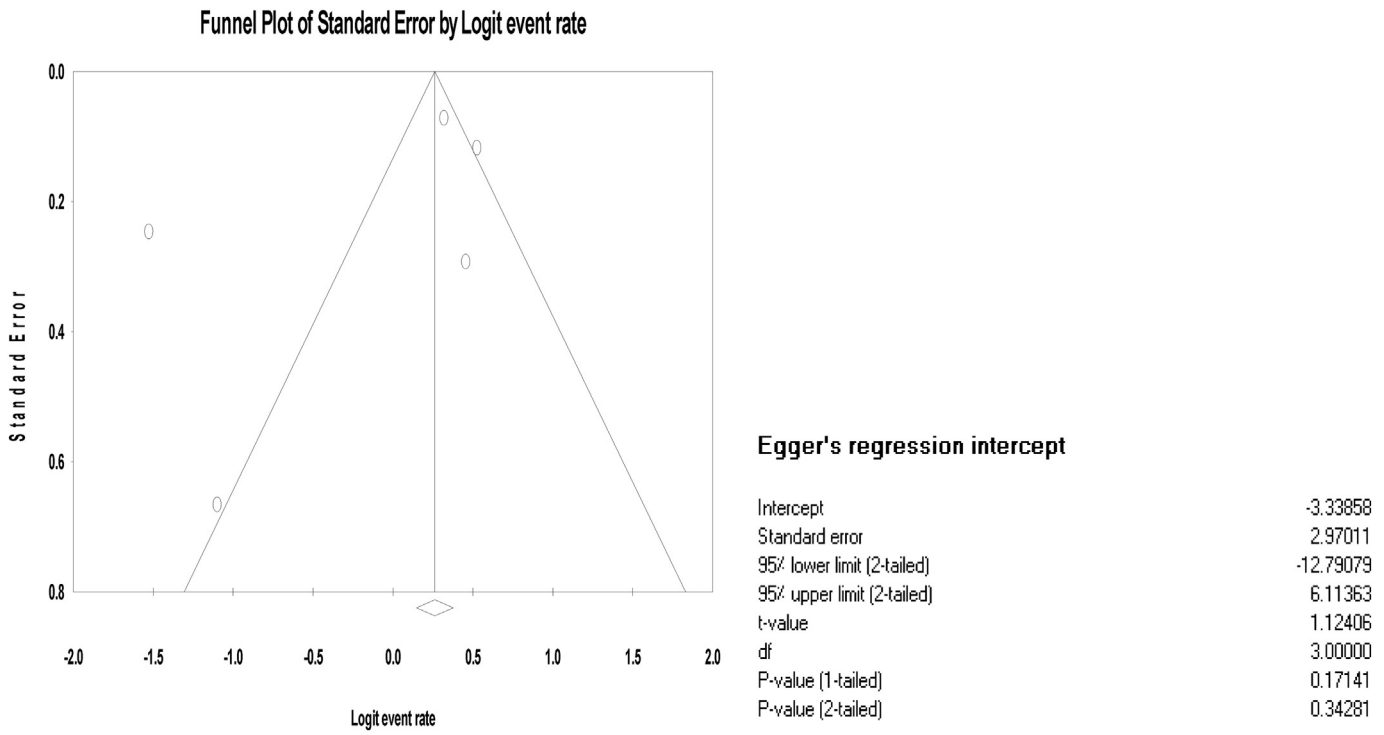

Fig. 5. Results of Publication Bias Tests for sensitivity: Funnel plot of standard error by Logit Event Rate and Egger's regression intercept.

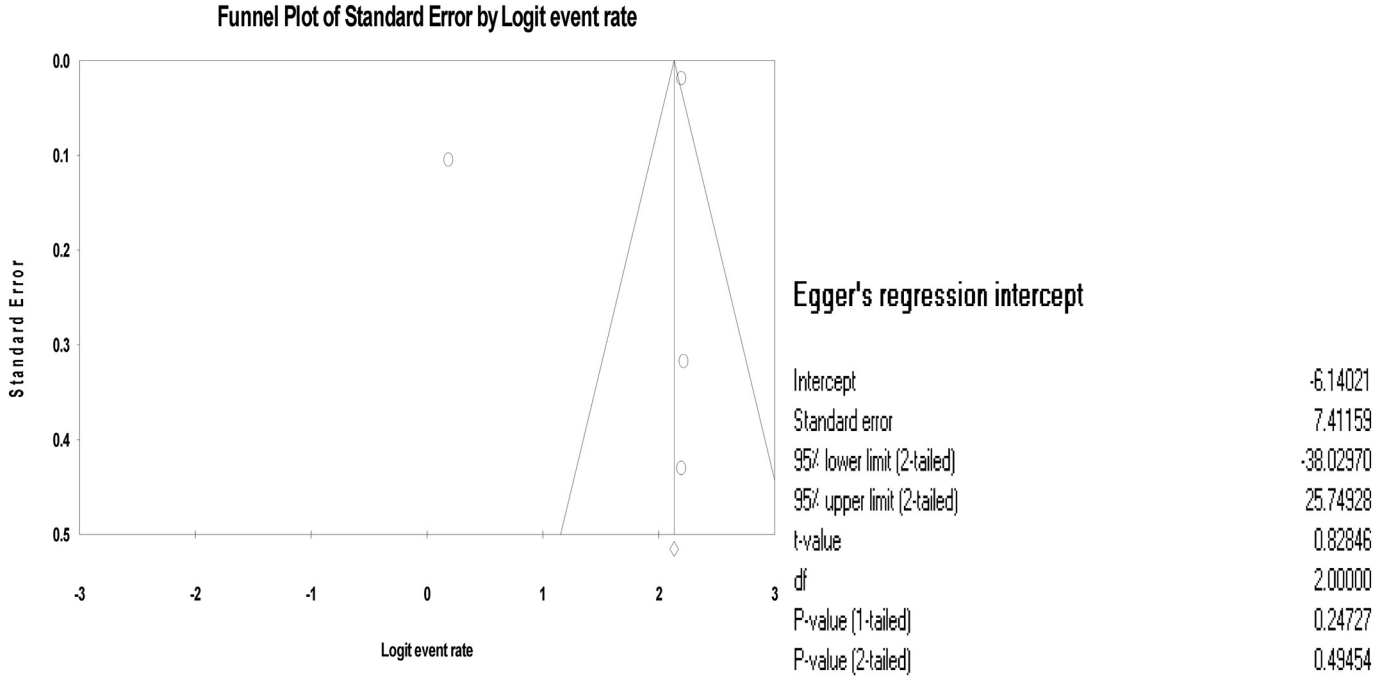

Fig. 6. Results of Publication Bias Tests for specificity: Funnel plot of standard error by Logit Event Rate and Egger's regression intercept.

increases physical activity, pay attention to weight control, alter dietary intake and use dietary supplement may be effective ways in lessening its severity, delaying or preventing onset of GDM and improve maternal and fetal health outcomes.

Future research could assess the relation and Predictive value of PAPP-A for other types of diabetes. Further studies should be included PAPP-A as a continuous variable and its correlation with other prognostic markers available during each trimester of pregnancy such as NT, PP13 and β-hCG. Also during the study we encounter a series of other complications in pregnancy which was associated with PAPP-A such as preeclampsia, low birth weight, abortion and etc. Future work can be done on these variables. One

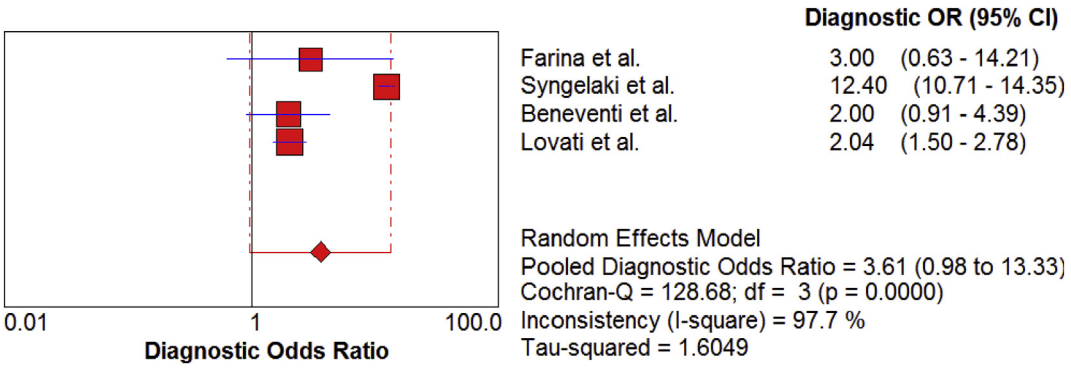

Fig. 7. Diagnostic odds ratio forest plot for PAPP-A to predict GDM.

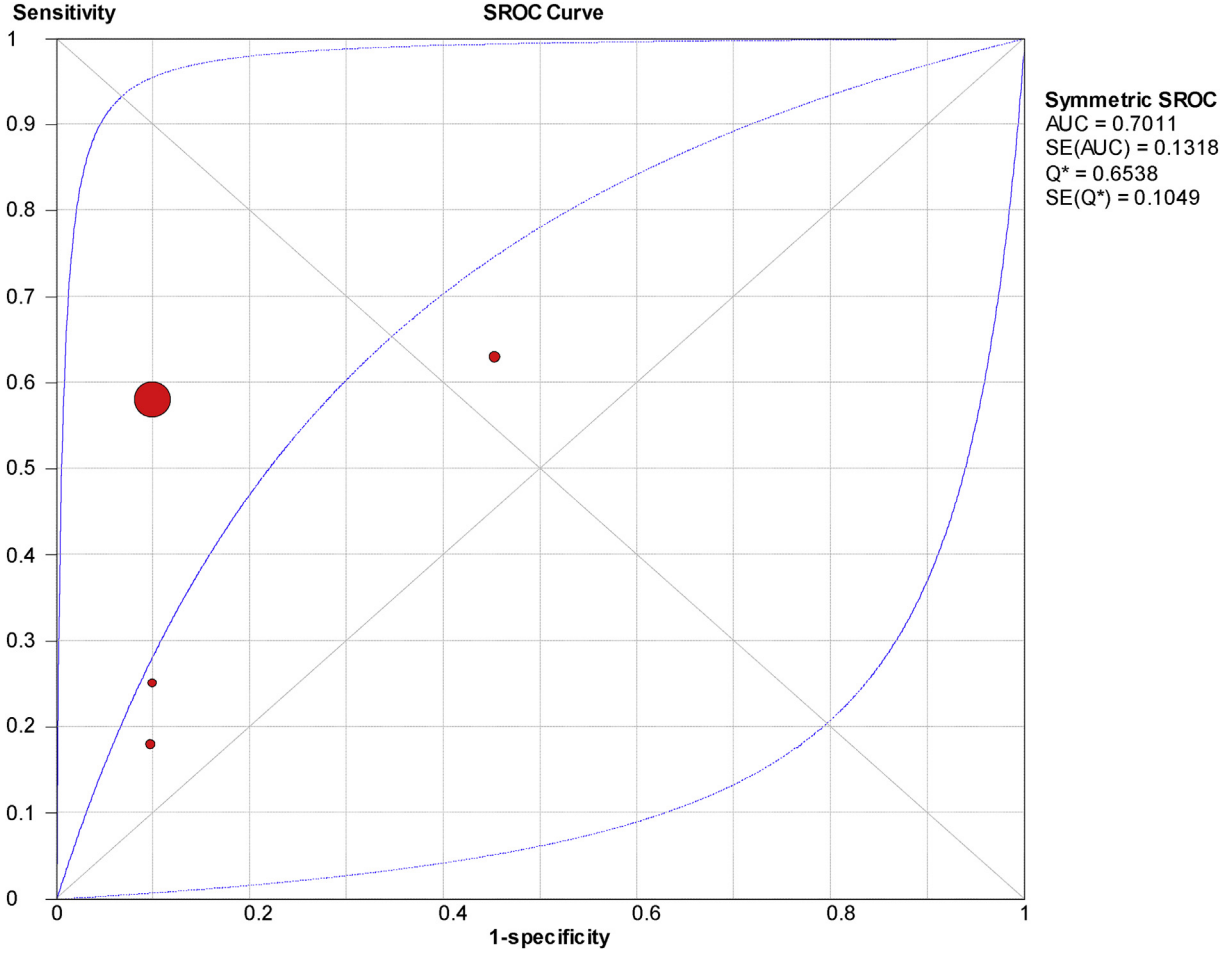

Fig. 8. Summary receiver operating characteristic curve (SROC) for PAPP-A. Each solid circle represents each study in the meta-analysis.

another important part that future studies should consider and improve their knowledge is biological mechanisms for the abnormal clinical tests which resulting in diabetes.

Conclusions

According to the results of this study low maternal serum PAPP-A in the first trimester has low predictive accuracy for gestational diabetes mellitus. However this variable may be useful in prediction when we combined with other tests. GDM is a silent disease and it has insufficient clear related symptoms, so PAPP-A level could be a potential diagnostic risk factor for evaluating GDM. This result could be useful clue for implication for clinical staff.

Declaration of conflicting interests

The authors declared no conflicts of interest.

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