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The association between pulse wave velocity and pregnancy-associated diseases: A systematic review and meta-analysis

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ABSTRACT

Background: Maintaining healthy vascular structure and function is important for a healthy pregnancy. Obesity is a well-known predictor for poor postoperative outcomes of vascular surgery. However, the association between pulse wave velocity (PWV), a well-recognized parameter for arterial stiffness assessment, and pregnancy-associated diseases is still unclear. Therefore, we conducted this systematic review, and a meta-analysis was performed to assess the relevant associations.

Methods: We systematically searched the Web of Science and PubMed databases to obtain articles on PWV and pregnancy-associated diseases published before April 2023. The mean with standard deviation was used to assess the differences in PWV in pregnant women with or without relevant diseases. Subgroup analysis was conducted according to specific types of PWV. The Newcastle– Ottawa Scale was used to evaluate the quality of the enrolled studies.

Results: A total of 6488 individuals from 21 studies were included. All enrolled studies were highquality. Overall, the PWV was elevated in pregnant women who suffered from preeclampsia (mean difference (MD) = 0.67, 95 % confidence interval (CI): 0.51,0.83, P < 0.00001), hypertension (MD = 1.04, 95 % CI: 1.00,1.08, P < 0.00001), gestational diabetes mellitus (MD = 0.34, 95%CI: 0.19,0.48, P < 0.00001), and diabetes (MD = 0.49, 95%CI: 0.27,0.70, P < 0.00001). Subgroup analysis based on specific types of PWV showed similar results.

Conclusion: In our study, PWV is elevated in pregnancy-associated diseases, including preeclampsia, hypertension, and diabetes. The PWV assessment should be regarded as a clinical routine for pregnant women to prevent and manage cardiovascular diseases during pregnancy.

1. Introduction

With the younger onset of cardiometabolic disease and the delayed age of childbearing, the incidence of comorbidities and

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complications during pregnancy, such as pre-eclampsia and gestational diabetes, is increasing [1–5]. These complications can lead to low birth weight babies, increased maternal comorbidities, and even miscarriage and maternal death [6–9]. Maintaining healthy vascular structure and function is important for a healthy pregnancy. Arteriosclerosis is one of the manifestations of abnormal vascular status. Arteriosclerosis is associated with abnormal regulation of blood pressure, which in turn increases the risk of developing hyperemesis gravidarum and pre-eclampsia [10,11]. Arteriosclerosis is also affected by metabolic-related risk factors such as diabetes [12]. It is, therefore, necessary to analyze the link between arteriosclerosis and comorbidities and complications in pregnancy.

PWV, a non-invasive measure of arterial elasticity, represents an essential index for evaluating cardiovascular health and atherosclerosis burden in various populations [13,14]. Increased PWV values have been consistently associated with the development and progression of cardiovascular diseases, including arteriosclerosis, hypertension, and atrial fibrillation [15,16]. Nevertheless, the relationship between pre-eclampsia and PWV alterations remains unexplored, warranting further investigation to understand better the pathophysiological mechanisms involved.

PWV has been observed to be elevated to varying degrees during different gestational periods [17]. Several pregnancy-related comorbidities, including hypertension with pregnancy, gestational diabetes mellitus, and gestational hypertension, increase the risk of adverse pregnancy outcomes such as pre-eclampsia. The development of these conditions is characterized by alterations in placental blood flow resistance, abnormal endothelial cell function, and changes in blood composition, which in turn may impact vascular elasticity. However, there remains a need to clarify the specific circumstances in which pregnant women exhibit elevated PWV compared to healthy pregnant women and understand the relationship between elevated PWV and pregnancy-associated diseases. Accordingly, this study aims to investigate the association between PWV and pregnancy-associated diseases to characterize this relationship further.

2. Materials and methods

This work was executed by the Preferred Reporting Items for Systemic Reviews and Meta-analysis(PRISMA) guidelines [18]. The protocol for this systematic review was developed prospectively and registered in PROSPERO (CRD42023438243).

2.1. Literature search

We conducted a systematic literature search by searching PubMed and Web of Science in April 2023. Studies that assessed the association between PWV and pregnancy were identified through a full-text review. The following terms and their combinations were employed: "PWV," "pulse wave velocity," "pregnancy," "gestational," "preeclampsia," "gestational diabetes mellitus," "GDM," "gestational hypertension," "hypertension with pregnancy."

2.2. Selection criteria

The inclusion criteria were as follows [1]: studies that assessed the association between PWV and pregnancy-associated disease, including preeclampsia, gestational diabetes, gestational hypertension, and chronic hypertension with pregnancy-associated disease [2]; the results contained mean with the standard deviation or median with quartile of any types of PWV in pregnant women with or without diseases mentioned above.

The exclusion criteria were as follows [1]: studies that were reviews, letters, meeting abstracts, case reports, commentary, or editorials [2]; duplicate studies with overlapping data [3]; studies that reported invalid data that could not be pooled; and [4] the control population was non-pregnant women.

According to the selection criteria, the initial studies screening was based on titles and abstracts. Then, the full texts of the potential studies were assessed. An additional manual search of references from identified studies was also performed. All studies were independently screened by two reviewers (Jie Xu and Yucong Zhang). A third researcher (Yue Huang) was consulted to resolve disagreements.

2.3. Data extraction and quality assessment

Data extraction was conducted by two independent reviewers. Sample size, age, BMI, types of PWV, and types of pregnancyassociated disease were collected as baseline data.

To assess the association between PWV and pregnancy-associated disease, we extracted the results of the PWV assessment.

Two reviewers independently assessed the quality of enrolled studies by using the Newcastle–Ottawa Quality Assessment Scale (NOS)(56). A third reviewer was discussed to resolve discrepancies. Funnel plots were applied to examine the potential publication bias for comparisons that included more than 5 studies.

2.4. Data analysis

Medians with quartiles were transformed into means with standard deviations for pooled estimates by using the webpage tool in the BOX-COX manner developed by McGrath et al. [19]. RevMan 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct the meta-analysis. A random-effects model was applied for pooled analysis to achieve conservative results. Heterogeneity was tested by the chi-squared test and I² statistic. p < 0.05 or I² >50 % indicated significant heterogeneity. The overall effects were

determined by the Z test, and p < 0.05 was considered statistically significant. Subgroup analysis was performed based on specific adverse events. Subgroup analysis was conducted according to specific types of PWV.

3. Results

After removing duplicate articles, 443 articles were identified in the initial database search. After screening titles and abstracts, 47 articles remained for further full-text evaluation. Finally, 21 articles were included in the meta-analysis [20–40] (see Fig. 1). Supplementary Table 1 summarizes the basic information and patient baseline characteristics of these studies. Supplementary Table 2 summarizes the quality assessment of articles included by the Newcastle-Ottawa Scale.

3.1. Differences in PWV in pregnant women with or without preeclampsia

Ten cross-sectional studies assessed PWV at the time of preeclampsia [20–28,38]. The pooled results showed that the PWV (mean difference (MD) = 0.67, 95 % confidence interval (CI): 0.51,0.83, P < 0.00001) was significantly higher in women with preeclampsia than those without preeclampsia. However, Nienke et al. [27] did not find a significant association between cfPWV and preeclampsia development (see Fig. 2). In the subgroup analyses, both cfPWV and apPWV increased significantly, similar to the overall results. Publication bias was assessed by a funnel plot (Supplementary Fig. 1), which indicated moderate publication bias.

3.2. Differences in PWV in pregnancies with or without hypertension

Three studies reported the PWV in pregnancies with hypertension [21,37,40]. The PWV (MD = 1.04, 95 % CI: 1.00,1.08, P < 0.00001) was elevated in pregnancies with hypertension, including hcPWV and APWV (see Fig. 3).

3.3. Differences in PWV in pregnancies with or without gestational diabetes mellitus (GDM)

Seven studies reported PWV in pregnancies with GDM(29,30,30,33–35,39). The pooled results showed that PWV (MD = 0.34, 95%

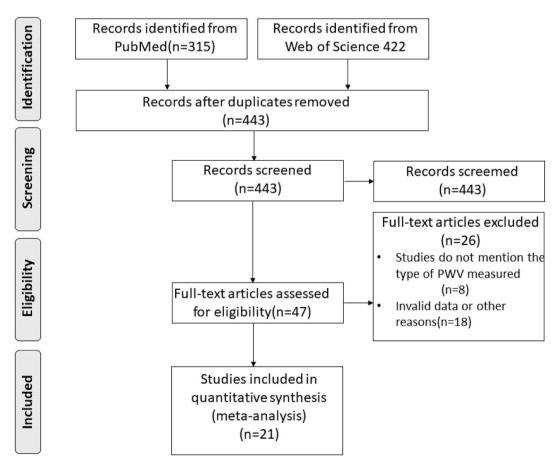
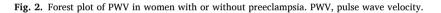


Fig. 1. Preferred reporting items for systemic reviews and meta-analysis flow diagram of literature screening.

	Preeclampsia wild pregnancy				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
1.1.1 cfPWV									
Charlotte 2020 Quebec, Canada	7.1	1.1	12	6	0.7	12	4.7%	1.10 [0.36, 1.84]	
Christos 2022 Thessaloniki Greece	6.3	2.14	46	5.5	0.46	46	6.4%	0.80 [0.17, 1.43]	
Dominique 2017 Antwerp, Belgium	7.66	0.93	14	6.03	0.78	14	6.3%	1.63 [0.99, 2.27]	
MAXIMILIAN B 2013 Vienna, Austria	8.1	0.7	11	7.3	1.5	10	2.5%	0.80 [-0.22, 1.82]	<u>+</u>
Nienke 2018 Rotterdam, The Netherlands	7.6	1.1	89	7.6	1.1	4556	47.8%	0.00 [-0.23, 0.23]	•
Virginia 2020 Iowa City	5.9	1.1	18	5	0.8	121	9.1%	0.90 [0.37, 1.43]	
Witvrouwen 2021 Belgium	7.52	0.77	24	6	0.7	30	16.1%	1.52 [1.12, 1.92]	+
Subtotal (95% CI)			214			4789	92.8%	0.59 [0.43, 0.76]	•
Heterogeneity: $Chi^2 = 60.21$, df = 6 (P < 0.00	001); l ² :	= 90%							
Test for overall effect: Z = 7.04 (P < 0.00001))								
1.1.2 APWV									
Irene 2014 Chios, Greece	10.2	1.9	21	7.2	1.1	97	3.6%	3.00 [2.16, 3.84]	
Tihtonen 2006 Tampere, Finland	13.8	3.9	20	9.6	1	29	0.8%	4.20 [2.45, 5.95]	
Subtotal (95% CI)			41			126	4.4%	3.23 [2.47, 3.98]	•
Heterogeneity: $Chi^{2} = 1.47$, $df = 1$ (P = 0.23);	I ² = 329	6							
1.1.3 crPWV									
Torrado 2012 Montevideo Uruquay	6	0.7	7	6.9	1.5	13	2.7%	-0.90 [-1.87, 0.07]	
Subtotal (95% CI)			7			13	2.7%	-0.90 [-1.87, 0.07]	•
Total (95% CI)			262			4928	100.0%	0.67 [0.51. 0.83]	•
	0001) P	² = 929							
		527	~						
			0001)	P - 96 3	96				Favours [HP] Favours [PE]
Heterogeneity: Chi [#] = 1.47, df = 1 (P = 0.23); Test for overall effect: Z = 8.34 (P < 0.00001) 1.1.3 crPWV Torrado 2012 Montevideo Uruguay) 6 0001); P)	0.7 *= 929	7 7 262	6.9 ř = 96.3	1.5	13 13	2.7% 2.7%	-0.90 [-1.87, 0.07]	-4 -2 0 2 4 Favours (HP) Favours (PE)



<u>an SD</u> 7.1 1.28	Total 20 20	Mean 5.3	SD 1.11	Total 447 447	Ueight 0.5% 0.5%	IV, Fixed, 95% Cl 1.80 [1.23, 2.37]	IV, Fixed, 95% Cl
7.1 1.28		5.3	1.11				
7.1 1.28		5.3	1.11				
	20			447	0.5%		
					0.3%	1.80 [1.23, 2.37]	
74 0.08	50	6.7	0.12	50	99.4%	1.04 [1.00, 1.08]	
	50			50	99.4%	1.04 [1.00, 1.08]	T
)							
29 2.8	38	6.25	3.23	95	0.1%	0.04 [-1.06, 1.14]	
	38			95	0.1%	0.04 [-1.06, 1.14]	
	108			592	100.0%	1.04 [1.00, 1.08]	
I ² = 80%						-	<u> </u>
							-2 -1 0 1 2
	07), I ² = 7	9.9%					Favours [control] Favours [HTN]
) 29 2.8 ; I [#] = 80%	50 29 2.8 38 38 108) ≠= 80%	50 29 2.8 38 6.25 38 108 ; I [#] = 80%	50 29 2.8 38 6.25 3.23 38 108	50 50 29 2.8 38 6.25 3.23 95 38 95 108 592 1 [#] = 80%	50 50 99.4%) 29 2.8 38 6.25 3.23 95 0.1% 38 95 0.1% 108 592 100.0%	50 50 99.4% 1.04 [1.00, 1.08] 29 2.8 38 6.25 3.23 95 0.1% 0.04 [-1.06, 1.14] 38 95 0.1% 0.04 [-1.06, 1.14] 108 592 100.0% 1.04 [-1.00, 1.08] ^p = 80%

Fig. 3. Forest plot of PWV in pregnancies with or Without hypertension. PWV, pulse wave velocity; HTN, hypertension.

CI: 0.19,0.48, P < 0.00001) was significantly increased in pregnant women with GDM than those without, including cfPWV and carotid-finger PWV, but not apPWV. However, two studies did not show a significant association between aortic PWV and the incidence of GDM (see Fig. 4). Publication bias was assessed by a funnel plot (Fig. S2), which indicated moderate publication bias.

3.4. Differences in PWV in pregnancies with or without diabetes

The pooled results showed that PWV (MD = 0.49, 95%CI: 0.27,0.70, P < 0.00001) was significantly higher in pregnant women with diabetes than those without diabetes, including cfPWV and hcPWV. The heterogeneity was significant (p = 0.007) among the included studies (see Fig. 5).

4. Discussion

PWV is the gold standard for assessing the degree of arteriosclerosis and evaluating the risk of cardiovascular disease (CVD)

		GDM		uncomplie	cated pregr	ancy		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
3.1.1 cfPWV									
Konstantina 2017Greece	5.51		13	5.25	0.72	16	6.0%	0.26 [-0.34, 0.86]	
Makrina 2010 United Kingdom	6		34	5.4	0.6	34	7.3%	0.60 [0.06, 1.14]	
Tiina Vilmi-Kerälä 2017 Finland	6.44	0.83	120	6.17	0.74	120	54.4%	0.27 [0.07, 0.47]	
Subtotal (95% CI)			167			170	67.7%	0.30 [0.13, 0.48]	•
Heterogeneity: Chi ² = 1.27, df = 2 (P		² = 0%	6						
Test for overall effect: Z = 3.35 (P = 0	1.0008)								
3.1.2 APWV									
Bulzico 2021 Rio deJaneiro, Brazil	7.2	0.9	24	7.3	1.2	27	6.4%	-0.10 [-0.68, 0.48]	
Evandelia 2018 Greece	5.5		21	5.1	0.7	16		0.40 [-0.12, 0.92]	
Subtotal (95% CI)	0.0	0.0	45	9.1	0.7	43		0.18 [-0.21, 0.56]	-
Heterogeneity: Chi ² = 1.60, df = 1 (P	= 0.21)	P = 37						on of our if or of	-
Test for overall effect: Z = 0.91 (P = 0		1 - 01							
	,								
3.1.3 carotid-finger PWV									
Privanka 2017 New Delhi, India	7.47	0.8	20	6.7	1.28	20	4.9%	0.77 (0.11, 1.43)	
Subtotal (95% CI)			20			20	4.9%	0.77 [0.11, 1.43]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.28 (P = 0	1.02)								
3.1.4 upper limb PWV									
Davenport 2011 Canada	8.46	0.52	10	7.93	0.41	10	12.8%	0.53 [0.12, 0.94]	
Subtotal (95% CI)			10			10	12.8%	0.53 [0.12, 0.94]	-
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.53 (P = 0	1.01)								
			240			242	400.00	0.04 10 40 0 103	
Total (95% CI)	0.445	17 0.0	242			243	100.0%	0.34 [0.19, 0.48]	
Heterogeneity: Chi ² = 6.15, df = 6 (P			þ						-2 -1 0 1 2
Test for overall effect: Z = 4.51 (P < 0				17 0.000					Favours [control] Favours [GDM]
Test for subaroup differences: Chi ² :	= 3.27. d	IT = 3 (F	r = 0.35), i* = 8.3%					

Fig. 4. Forest plot of PWV in Pregnancies with or Without GDM. PWV, pulse wave velocity; GDM, gestational diabetes mellitus.

	pregnancy	/ with diab	etes	uncomplica	ated pregr	ancy		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
4.1.1 cfPWV									
Anderson 2009 London, UK	6.8	1.2	34	5.6	1	34	16.6%	1.20 [0.67, 1.73]	
Makrina 2010 United Kingdom	5.7	1.1	37	5.6	0.9	37	21.8%	0.10 [-0.36, 0.56]	- - -
Subtotal (95% CI)			71			71	38.4%	0.58 [0.23, 0.92]	◆
Heterogeneity: Chi ² = 9.58, df = 1 (F	^o = 0.002); l ² :	= 90%							
Test for overall effect: Z = 3.27 (P =	0.001)								
4.1.2 heart-carotid PWV									
Kathrin 2020 Münster, Germany	5.73	0.99	59	5.3	1.11	447	61.6%	0.43 [0.16, 0.70]	
Subtotal (95% CI)			59			447	61.6%	0.43 [0.16, 0.70]	•
Heterogeneity: Not applicable									
Test for overall effect: $Z = 3.09$ (P =	0.002)								
Total (95% CI)			130			518	100.0%	0.49 [0.27, 0.70]	◆
Heterogeneity: Chi ² = 9.99, df = 2 (F	P = 0.007); P	= 80%							
Test for overall effect: Z = 4.45 (P <									-4 -2 0 2 4
Test for subaroup differences: Chi ²		1 (P = 0.52	2), I ² = 0%						Favours [control] Favours [diabetes]

Fig. 5. Forest plot of PWV in Pregnancies with or without Diabetes. PWV, pulse wave velocity.

occurrence. Our findings demonstrated that pregnant women with a history of pre-eclampsia exhibited elevated PWV, as do those with other pregnancy complications, which were consistent with previous studies evaluating endothelial function. These studies have reported decreased flow-mediated dilation in the brachial or radial arteries of women with pre-eclampsia, indicating endothelial dysfunction [41–43]. However, the causal relationship between changes in PWV and the development of pre-eclampsia remains unclear.

Preeclampsia is a multisystem disorder specific to pregnancy, characterized by hypertension and proteinuria [44]. It is considered one of the most prevalent pregnancy complications worldwide, contributing to maternal morbidity and mortality rates and preterm neonatal delivery [45,46]. Furthermore, accumulating evidence has highlighted a significant association between pre-eclampsia and increased long-term risks of cardiovascular disease. The pathophysiology underlying pre-eclampsia remains incompletely understood. However, current research suggests that an intricate interplay between dysregulation of the renin-angiotensin-aldosterone system, endothelial dysfunction, and alterations in hemostasis and blood composition contributes to disease development. Notably, placental abnormalities, including inadequate trophoblast invasion and the formation of a shallow, defective spiral artery, lead to impaired uteroplacental blood flow, oxidative stress, and systemic inflammation.

Gestation with hypertension was also associated with a significant elevation in PWV compared to normal pregnancies, as reported by prior research. This elevation may be attributed to arterial remodeling and thickening resulting from vascular injury and the inflammatory response of hypertension [47]. Furthermore, hypertension during pregnancy often leads to alterations in various pathophysiological parameters, such as increased blood volume, cardiac output, and peripheral vascular resistance, which may contribute to elevated PWV. These changes further increase the risk of cardiovascular disease and adversely affect maternal and fetal health.

Our meta-analysis found that gestational diabetes mellitus (GDM) similarly elevated PWV in pregnant women. To the best of our knowledge, this is the first meta-analysis reporting the effect of GDM on arterial stiffness during pregnancy. The elevation in PWV was more pronounced in peripheral arteries compared to the aorta, potentially due to a slower peripheral vascular blood flow leading to a more pronounced persistent hyperglycemic state. This hyperglycemic state induces an inflammatory response and impairs endothelial function, ultimately resulting in vascular sclerosis [48–50]. Additionally, it has been established that women with GDM have a significantly higher risk of developing pre-eclampsia, which may explain why GDM is associated with adverse pregnancy outcomes. The role of PWV in the development of pre-eclampsia in patients with gestational diabetes should be investigated in the future.

Furthermore, pregnant women with pre-existing diabetes mellitus also exhibited elevated PWV compared to normal pregnancies, although the magnitude of this change was less pronounced than in women with GDM. This difference may be attributed to the altered hormone levels and blood flow in pregnant women with diabetes mellitus. Although insufficient evidence currently supports an increased risk of pre-eclampsia in women with diabetes mellitus during pregnancy, the presence of common factors contributing to vascular stiffness in such patients cannot be ignored.

The current studies regarding PWV and pregnancy were cross-sectional studies; cohort studies should be conducted to provide longitudinal evidence further to confirm the association between complicated pregnancy and PWV. In addition, future studies should identify appropriate kinds of PWV for predicting the risk of cardiovascular diseases. The PWV change before pregnancy, during pregnancy, and after delivery should be analyzed, especially for different stages of conception. The PWV examination should be regarded as a clinical routine before pregnancy, which may be beneficial for preventing and managing cardiovascular diseases during pregnancy. Moreover, it is of great significance to investigate the role of pregnancy in the development of cardiovascular diseases for arteriosclerosis women, which requires much longer follow-up and comparison with women without a history of pregnancy. In-time and effective management strategy should be established for pregnant women with arteriosclerosis to prevent further cardiovascular diseases.

5. Limitation

Some limitations of the current study should be noted. All included studies were cross-sectional evidence, which could not confirm the causal relationship between elevated PWV and complications in pregnancy. Second, the types of PWV varied among the included studies, although we conducted relevant subgroup analysis.

6. Conclusion

In our study, PWV is elevated in pregnancy-associated diseases, including preeclampsia, hypertension, and diabetes. The PWV assessment should be regarded as a clinical routine for pregnant women to prevent and managing cardiovascular diseases during pregnancy.

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CRediT authorship contribution statement

Jie Xu: Writing – original draft, Formal Analysis, Investigation. Yucong Zhang: Writing – original draft, Formal Analysis, Investigation. Yue Huang: Formal Analysis, Investigation, Validation. Hao Nie: Formal Analysis, Investigation, Visualization. Jinhua Yan: Writing – review & editing. Lei Ruan: Supervision, Project administration. Cuntai Zhang: Conceptualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29281.

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