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ORIGINAL ARTICLE

Plasminogen activator inhibitor-1 levels in prior gestational diabetes mellitus: A systematic review and meta-analysis

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Abstract

Objective Conflicting results on the association of plasminogen activator inhibitor-1 (PAI-1) with prior gestational diabetes mellitus (*p*GDM) have been observed among studies that imply the need to perform a meta-analysis.

Methods Literature that determined the levels of PAI-1 in patients with *p*GDM and non-GDM was retrieved from various database websites. Relevant data were extracted from each study and collated. For the data analysis, Review Manager ver. 5.4 was used. The studies were pooled to compute the standardized mean difference (SMD) and 95% confidence interval (CI) between *p*GDM and non-GDM groups.

Results Overall results were heterogeneous, which prompted the identification of the cause using a Galbraith plot. Post-outlier outcomes demonstrate that higher levels of PAI-1 are observed among women with *p*GDM than those with no history of the disease.

Conclusion PAI-1 is significantly associated with GDM, especially among patients with *p*GDM. Further studies should be conducted on the relation of serum PAI-1 with other diabetes-related markers and variables to verify these findings.

Keywords PAI-1 · Gestational diabetes mellitus · Prior GDM · Coagulation · Meta-analysis

Introduction

Pregnancy is associated with numerous physiological changes, which sometimes may lead to the development of pregnancy-related complications. An example is the increasing prevalence of hemostatic disorders in pregnant women. This arises from increased coagulation factors, including plasminogen activator inhibitor-1 (PAI-1) [1], throughout pregnancy [2] and the puerperium [1, 3]. PAI-1 is a serine protease inhibitor produced mainly in the liver [4] and other types of cells like endothelial cells, megakaryocytes, and adipocytes [5]. It inhibits fibrinolysis by inhibiting activators of plasminogen, the inactive form of plasmin.

Increased levels of PAI-1 are associated with numerous metabolic disorders, like cardiometabolic disorders [6], obesity [7], and diabetes [8]. Of intriguing interest here is the association of increased PAI-1 with gestational diabetes mellitus (GDM). GDM is a type of diabetes recognized at the onset of pregnancy, which is seen in approximately 7% of pregnancy complications [9]. Due to hormonal changes in pregnancy, there is an associated increase in adipose tissue deposits [10], which can also produce PAI-1 [7]. As a result, PAI-1 levels are elevated in patients with GDM [11, 12]. Few studies have already been conducted that determined the association of the protein with GDM, especially after delivery [13–22]. However, results vary with each other, which necessitates a meta-analysis to strengthen the association, if there is one.

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Materials and methods

Study design

Articles used for this study were searched in PubMed, ScienceDirect, Google Scholar (title search only), and Cochrane Library using the key search term combination: "gestational diabetes" OR "GDM" AND "plasminogen activator inhibitor-1" and OR "PAI-1" as of June 22, 2023. The resulting studies were first screened by checking their titles and abstracts. After duplicate and inappropriate studies were removed, full texts of the remaining articles were obtained and manually checked for their relevance. Also, cited references from each eligible study were examined.

The following inclusion criteria were used: (a) studies that measured PAI-1 levels in ng/mL; (b) studies that included prior GDM cases; (c) studies that included non-GDM controls; and (d) studies that were written in English. All studies identified were investigated for eligibility by the authors.

Data extraction and conversion

The following data were obtained from all eligible studies: (a) first author's last name; (b) date of publication; (c) country where the study was conducted; (d) time when blood samples were obtained; (e) number of cases vs. controls; (f) the total number of participants; and (g) concentration of PAI-1 from cases and control groups. This study defined prior GDM (*p*GDM) when blood collection was done after delivery. Two authors extracted the data (RET and MJD) and agreed on all the items. Disagreements (if any) were resolved by a third person (MC).

For studies that expressed PAI-1 levels in median and interquartile, we converted the measures into their approximate means and standard deviation (SD) using the procedure of Hozo et al. [23]. To avoid discrepancies caused by data conversion, only values in nanograms per milliliter (ng/mL) were used for the study.

Quality assessment of the included studies

The quality of the methodology of all included studies was assessed using the Newcastle–Ottawa Scale (NOS). The resulting studies were each rated based on the respondents' selection, comparability, and exposure. The scoring system utilized has a maximum rating of nine points. Accumulated scores of ≤ 4 indicate low-quality studies. On the other hand, scores of 5–6 points indicate moderate-quality studies, whereas scores of ≥ 7 points indicate high-quality studies [24].

Statistical analysis, sensitivity analysis, and publication *bias* testing

The protocol used for this meta-analysis was based on the procedure from existing studies [25, 26] in treating mean and SD. The standardized mean difference (SMD) and 95% confidence interval (CI) of the levels of PAI-1 between *p*GDM and non-GDM were calculated from each study and pooled. The pooled SMD estimates were determined either by the fixed- or random-effects model, depending on heterogeneity [27, 28]. Heterogeneity was examined using a chi-based Q test, and its degree was measured using I^2 statistics [29, 30]. All p-values (P^A) for association were two-sided with a significance threshold set at < 0.05. In contrast, the p-value (P^H) for heterogeneity is set at < 0.10 due to the low power of the test [31]. All statistical analysis was performed using Review Manager ver. 5.4. The robustness of the pooled effects was determined using sensitivity analysis. This was done by repeating the overall statistical analysis while omitting one study at a time. This was done to check the influence of the individual study in the pooled SMD. On the other hand, publication bias was no longer assessed due to the low number of studies in the post-outlier analysis [32].

Results

Search results and characteristics of the included studies

Figure 1 summarizes the selected studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. The literature search yielded a total of 219 studies that were manually checked. After the omission of duplicates, animal studies, reviews, and commentaries, studies were screened following the set inclusion criteria, resulting in ten studies being included in the systematic review. However, from these studies, two papers were possible continuations of previous publications. Hence, in the performance of the meta-analysis, the two old duplicate papers [14, 22] were excluded. On the other hand, for the remaining eight studies, two papers [16, 19] contained two sets of data for the GDM cohort. The paper of Farhan et al. in 2006 employed *p*GDM with impaired insulin sensitivity and those with normal insulin sensitivity. On the other hand, the study of Morimitsu et al. [16] also used two *p*GDM cohorts, namely, those with impaired glucose tolerance and those with normal glucose tolerance. Hence, for this reason, even if the number of studies included is only eight, the data sets used for analysis are increased to ten because of the multiple *p*GDM cohorts in the two studies. For the NOS score, we obtained a mean and SD of 5.9 ± 0.9

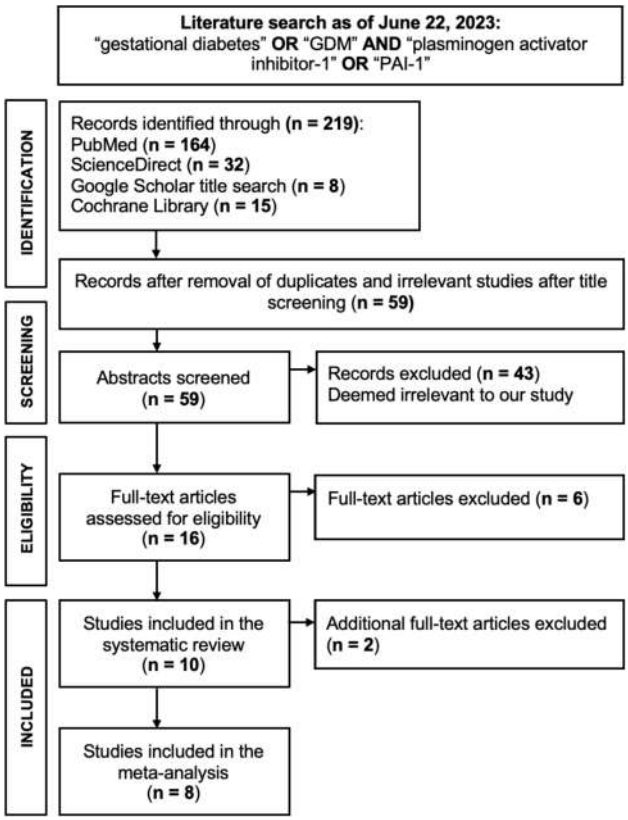

Fig. 1 Summary of literature search. GDM, gestational diabetes mellitus; PAI-1, plasminogen activator inhibitor-1

and a median of 6, indicating that the studies included were of moderate quality.

Table 1 summarizes the characteristics of the studies included. The year of publication ranged from 2005 to 2013. The total sample size included for the meta-analysis is 724 (237 healthy controls and 487 women with *p*GDM), with a narrow range of total sample sizes across all the studies (34 to 140). Other qualities, such as country of origin, the time of collection of the blood sample, and the subgroup used (if any), are summarized in Table 1.

Overall and post-outlier association

The results for the overall association are shown in Fig. 2. The association model used the random-effects model due to high heterogeneity ($I^2 = 98\%$), which prompted us to perform an outlier analysis using a funnel plot (Fig. 3). After removing the outlier data sets, homogeneity was achieved ($I^2 = 0\%$) after a repeat analysis (Fig. 4). The change in the I^2 and P^H values in the association model demonstrates that these studies are responsible for the inconsistency. The post-outlier fixed-effects model analysis showed that the PAI-1 was observed to be elevated (SMD 0.62; OR 0.40, 0.85; $P^A < 0.00001$) among those who previously had GDM.

Sensitivity analysis and publication *bias*

The outcome from the comparison was robust, indicating the stability of our findings (data not shown). Publication bias analysis was no longer performed due to the limited number of studies per association model.

Table 1 Characteristics of the included studies

Author's name and date	Country	Time of analysis	*n*	Subgroup	PAI-1 levels of controls			PAI-1 levels of *p*GDM		
					Mean	SD	*n*	Mean	SD	*n*
Akinci (2008) [a]	Turkey	NM	76	None	29.18	2.68	30	42.99	2.88	46
Akinci (2011)	Turkey	NM	71	None	135.31	45.19	56	165.67	42.89	15
Bayraktar (2011)	Turkey	NM	116	None	108.55	27.21	35	124.07	27.25	81
Farhan (2006)	Austria	3 months postpartum	94	IIS	15.90	1.50	20	37.20	4.80	37
				NIS				20.50	1.90	37
Gobl (2013)	Austria	3–6 months postpartum	140	None	18.30	15.70	33	28.30	22.50	107
Heitriter (2005)	USA	12 months postpartum	36	Non-obese	16.50	14.00	23	30.90	20.30	13
Morimitsu (2007)	Brazil	4–5 months postpartum	34	IGT	6.30	5.90	11	27.20	23.10	15
				NGT				13.70	15.40	8
Sokup (2011)[a]	Poland	2–24 months postpartum	165	None	71.36	7.82	40	57.09	6.88	125
Sokup (2012)	Poland	2–24 months postpartum	125	None	71.36	7.82	40	57.09	5.53	85
Winzer (2004)	Austria	12 months postpartum	108	None	15.60	1.70	19	28.70	2.10	89

N total number of participants, *PAI-1* plasminogen activator inhibitor-1, *pGDM* prior GDM, *SD* standard deviation, *n* total number of participants for the group, *USA* United States of America, *NM* not mentioned, *IIS* impaired insulin sensitivity, *NIS* normal insulin sensitivity, *IGT* impaired glucose tolerance, *NGT* normal glucose tolerance

[a]Excluded from the meta-analysis

Study or Subgroup	pGDM Mean	pGDM SD	pGDM Total	Non-GDM Mean	Non-GDM SD	Non-GDM Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akinci 2011	165.67	42.89	15	135.31	45.19	56	10.2%	0.67 [0.09, 1.25]
Bayraktar 2011	124.07	27.25	81	108.55	27.21	35	10.3%	0.57 [0.16, 0.97]
Farhan 2006 IIS	37.2	4.8	37	15.9	1.5	20	9.5%	5.28 [4.13, 6.42]
Farhan 2006 NIS	20.5	1.9	37	15.9	1.5	20	10.0%	2.56 [1.83, 3.29]
Gobl 2013	28.3	22.5	107	18.3	15.7	33	10.3%	0.47 [0.08, 0.87]
Heitritter 2005	30.9	20.3	13	16.5	14	23	10.0%	0.85 [0.14, 1.56]
Morimitsu 2007 IGT	27.2	23.1	15	6.3	5.9	11	9.9%	1.12 [0.28, 1.97]
Morimitsu 2007 NGT	13.7	15.4	8	6.3	5.9	11	9.8%	0.65 [-0.29, 1.59]
Sokup 2012	57.09	5.53	85	71.36	7.82	40	10.2%	-2.23 [-2.70, -1.77]
Winzer 2004	28.7	2.1	89	15.6	1.7	19	9.7%	6.38 [5.38, 7.38]
Total (95% CI)			**487**			**268**	**100.0%**	**1.59 [0.35, 2.83]**

Heterogeneity: $Tau^2 = 3.85$; $Chi^2 = 363.35$, df = 9 ($P < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 2.51$ ($P = 0.01$)

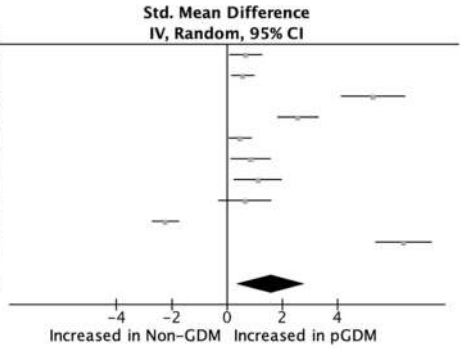

Fig. 2 Forest plot analysis of cases versus controls for the overall association of PAI-1 with *p*GDM. GDM, gestational diabetes mellitus; SD, standard deviation; CI, confidence interval; df, degrees of freedom. Total = number of participants in the cohort tested

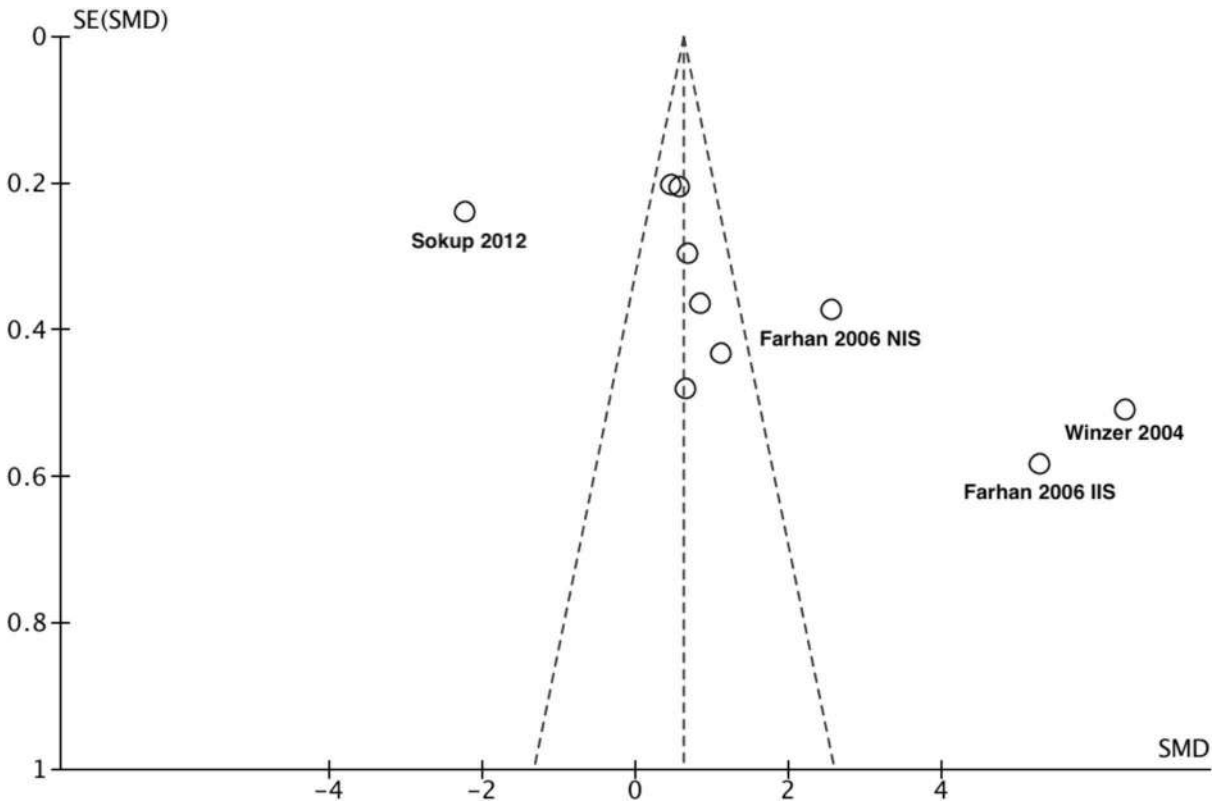

Fig. 3 Funnel plot analysis for the identification of outlier studies. SE, standard error; SMD, standardized mean difference; NIS, normal insulin resistance; IIS, impaired insulin resistance

Discussion

Summary and interpretation of findings

The present meta-analysis summarized the results of 12 studies involving 1226 pregnant women. By pooling the SMDs and 95% CIs from the individual studies, we were able to show that serum PAI-1 is associated with *p*GDM. Results of the post-outlier outcomes suggest that PAI-1 is significantly higher among participants with a previous history of GDM than those pregnant women without a history of GDM. These significant findings observed in the present study provide strong evidence of the potential effect of GDM on serum PAI-1 levels. This is supported by the homogeneity of the post-outlier results, indicating the combinability of the studies. Moreover, a high degree of significance, consistent precision of effects, and robustness

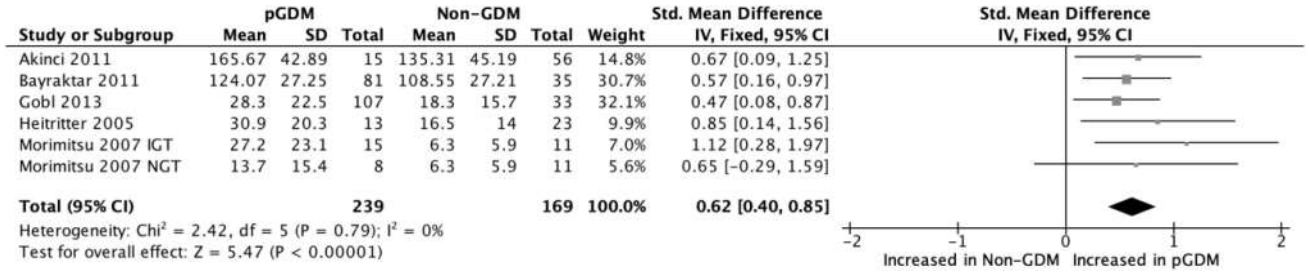

Fig. 4 Forest plot analysis of cases versus controls for the post-outlier association of PAI-1 with *p*GDM. GDM, gestational diabetes mellitus; SD, standard deviation; CI, confidence interval; df, degrees of freedom. Total = number of participants in the cohort tested

of the post-outlier outcomes enhance the evidence presented in this meta-analysis.

Effect of pregnancy on PAI-1 levels and its association with a thrombotic state

Studies have shown that thromboembolic events are common among pregnant women due to physiological and hormonal changes; a pregnant woman is four- to sixfold at risk for thrombosis compared to a non-pregnant woman [34]. To prevent postpartum bleeding, the pregnant mother adapts its homeostatic system by increasing the production of its coagulation factors like fibrinogen, factor VII, factor VIII, von Willebrand factor, and factor X [35], thereby increasing the ability of the body to form thrombi. In addition, fibrinolytic factor tissue plasminogen activator (tPA) rises throughout pregnancy [11, 36]. However, the same studies also suggest the increase of its antagonist, PAI-1, especially during the third trimester and in the puerperium. PAI-1 is the major serine protease inhibitor compared to PAI-2 and PAI-3, with approximately 60% inhibitory activity in fibrinolysis [34, 37]. This protein regulates the activation of plasminogen into plasmin by inhibiting tPA and urokinase. An increase in PAI-1 could lead to a decrease in clot breakdown, increasing the risk of deep vein thrombosis in pregnant women [38].

Hypofibrinolysis in pregnancy is mainly because of the significantly increased levels of PAI-1 from endothelial cells and PAI-2 from the placenta, which is seldom found in non-pregnant circulation. However, despite hypofibrinolysis, D-dimer increases by two- to fourfold as pregnancy progresses [34]. This is due to excessive thrombin formation brought about by increased clotting factors as manifested through increased prothrombin fragments and fibrinopeptide A, consistent with a mild degree of local intravascular coagulation in some women early in pregnancy [3]. Plasmin inhibitor (alpha 2-antiplasmin) is found to be slightly increased or unchanged during pregnancy [39]. These changes with inhibitors partly explain the higher incidence of thrombotic state during pregnancy.

Increased PAI-1 levels are found in patients with recurrent pregnancy losses (RPL), preeclampsia [40, 41], intrauterine growth restriction (IUGR), endometriosis, polycystic ovary syndrome (PCOS), and GDM [11].

Association of GDM with PAI-1 levels

Normally, the self-adaptive pregnancy mechanism of inducing a hypercoagulable state is in place to maintain the balance on hemostasis and prevent too much blood loss during delivery. However, in patients with GDM, this adaptive mechanism may shift to excessive hypercoagulability and hypofibrinolysis [16]. Plasminogen, a serine protease responsible for fibrin degradation when converted to plasmin, is activated by a tissue-plasminogen activator (tPA) and urokinase (uPA). These activators, both tPA and uPA, are inhibited primarily by PAI-1, especially during pregnancy, thus suppressing the plasmin formation and lysis of fibrin clots. Most of these inhibitors in circulation are synthesized by adipose tissue [42] and an increase in adipose tissue deposits is observed among GDM patients. This compensates for the developing fetus's increasing demand for nutrients, such as glucose [43].

Consequently, pregnant women's overall body mass index is higher than normal women's [44]. This increase is usually observed in the second and third trimesters [45], with most adipose tissue being visceral adipose tissue (VAT) in the metabolically active areas of the peritoneum [46]. Subcutaneous adipose tissue (SCAT), on the other hand, is also one of the body compartments where adipose tissue storage occurs. As this increases in size, together with VAT, it also increases the risk of developing diabetes, atherosclerosis, dyslipidemia, and metabolic syndromes in both pregnant and non-pregnant women, the latter being more affected [47]. Although VAT thickness measurement is a more sensitive predictor of GDM [48], a study conducted by Kansu-Celik et al. in 2018 reported that measuring SCAT thickness may also be a useful risk predictor of GDM during early pregnancy [49]. It has been observed that PAI-1 is overexpressed in ectopic fat, especially in macrophages. The macrophage

and adipose tissue have been shown to respond to inducers of PAI-1 synthesis, which explains an increase of PAI-1 during obesity [7]. Certain adipokines like PAI-1 have been associated with various diseases, including insulin resistance and cardiovascular disease [50]. Kaji et al. also explained that metabolic conditions like obesity and inflammation lead to adipocyte hypertrophy and impaired regulation of adipokine production.

According to the study conducted by Mehmood et al. in 2018, values of PAI-1 in patients with GDM progressively increased at more than 2-year intervals postpartum. Mothers who previously developed GDM have higher PAI-1 than those with current conditions. Another data from Morimitsu et al. [16] showed that elevated PAI-1 concentrations in the circulation are associated with women with a GDM history, especially those with impaired insulin sensitivity. They concluded that the increased concentration of this inhibitor begins between 16 and 24 weeks after delivery. Furthermore, the elevation of PAI-1 in patients with GDM also depends on abdominal obesity. They also concluded that PAI-1 levels do not decrease in women who developed type 2 diabetes mellitus after pregnancy, even if the BMI of patients has improved over time [51]. These conclusions are consistent with the results of this study, where PAI-1 is increased in patients who developed GDM earlier in time than those who have presently elapsing GDM.

Role of PAI-1 in the development of cardiometabolic complications

The risk of cardiovascular diseases (CVDs) is higher in cases of hypercoagulable states. Although usually asymptomatic, atherosclerosis-induced vascular injury could trigger platelet activation and adhesion. The formation of thrombi around damaged vessel walls is called atherothrombosis [6]. This is the leading cause of mortality among CVDs, accounting for an estimated 20% of complications from stroke [6]. As the integrity of vascular walls deteriorates over time due to various metabolic factors, these walls, which form plaques, will likely rupture [52]. Upon rupturing, tissue factor is released from these plaques and triggers the coagulation cascade, activating the extrinsic pathway [53]. These thrombi prevent sufficient blood flow, causing ischemic episodes [54]. Due to PAI-1 being an antifibrinolytic protein, numerous studies have investigated its association with CVDs. It has been shown that an increase in circulating PAI-1 also correlates with an increased risk for myocardial infarction [55], thus being a good predictor for the latter's development [56]. Because of the relation between diabetes and CVDs, an increase of PAI-1 in circulation is seen as a novel risk factor for both [57, 58] and as a potential target for therapeutic drug development [59] using PAI-1 inhibitors [60].

Limitations of the study

Interpreting these results warrants awareness of the study's limitations, such as (i) inconsistent sources of cases and controls due to the difference in the inclusion criteria used as well as the time of sample collection; (ii) failure to note the method used for serum PAI-1 analysis; (iii) failure to include other risk factors that could influence serum PAI-1 levels; and (iv) failure to include non-pregnant controls.

Conclusion

To our knowledge, this is the first meta-analysis that explored the association of serum PAI-1 with *p*GDM. Overall, our findings suggest that serum PAI-1 is significantly associated with *p*GDM. However, given the limitations of the present study, findings should be treated with caution, mainly when applied to clinical practice. Further studies regarding the relation of serum PAI-1 with other diabetes-related markers and variables should be done to understand its role in GDM. Also, population-based studies can be done to assess population variability of the results.

Author contribution All authors have contributed substantially to collecting and analyzing the data and writing and critically revising the manuscript.

Declarations

Ethics approval This article does not contain any studies with human or animal subjects.

Informed consent Not applicable.

Competing interests The authors declare no competing interests.

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