Relationship between Periodontitis and Pre-Eclampsia: A Meta-Analysis

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Abstract

**Background:** Studies have suggested controversial results regarding a possible association between pre-eclampsia (PE) and periodontal disease (PD) and no meta-analysis has been performed to clarify this issue.

**Methods:** A literature search of electronic databases was performed for articles published through March 24, 2013, followed by a manual search of several dental and medical journals. The meta-analysis was conducted according to the recommendations of the Cochrane Collaboration and PRISMA. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Heterogeneity was assessed with the $\chi^2$-based Cochran $Q$ test and I$^2$ statistic. The level of significance was set at $P<0.05$.

**Results:** Fifteen studies were included, including three cohort and 12 case-control studies. A positive association was found between PE and PD (OR 2.17, 95% CI 1.38–3.41, $P=0.0008$). However, a high and significant heterogeneity was found ($\chi^2=62.42, P<0.00001, I^2=75\%$). In most cases, subgroup analysis had low power to detect significant differences between PE and non-PE groups.

**Conclusion:** Based on the findings of the meta-analysis, PD appears to be a possible risk factor for PE. However, given the important differences in the definitions and diagnoses of PD and PE among the studies, as well as their lack of good methodological quality, future trials are needed to confirm the results of the present meta-analysis.

Introduction

Infection and inflammation continue to be at the forefront of etiologic theories as causative factors of adverse pregnancy outcomes, such as stillbirth and growth restriction, that affect many women each year. Previous studies have demonstrated a link between infection or inflammation and preterm birth, preeclampsia (PE), and other adverse outcomes thought to be secondary to poor placentation [1–4]. The prevalence of PE, a multisystem disorder of unclear etiology that is exclusive to human pregnancy, ranges from 2% to 7% in developed countries. PE results in high maternal and neonatal morbidity and mortality rates, attributable to complications affecting different organs and systems. In emerging countries, the prevalence of PE is more than 10% [4], and the condition is the main cause of maternal death [5].

PE occurs usually after 20 weeks of gestation. It is characterized by an abnormal vascular response to placentation, manifesting as generalized vasospasm, activation of the coagulation system, and reduced organ perfusion affecting the kidney, liver, and brain [4]. Two syndromes are included in the definition of PE: maternal, characterized by endothelial cell activation, perturbations in volume and blood pressure control, gradual maternal blood pressure elevation, proteinuria, and generalized edema; and fetal, manifested primarily by intrauterine growth restriction [6–8]. Putative PE risk factors include advanced maternal age, multifetal pregnancies, maternal prepregnancy obesity, pregestational hypertension, renal disorders, and diabetes mellitus [9–12]. In recent years, infection has been reported to be important in the pathogenesis of PE, both in terms of its initiation and its potentiation [7,8,13].

Several studies have suggested that periodontal disease (PD), a chronic inflammatory oral infection, may be associated with an increased risk for PE development [14–19]. PD affects 20% to 50% of pregnant women, especially economically disadvantaged women [20,21]. In this inflammatory pathology, the dental plaque – which is a biofilm predominated by Gram-negative anaerobic microorganisms – destroys the tooth-supporting tissues. Oral microorganisms initiate PD, but the periodontal breakdown is primarily mediated by the host inflammatory response [22,23]. PD may burden pregnant women systemically with endotoxins, inflammatory cytokines, and oxidative stressors at the maternal-fetal interface [17]. Thus, PD may be a vascular stressor that plays a role in the development of PE in pregnant women.

Contradictory findings exist regarding the relationship between PD and PE [15,24–26], and a previous systematic review did not clarify this possible association [27]. Therefore, there is a need for a systemic assessment of the literature on the possible association between PD and PE. The aim of the present systematic review and
meta-analysis was to assess the scientific evidence on the possible association between PD and PE.

**Materials and Methods**

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis [28] (PRISMA) guidelines.

**Search**

The following databases were searched from their earliest records through March 24, 2013: MEDLINE, Cochrane Controlled Clinical Trial Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CINAHL, Science Direct, ISI Web of Knowledge, and SCOPUS. The following search algorithm was used to explore databases, by using Boolean operators and the asterisk symbol (*) as truncation: (“Periodontitis”[Mesh] OR “Chronic Periodontitis”[Mesh] OR “Periodontal Diseases”[Mesh] OR “Periodontal Pocket”[Mesh] OR “Periodontal Attachment Loss”[Mesh] OR “Tooth Mobility”[Mesh] OR periodontitis OR periodontal disease* OR periodontal pocket* OR attachment loss OR alveolar bone loss OR pocket depth OR clinical attachment level AND (“Pre-Eclampsia”[Mesh] OR “Eclampsia”[Mesh] OR “Hypertension, Pregnancy-Induced”[Mesh] OR preeclampsia OR pre-eclampsia OR eclampsia OR gestosis OR pregnancy hypertension OR pregnancy hypertensive). In the CINAHL, SCOPUS, ISI Web of Knowledge, and Science Direct databases, the MeSH terms were not used.

In addition, a manual search was performed of issues of the last 15 years of the following journals: *Journal of Periodontology, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal*
Table 1. List of excluded studies and reasons for exclusion.

| Study              | Year of publication | Criteria for exclusion | Type of study         |
|--------------------|---------------------|------------------------|----------------------|
| Swati et al. [35]  | 2012                | A.2                    | Case-control study   |
| Abati et al. [45]  | 2012                | B.3                    | Case-control study   |
| Boggess et al. [36]| 2012                | A.3                    | Cross-sectional study|
| Cetin et al. [37]  | 2012                | A.1                    | Review               |
| Hiroto et al. [46] | 2012                | B.5                    | Case-control study   |
| Piscoya et al. [38]| 2012                | A.3                    | Case-control study   |
| Swati et al. [47]  | 2012                | A.2                    | Case-control study   |
| Lopez-Jaramillo et al. [39]| 2011            | A.1                    | Comment              |
| Sayar et al. [48]  | 2011                | B.2                    | Case-control study   |
| Matevosyan [40]    | 2011                | A.1                    | Meta-analysis        |
| Kunnen et al. [27] | 2010                | A.1                    | Systematic review    |
| Horton et al. [49] | 2010                | B.4                    | Cohort study         |
| Nabet et al. [50]  | 2010                | B.5                    | Case-control         |
| Vergnes [41]       | 2008                | A.1                    | Systematic review    |
| Ruma et al. [51]   | 2008                | B.4                    | Cohort study         |
| Conde-Agudelo et al. [42]| 2008            | A.1                    | Systematic review    |
| Dasanayake [43]    | 2007                | A.1                    | Comment              |
| Canacki et al. [52]| 2007                | B.4                    | Case-control         |
| Cota et al. [53]   | 2006                | B.4                    | Case-control         |
| Khader et al. [54] | 2006                | B.3                    | Meta-analysis        |
| Castaldi et al. [55]| 2006              | B.5                    | Cross-sectional study|
| Boggess et al. [56]| 2006                | B.4                    | Cross-sectional study|
| Meurman et al. [57]| 2006                | B.2                    | Retrospective study  |
| Contreras et al. [58]| 2006              | B.2                    | Case-control study   |
| Xiong et al. [21]  | 2006                | A.1                    | Systematic review    |
| Gettinger-Barak et al. [59]| 2005          | B.2                    | Case-control study   |

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Study Selection

Screening was performed independently by two blinded reviewers (FS and MS). Interreviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.61 [29,30]. In case of disagreement on the inclusion or the exclusion of studies, this issue was discussed until consensus was reached by the reviewers who selected the studies (FS and MS).

Eligibility Criteria

The study selection process was performed by two blinded reviewers (RG and AM) in two phases. In the first phase, the studies were analyzed according to the following inclusion criteria (A): 1) cross-sectional, prospective cohort or case-control studies, 2) studies analyzing the association between PD and PE, 3) PD defined by clinical or radiographic parameters, 4) studies reporting clear definition of PD and PE, and 5) studies conducted on adult human subjects (age >18 years). Only studies that met all inclusion criteria in (A) were admitted to the second phase, which consisted of the analysis of the preselected studies according to the following exclusion criteria (B): 1) studies including patients with systemic disease, 2) studies that did not report adjustment for known confounder factors, 3) studies not reporting adequate data, 4) ancillary or duplicate studies, and 5) no outcome of interest.

Data Extraction

Data were collected by two independent reviewers (FS and RG). The following data were extracted from the included studies: year of publication, country, study design, demographic characteristics of participants, definition of PE and PD, and main findings. If data were presented both numerically (in tables or text) and graphically (in figures), only numeric data were considered for extraction. The reviewers cross-checked all extracted data. Disagreements were resolved by discussion until consensus was reached.

Risk of Bias

Assessment of risk of bias was performed according to the Newcastle-Ottawa Scale by two independent reviewers (FS and AP). The level of agreement between reviewers was 0.76.
| Author, Year | Design | Country (Race/ethnicity) | Population | Age (y) | Definition of PE | Definition of PD | Findings |
|--------------|--------|--------------------------|------------|---------|------------------|----------------|----------|
| Canakci, 2007 | C/C | Erzurum, Turkey | 20 Mild PE, 18 Severe PE, 21 Control | Mild PE: 24.1±3.9; Severe PE: 23.6±4.2; Control: 24.7±4.5 | BP > 140/90 mmHg and PU (300 mg/24h US) | BOP and ≥4 mm PPD on 1–15 sites (Mild PD) or ≥15 sites (Severe PD) | There was a significant association between mild to severe PE and severe PD. |
| Chaparro, 2012 | C/C | Santiago, Chile | 11 PE, 43 Control | PE: 28.91±6.11; Control: 27.19±7.18 | BP > 140/90 mmHg and PU (300 mg/24h US) | ≥4 teeth w/ ≥1 sites w/PPD ≥4 mm and CAL ≥3 and BOP | Increased IL-6 levels in GCF (OR = 1.06, P = 0.02, CI 95% 1.007–1.117) in early pregnancy were associated with increased PE risk. |
| Ha, 2011 | C/C | Seoul, Korea | 16 PE, 48 Control | PE: 32.69±5.30 (21–40); Control: 32.69±4.40 (21–40) | BP > 140/90 mmHg on 2 occasions and 1+ or more PU on a random US | CAL ≥3.5 mm on 2–3 sites (Localized PD) or on ≥4 sites (Generalized PD) of different teeth | PE could be associated with maternal PD. |
| Wang, 2012 | C/C | Niigata, Japan (Japanese) | 13 PE, 106 Control | - | BP > 140/90 mmHg on 2 occasions after 20 GW and PU ≥300 mg/d after 20 GW | >60% of sites with CAL ≥3 mm | Polymorphism and subgingival DNA level of A. actinomycetemcomitans were significantly associated with PE, independent of PD. |
| Srinivas, 2009 | Co | Philadelphia, PA, USA (AA) | 876 Patients | - | >140/90 mmHg with PU | CAL ≥3 mm on ≥3 teeth | No significant association was found between PD and PE. |
| Siqueira, 2008 | C/C | Belo Horizonte (Multiethnic) | 164 PE, 1042 Control | - | SBP > 140 or DBP > 90 mmHg on 2 occasions after 20 GW and 1+ or more PU | ≥4 mm and CAL ≥3 mm at the same site in ≥4 teeth | Maternal PD was observed to be a risk factor associated with PE. |
| Boggess, 2003 | Co | NC, USA (Multiethnic) | 39 PE, 763 Control | - | SBP > 140 or DBP > 90 mmHg on 2 occasions and 1+ or more PU | PPD ≥4 mm on 1–15 teeth or BOP+ (Mild PD) PPD ≥4 mm on ≥15 teeth (Severe PD) | Severe PD at delivery was associated with increased PE risk (adj OR 2.4, 95% CI 1.1–5.3). |
| Da Silva, 2012 | C/C | Recife, Brazil | 284 PE, 290 Control | - | SBP > 140 or DBP > 90 mmHg and PU ≥300 mg/24h or 2+ PU on dipsticks, developed after 20 GW | ≥4 teeth with ≥1 sites with PPD ≥4 mm and AL ≥3 mm in the same site | PD could be a risk factor for PE. |
| Shetty, 2010 | C/C | 30 PE, 100 Control | - | SBP > 140 or DBP > 90 mmHg on ≥2 occasions 4h apart and 1+ or more PU by dipstick on random US | CAL ≥3 mm and PPD ≥4 mm | PD at enrollment (OR = 5.78, 95% CI 2.41–13.89) and w/i 48h of delivery (OR = 20.15, 95% CI 4.55–89.29) may be associated with increased PE risk. |
| Taghzouti, 2012 | C/C | Quebec, Canada (Multiethnic) | 92 PE, 245 Control | - | SBP > 140 or DBP > 90 mmHg and 1+ or more PU | ≥4 sites with PPD ≥5 mm and CAL ≥3 mm at the same sites | PD was not associated with PE (adj OR = 1.13, 95% CI = 0.59 to 2.17). |
| Kumar, 2012 | Co | New Delhi | 35 PE, 305 Control | PE: 22.32±2.75; Control: 22.32±2.79 | SBP > 140 or DBP > 90 mmHg and PU ≥300 mg/24h or 2+ PU on dipsticks, developed after 20 GW | CAL and PPD ≥4 mm in ≥1 sites | PD was significantly associated with PE. |
| Canakci, 2004 | C/C | Erzurum, Turkey (Turkish) | 41 PE, 41 Control | PE: 25.9±5.9; Control: 25.8±5.8 | SBP ≥140 or DBP ≥90 mmHg and PU ≥300 mg/24h or 2+ PU on dipsticks, on 2 occasions ≥6h apart if 24h US is unavailable | ≥ 4 teeth with ≥1 sites with PPD ≥4 mm and BOP+ and CAL ≥3 mm at the same site | No. of sites with PD ≥4 mm and CAL ≥3 mm was higher among PE patients than among controls (P<0.01). |
### Table 2. Cont.

| Author, Year           | Country (Race/ethnicity) | Population | Age (y) | Definition of PE                                                                 | Definition of PD                                                                 | Findings                                                                 |
|------------------------|--------------------------|------------|---------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Lohsoonthorn, 2009     | Bangkok, Thailand         | 150 PE, 150 | -       | $SBP \geq 140$ or $DBP \geq 90$ mmHg and $PU$                                       | $1$ teeth (Mild PD) or $2$ nonadjacent teeth (Moderate PD) or $3$ teeth (Severe PD) | Severe clinical PD was not associated with an increased risk of PE (adj OR $= 0.009$). |
|                        |                          | Control    | 30 mg/dl | $BOP$ and PPD $\geq 3$ mm and CAL $\geq 5$ mm with $4$ random specimens collected apart. |                                                                               |                                                                                                                                      |
| Kunnen, 2007           | Groningen, The Netherlands (Caucasian) | 17 PE, 35 | 29.5 $6$ | $SBP \geq 140$ or $DBP \geq 90$ mmHg on $2$ occasions and $PU$                   | BOP and PPD $\geq 4$ mm and CAL $\geq 4$ mm on $1$ – $15$ sites with $PE$ (Mild PD) | Severe PD was found in $82\%$ of the PE patients and $37\%$ of the control group. There was an association between PD and PE (adj OR $= 3.73$, 95% CI $= 1.32–10.58$). |
|                        |                          | Control    | 31.7 $5.37$ | 30 mg/dl (or $1$ + on a urine dipstick) on $2$ random specimens collected within $4$h apart. |                                                                               |                                                                                                                                      |
| Politano, 2011         | Sao Paulo, Brazil         | 58 PE, 58  | 28.62 $6.93$; $SBP \geq 140$ or $DBP \geq 90$ mmHg after $20$ – $2$ sites with PPD $\geq 4$ mm and CAL $\geq 4$ mm with $BOP$ |                                                                               | There was an association between PD and PE (adj OR $= 3.73$, 95% CI $= 1.32–10.58$). |
|                        |                          | Control    | 26.62 $5.37$ | 300 mg GW and $PU$                                                               |                                                                               |                                                                                                                                      |

**Legend:** C/C, case-control study; Co, cohort study; AA, African-American; GW, gestational weeks; adj, adjusted; US, urine specimen; PD, periodontal disease; PE, pre-eclampsia; PU, proteinuria; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCF, gingival crevicular fluid.

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**Quantitative Analysis**

**Measure of effect size.** Data were combined for meta-analysis with a statistical software (RevMan, Version 5, 2008, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). For dichotomous data, the odds ratio (OR) and 95% confidence interval (CI) were calculated. Due to the expected interstudy heterogeneity, a random effect model was used. The pooled effect was considered significant if $P$ was $< 0.05$. Forest plots for each meta-analysis present the raw data, OR (displayed as blocks), and CIs (displayed as lines) for the chosen effect, the heterogeneity statistic ($I^2$), total number of participants per group, and overall OR in the random effect model.

**Subgroup analysis.** Subgroup analysis was performed according to the type of study (cohort or case-control study), severity of PD (mild, moderate, or severe), definition of PD (defined by probing pocket depth [PPD] and/or clinical attachment level [CAL]) and security of PD diagnosis (defined according to the criteria suggested by Nibali et al. 2013 [31]).

**Heterogeneity.** Heterogeneity was assessed by the $\chi^2$-based Q-statistic method and I² measurement, with significance indicated by $P<0.1$.

**Publication bias.** The publication bias was investigated by two methods. Visual detection was used to analyze the funnel plots [32]. Quantitative analysis was performed by the regression asymmetry test [33] and the trim-and-fill method [34]. Publication bias was assessed with an additional statistical software (Stata IC version 10.1, StataCorp, College Station, Texas).

### Results

**Search Results**

A total of 348 articles were found through the electronic and manual searches. After removing duplicates, 275 articles were found (inter-reviewer agreement, $\kappa = 0.78$), including 84 in MEDLINE, 4 in Cochrane Controlled Clinical Trial Register, 69 in CINHAL, 55 in Science Direct, 9 in Scopus, and 55 in ISI Web of Knowledge. Then, 234 papers were excluded on the basis of the evaluation of the title and abstract, leaving 41 articles to be assessed for eligibility ($\kappa = 0.84$). Of these, 11 articles were excluded in the first phase of the selection process, for not satisfying one or more inclusion criteria ($\kappa = 1$) [19,35–44]. Fifteen of the remaining 30 [45–59] articles were further excluded ($\kappa = 1$). Finally, 15 studies [14,15,19,24–26,60–68] qualified for inclusion in the systematic review and meta-analysis ($\kappa = 1$). The list of the excluded studies and their reasons for exclusion are provided in Table 1. A PRISMA flowchart is provided in Figure 1.

**Description of Included Studies**

The main characteristics of the included studies are described in Table 2. Three of 15 included studies were cohort studies, whereas the remaining 12 were case-control studies. The definitions of PE and PD varied greatly among the included studies. The sample size varied from 54 patients in the study of Chaparro et al. [60] to 1206 in the study of Siqueira et al. [67]. Three studies [24,26,66] did not find a positive association between PD and PE, whereas the remaining studies reported a significant association.

**Quality Analysis**

None of the included studies reached the maximum score of the Newcastle Ottawa Scale (Table 3). Only two studies [63,64] gained the maximum score in the Selection outcome; nine studies [15,19,24,25,26,52,63,64,65] had the maximum score in the Comparability outcome; and all studies had a partial score in the Exposure outcome.
Results of the Meta-analysis

The results of the meta-analysis showed that an increased risk for PE was present for patients with PD (OR 2.17, 95% CI 1.38–3.41, \(P = 0.0008\); Figure 2); however, a high and significant heterogeneity was found \((\chi^2 = 62.42, P < 0.00001; I^2 = 75\%)\).

Subgroup analysis. An analysis of the results according to study type (Figure 3) revealed an increased risk of PE in PD patients in the case-control (OR 2.16, 95% CI 1.29–3.63, \(P = 0.004\)) and in the cohort studies (OR 2.20, 95% CI 0.66–7.36, \(P = 0.20\)). However, this increased risk only remained significant in the case-control subgroup. Heterogeneity was significant in both subgroups \((\chi^2 = 44.57, P < 0.00001, I^2 = 75\% \text{ for case-control, and } \chi^2 = 18.21, P = 0.0001, I^2 = 89\% \text{ for cohort studies})\).

When the meta-analysis results were analyzed according to the definition of PD, an increased risk of PE was observed in all subgroups (Figure 4). However, it was significant only in the subgroup in which PD was defined by PPD and CAL \((\chi^2 = 36.55, P < 0.0001, I^2 = 75\%)\) and by CAL alone \((\chi^2 = 11.26, P = 0.004; I^2 = 82\%)\), but not for those in which PD was defined by PPD alone \((\chi^2 = 0.16, P = 0.69; I^2 = 0\%)\).

When the results were analyzed according to PD severity, no significant risk was observed for mild PD or for severe PD (Figure 5). Heterogeneity was high in the subgroup with mild PD \((\chi^2 = 11.28, P = 0.01; I^2 = 73\%)\) and moderate in the subgroup...
with severe PD ($\chi^2 = 4.73, P = 0.09; I^2 = 58\%$). The analysis of results stratified according to the security of PD diagnosis showed that a higher risk of PE was present in both subgroups (Figure 6), but it was significant only in the subgroup with insecure diagnosis (OR 2.68; 95% CI 1.64–4.37, $P = 0.0001$). Heterogeneity was high in the subgroup with secure diagnosis ($\chi^2 = 31.26, P < 0.00001; I^2 = 87\%$) and moderate in the subgroup with unsecure diagnosis ($\chi^2 = 22.19, P = 0.008; I^2 = 59\%$).

Publication bias. An inspection of the funnel plot seemed to reveal an asymmetry (Figure 7). However, the trim and fill analysis did not indicate any missing studies (OR 3.49, 95% CI, 2.24–4.75, $P = 0.2$; Figure 8). Egger’s regression asymmetry test indicated that the differences between the original estimate and the adjusted effect were not significant.

Discussion

The aim of the present meta-analysis was to assess the potential association between PE and PD. The results seemed to indicate that PD is a risk factor for PE. Important differences were observed when the results were stratified into subgroups. In particular, when we analyzed the results according to the type of study design, the case-control studies, despite suffering from more confounding biases compared to cohort studies, revealed a significantly greater OR of PE for PD. The meta-analysis of cohort studies did not reveal any significant differences. However, the meta-analyses of subgroups potentially suffered from low power, due to the small number of included studies in each subgroup.

When analyzed according to the definition of PD, the meta-analysis performed with studies analyzing PD by PPD and CAL showed significant differences, whereas the meta-analysis of studies that defined PD by PPD alone or CAL alone did not. The definition of PD by PPD and CAL may be more appropriate, but only a few studies were included in the CAL and PPD subgroups (three and two studies, respectively). No differences were detected in the subgroup analysis of PD severity. Subgroup analysis for the security of diagnosis revealed that the insecure diagnosis subgroup, but not the secure diagnosis subgroup, reported a higher and significant risk of PE. Overall, given the small number of studies included in each subgroup and the corresponding low power to detect differences, it was difficult to assess the influence of the severity, the definition, and the security of diagnosis of PD on the association between PD and PE.

The present meta-analysis had several limitations. First, although meta-analysis is a useful tool in epidemiology, important issues related to methodology may limit its benefits. Among observational study designs, the case-control approach is not the best design. Thus, evidence from these studies is likely to be less accurate and possibly more influenced by recall bias compared to that from cohort studies. Second, we could not analyze the influence of the methodological quality on the results of the meta-analysis. Third, the funnel plot of publication bias was asymmetrical, and publication bias could not be excluded. This finding suggests that we may have missed important unpublished studies.
### Figure 4. Forest plot for the subgroup analysis according to the PD definition.

| Study or Subgroup | Pre-eclamptic Events | Healthy Events | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|----------------------|----------------|-------------------------------|-------------------------------|
|                   | Total                | Total          |                               |                               |
| **1.2.1 PD defined by CAL and PPD** |                      |                |                               |                               |
| Boggess et al. 2003 | 23                   | 34             | 362                           | 729                           | 8.1%                          | 2.12 [1.02, 4.41] |
| Canakci et al. 2004 | 24                   | 41             | 11                            | 41                            | 7.1%                          | 3.85 [1.52, 9.75] |
| Chaparro et al. 2012 | 9                    | 11             | 33                            | 43                            | 4.0%                          | 1.36 [0.25, 7.37] |
| Kumar et al. 2012  | 18                   | 35             | 43                            | 305                           | 8.1%                          | 6.45 [3.09, 13.48] |
| Lohsoonthorn et al. 2009 | 128               | 150            | 129                           | 150                           | 8.5%                          | 0.95 [0.50, 1.81] |
| Polianno et al. 2011 | 41                   | 58             | 29                            | 58                            | 7.9%                          | 2.41 [1.12, 5.18] |
| Shetty et al. 2010 | 30                   | 30             | 86                            | 100                           | 1.9%                          | 10.23 [0.59, 176.64] |
| Silva et al. 2012 | 54                   | 284            | 8                             | 290                           | 7.9%                          | 8.28 [3.86, 17.74] |
| Siqueira et al. 2008 | 93                   | 164            | 406                           | 1042                          | 9.9%                          | 2.05 [1.47, 2.96] |
| Taghzouti et al. 2011 | 17                  | 92             | 47                            | 245                           | 8.7%                          | 0.95 [0.52, 1.77] |
| **Subtotal (95% CI)** | **899**              | **3003**       | **722%**                      |                                |                               |
| Total events      | 437                  | 1154           |                               |                               |                               |
| Heterogeneity: Tau² = 0.40; Chi² = 36.55, df = 9 (P < 0.0001); I² = 75% |
| Test for overall effect: Z = 3.73 (P = 0.0002) |

| **1.2.2 PD defined by CAL alone** |                      |                |                               |                               |
| Ha et al. 2011     | 12                   | 16             | 13                            | 48                            | 5.4%                          | 8.08 [2.20, 29.59] |
| Srinivas et al. 2009 | 16                   | 48             | 295                           | 770                           | 8.7%                          | 0.81 [0.43, 1.49] |
| Wang et al. 2012   | 7                    | 13             | 71                            | 106                           | 6.0%                          | 0.58 [0.18, 1.84] |
| **Subtotal (95% CI)** | **77**               | **924**        | **20.1%**                     |                                |                               |
| Total events       | 35                   | 379            |                               |                               |                               |
| Heterogeneity: Tau² = 1.21; Chi² = 11.26, df = 2 (P = 0.004); I² = 82% |
| Test for overall effect: Z = 0.53 (P = 0.60) |

| **1.2.3 PD defined by PPD alone** |                      |                |                               |                               |
| Canakci et al. 2007 | 23                   | 38             | 7                             | 21                            | 6.2%                          | 3.07 [1.00, 9.36] |
| Kunnen et al. 2007  | 17                   | 17             | 34                            | 35                            | 1.5%                          | 1.52 [0.06, 39.32] |
| **Subtotal (95% CI)** | **55**               | **56**         | **7.7%**                      |                                |                               |
| Total events       | 40                   | 41             |                               |                               |                               |
| Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0% |
| Test for overall effect: Z = 1.94 (P = 0.05) |

| Total (95% CI)      | 1031                  | 3983           | 100%                          | 2.23 [1.45, 3.43] |
| Total events       | 512                   | 1574           |                               |                               |
| Heterogeneity: Tau² = 0.46; Chi² = 55.25, df = 14 (P < 0.0001); I² = 75% |
| Test for overall effect: Z = 3.64 (P = 0.0003) |

Test for subgroup differences: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%

### Figure 5. Forest plot for the subgroup analysis according to the PD severity.

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| Study or Subgroup | Pre-eclamptic Events | Healthy Events | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|----------------------|----------------|-------------------------------|-------------------------------|
|                   | Total                | Total          |                               |                               |
| **1.3.1 Mild PD** |                      |                |                               |                               |
| Boggess et al. 2003 | 27                   | 39             | 469                           | 811                           | 16.6%                          | 1.64 [0.82, 3.28] |
| Kunnen et al. 2007 | 3                    | 17             | 21                            | 35                            | 10.2%                          | 0.14 [0.03, 0.59] |
| Lohsoonthorn et al. 2009 | 74               | 159            | 81                            | 150                           | 18.7%                          | 0.74 [0.47, 1.16] |
| Shetty et al. 2010  | 11                   | 30             | 55                            | 100                           | 15.2%                          | 0.47 [0.20, 1.10] |
| **Subtotal (95% CI)** | **245**              | **1096**       | **60.7%**                     |                                |                               |
| Total events      | 115                  | 626            |                               |                               |                               |
| Heterogeneity: Tau² = 0.39; Chi² = 11.28, df = 3 (P = 0.01); I² = 73% |
| Test for overall effect: Z = 1.18 (P = 0.24) |

| **1.3.2 Severe PD** |                      |                |                               |                               |
| Boggess et al. 2003 | 7                    | 39             | 118                           | 811                           | 15.2%                          | 1.28 [0.55, 2.98] |
| Kunnen et al. 2007 | 14                   | 17             | 13                            | 35                            | 10.1%                          | 7.90 [1.90, 32.77] |
| Lohsoonthorn et al. 2009 | 12               | 150            | 7                             | 150                           | 14.0%                          | 1.78 [0.68, 4.64] |
| **Subtotal (95% CI)** | **206**              | **996**        | **39.3%**                     |                                |                               |
| Total events      | 33                   | 138            |                               |                               |                               |
| Heterogeneity: Tau² = 0.38; Chi² = 4.73, df = 2 (P = 0.09); I² = 58% |
| Test for overall effect: Z = 1.72 (P = 0.09) |

| Total (95% CI)      | 451                  | 2092           | 100%                          | 1.04 [0.55, 1.97] |
| Total events       | 148                  | 764            |                               |                               |
| Heterogeneity: Tau² = 0.51; Chi² = 23.67, df = 6 (P = 0.0006); I² = 75% |
| Test for overall effect: Z = 0.13 (P = 0.89) |

Test for subgroup differences: Chi² = 4.33, df = 1 (P = 0.04), I² = 76.9%
with results that are inconsistent with our findings. Nevertheless, the trim and fill analysis indicated that no other adjunctive study was missed. Egger’s regression test revealed that the differences between the original and the adjusted analyses were not significant. The filled funnel plot showed that no additional unpublished study was needed. Fourth, although all of the included studies reported an adjusted analysis for important and known confounders, important differences were noted in the definitions of PD and PE. No general consensuses have been reached in the definition and diagnosis of PD [69-74]. The heterogeneity in these definitions may have influenced the results and introduced a bias into the meta-analysis. Therefore, given the methodological shortcomings, future studies are needed to confirm our results.

Figure 6. Forest plot for the subgroup analysis according to the PD diagnosis.
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Figure 7. Funnel plot for the association between PD and PE.
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Figure 8. Trim and filled funnel plot for the association between PD and PE.
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Conclusions
Based on the findings of the meta-analysis, PD appears to be a possible risk factor for PE. However, the included studies demonstrated important differences in the definitions and diagnoses of PD and PE, and lacked good methodological quality. Therefore, future studies are needed to confirm the results of the present meta-analysis. These studies should have high methodological quality, with adjustment for known confounding factors, and should report a clear and secure diagnosis of PD.

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