PLACENTAL HISTOPATHOLOGY ASSOCIATED WITH PREECLAMPSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Short Title: Placental histopathology and preeclampsia

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ABSTRACT

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Objectives:

Preeclampsia is associated with impaired trophoblast invasion and typical villous and vascular placental lesions. The primary aim was to conduct a systematic review in order to quantify the prevalence of placental histopathological lesions in pregnancies complicated by preeclampsia.

Methods:

MEDLINE, EMBASE and CINAHL were searched electronically and relevant articles reporting placental histopathological lesions were assessed according to the following criteria: study design, number of pregnancies, type of preeclampsia and whether the pathologist was blinded to the clinical information. Prospective and retrospective case-control studies, including 100 pregnancies or more in total, were included. The number of the most prevalent histological lesions according to the Perinatal Section of the Society for Pediatric Pathology classification was extracted and categorized in two main groups, “villous lesions” and “vascular lesions”. Random-effect meta-analysis of proportions was used for analysis. Between-study heterogeneity was assessed using the I^2 statistic.

Results:

The search yielded 717 citations and a total of 8 studies were included in the review. In unblinded studies, the pooled prevalence of villous lesions was 11.6% (95% CI 6.4-18.1%) and 48.2% (95% CI 19.1-77.9%) in normal and preeclamptic pregnancies, giving a pooled odds ratio (OR) of 7.59 (95% CI 2.16-26.62). In blinded studies, the pooled prevalence of villous lesions was 18.5% (95% CI 1.4-

48.7%) and 42.0% (95% CI 13.3-74.2%) in normal and preeclamptic pregnancies, giving a pooled OR of 4.28 (95% CI 1.16-15.76). In unblinded studies, the pooled prevalence of vascular lesions was 8.1% (95% CI 4.5-13.2%) and 37.3% (CI 3.1-82.4%), giving a pooled OR of 20.34 (95% CI 11.53-35.89). In blinded studies, the pooled prevalence of vascular lesions was 9.8% (95% CI 0.7-27.8%) and 38.9% (24.1-54.8%), giving a pooled OR of 7.08 (95% CI 2.55-19.61).

Conclusions:

The prevalence of both placental villous and vascular histopathological lesions is higher, by a factor of four to seven-fold, in preeclampsia compared to normal pregnancies in blinded studies. Greater differences are reported in unblinded studies. Despite the fact that the probability (point prevalence) of finding abnormal placenta pathology is higher in preeclampsia, placental lesions are not specific to the diagnosis of preeclampsia.

INTRODUCTION

Remodelling of the maternal uterine spiral arteries by the invading trophoblast and increased perfusion of the intervillous placental space is needed for the normal development of a pregnancy. In spite of the numerous theories on the pathophysiology of preeclampsia, it is commonly accepted that preeclampsia is inevitably associated with defective trophoblast invasion and failure of these physiological modifications. This results in placental hypoxia and/or 'stress' and the typical villous and vascular placental lesions associated with preeclampsia [1, 2, 3]. However, the literature on the prevalence, nature and severity of the placental histopathological lesions in preeclampsia is conflicting [4, 5, 6, 7, 8, 9, 10, 11]. The lack of agreement between studies may result from the conduct of the studies, with retrospective studies being prone to selection bias [8] and unblinded studies being susceptible to operator bias [4, 5, 6, 7]. Furthermore, prior to the recommendations of the Society for Pediatric Pathology for classification for placental pathology, many of the original investigations were prone to lack of or varied criteria for defining placental histological features, thereby making the assessment subjective [12] . The aim of this study is to perform a systematic review and meta-analysis in order to quantify the prevalence of the placental histopathological lesions in preeclampsia. A secondary aim is to evaluate the effect of the type/severity of preeclampsia and whether the controls were gestational age matched to cases.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analysis [13, 14, 15]. MEDLINE (1966 - March 2016), EMBASE (1974 - March 2016) and CINAHL (since inception - March 2016) were searched electronically on 29th March 2016 utilizing combinations of the relevant MeSH terms, key words, and word variants for “preeclampsia”, “placenta”, “histology”, “pathology”, “lesions”, “vascular”, “ischemic” (Supplementary Table 1). The search was restricted to the English language and to human studies. Reference lists of relevant articles and reviews were hand searched for additional reports. The MOOSE guidelines were followed [15]. The study was registered with the PROSPERO database (Registration number CRD42017054758).

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, study design, type of preeclampsia and whether the pathologist was blinded to the clinical information. Studies reporting placental histopathological lesions were included. All abstracts were reviewed independently by two authors (MLF, JS). Each of these two authors evaluated the abstracts regarding whether they would fulfil the inclusion criteria or not. Agreement about potential relevance was reached by consensus, and full text copies of those papers were obtained. In particular, the

consensus was reached when both authors independently considered a specific study potentially relevant. In case of disagreement or inconsistencies between the two reviewers, the consensus was reached by the additional consultation of a third senior author (BT). The same two reviewers independently extracted data regarding study characteristics and the outcomes. Relevant extractable information was available from all articles precluding the need to contact authors directly. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Prospective and retrospective case-control studies, including 100 pregnancies or more in total, were included. Case series, cohort studies, case reports, conference abstracts and editorials were excluded. Case-control studies, enrolling less than 100 pregnancies, were excluded, in order to make sure that only studies which are adequately powered were included and to avoid reporting bias in small studies. Studies where the data on robust outcomes could be extracted were included. The number of each type of histological lesion (according to the Perinatal Section of the Society for Pediatric Pathology classification) in the cases (pregnancies complicated by preeclampsia) and normotensive controls was extracted. In view of the fact that more than one type of lesion could be present, the number of the most prevalent histological lesion was extracted for each study, categorizing them in two main groups, “villous lesions” and “vascular lesions”.

Risk of bias, summary measures and synthesis of the results

Quality assessment of the included studies was performed using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria [15] . We used random-effect meta-analyses of proportions to combine data on the prevalence of the placental pathological lesions in pregnancies complicated by preeclampsia [16, 17] . We planned a priori sensitivity analysis according to the type of preeclampsia, whether the pathologist was blinded to the clinical information or not and whether the cases were gestational age matched to controls or not. Between-study heterogeneity was assessed using the I^2 statistic [18]. Publication bias was explored using funnel plots and was assessed statistically using Egger test (which uses the actual values of the effect sizes and their precision, rather than ranks)[19]. The assessment of the potential publication bias was problematic because of the low number of individual studies, which strongly limits the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry [20].

Statistical analyses were performed using Stata 11 (release 11.2. College Station, Texas, USA) and Stats Direct (Version 2.7.8, Stats Direct Ltd, 9 Bonville Chase, Altrincham, Cheshire WA14 4QA, UK) statistical software.

RESULTS

Steps for study selection are reported in Figure 1 and characteristics of each study are reported in Table 1.

The search yielded 717 citations; of these, 641 were excluded by review of the title or abstract, as they did not meet the selection criteria, contain original data, were not relevant or were duplicates (Figure 1). Full manuscripts were retrieved for the remaining 76, and a total of 8 studies were included in the review (Table 1). The pooled prevalence of histological lesions and corresponding pooled ORs for blinded (n=4) and unblinded (n=4) studies are shown in Table 2. Quality assessment of the included studies was performed using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria (Figure 2).

Villous lesions in pregnancies complicated by preeclampsia

Although the pooled prevalence of villous lesions in preeclamptic pregnancies was similar among blinded and unblinded studies, the pooled prevalence of lesions in normal pregnancy was 18.5% (95% CI 1.4-48.7%) in blinded and 11.6% (95% CI 6.4-18.1%) in unblinded studies. The pooled ORs (Figure 3, Table 2) for all, blinded and unblinded studies were 5.79 (95% CI 2.66-12.59, I^2 92.7%), 4.28 (95% CI 1.16-15.76, I^2 88.4%) and 7.59 (95% CI 2.16-26.62, I^2 95.7%), respectively. The pooled OR in the five studies with gestational age matched cases and controls was 6.86 (95% CI 2.31-20.40, I^2 95.3%, Supplementary Figure 1). Only three studies had extractable data on pregnancies complicated by late-onset preeclampsia, with

a pooled prevalence of villous lesions in cases of 24.7% (95% CI 7.3-48%) and a pooled OR of 3.78 (95% CI 1.24-11.47, I^2 73.1%, Supplementary Figure 2).

Vascular lesions in pregnancies complicated by preeclampsia

Five studies had extractable data on vascular placental lesions. Although the pooled prevalence of vascular lesions in preeclamptic pregnancies was similar among blinded and unblinded studies, the pooled prevalence of lesions in normal pregnancy was 9.8% (95% CI 0.7-27.8%) in blinded and 8.1% (95% CI 4.5-13.2%) in unblinded studies. The pooled ORs (Figure 4, Table 2) for all, blinded and unblinded studies were 14.0 (95% CI 7.43-26.37, I^2 73.5%), 7.08 (95% CI 2.55-19.61) and 20.34 (95% CI 11.53-35.89, I^2 57.2%), respectively. The pooled OR in the four studies with gestational age matched cases and controls was 11.76 (95% CI 5.64-24.54, I^2 75.3%, Supplementary Figure 3). The available data on early and late preeclampsia precluded a meta-analysis.

DISCUSSION

Summary of findings

In well-conducted studies using the same objective criteria for diagnosis, preeclampsia is associated with a higher prevalence of both villous and vascular histological lesions of the placenta. The pooled OR of these placental lesions in preeclampsia was lower in studies where the pathologist was blinded to the diagnosis compared to unblinded studies - principally because of underestimation of the prevalence of lesions in normal pregnancies in unblinded analyses. Despite the higher point prevalence of villous and vascular placental lesions in preeclamptic pregnancies, the population prevalence of these lesions is much higher in normal pregnancies, as the latter constitute the majority (>95%) of pregnancies.

Association of placental lesions with preeclampsia

One of the most commonly used classifications in placental pathology is from the Perinatal Section of the Society for Pediatric Pathology, where three main categories have been suggested: lesions consistent with maternal vascular underperfusion, lesions consistent with fetal vascular thrombo-occlusive disease, and lesions consistent with amniotic fluid infection [12]. This study meta-analyses data from publications using this classification, and demonstrates a higher prevalence of both villous and vascular histopathological lesions in the placenta of preeclamptic compared to normal pregnancy. The latter finding is in keeping with those of previous studies conducted prior to agreed classifications or when using different histopathological classifications for placental lesions.

Influence of operator blinding on study findings

Blinding the operator to the clinical diagnosis resulted in an approximate halving of the odds ratio for the higher prevalence of histological lesions associated with preeclampsia compared to unblinded studies. In unblinded studies, vascular lesions are 20-times more prevalent in preeclampsia - when the operator was blinded, there was a three-fold drop to an odds ratio of seven. A closer assessment of the origins of this change demonstrates that operator blinding does not significantly influence the prevalence of lesions in preeclamptic pregnancy, but that in unblinded studies, the operator was much less likely to formally document histological lesions in pregnancies classified as normal. These findings stress the importance of operator blinding both in a research and clinical context to get impartial and unbiased reporting in placental pathology, as in other fields [21, 22].

Pooled and population prevalence of histological lesions

The pooled prevalence of abnormal placental histology is clearly higher in preeclamptic pregnancy, but in all but one study, a case-control approach was used where the proportion of preeclampsia cases was much higher than found in a routine population. Case-control studies provide a biased impression of the significance of study findings compared to population studies. For example in a hypothetical routine population of 1000 women with an estimated incidence of 5% (n=50 cases) of preeclampsia, vascular lesions or the placenta would be expected in approximately 56 normal pregnancies and 21 preeclamptic pregnancies. Even

though the probability (point prevalence) of finding abnormal placental pathology in a normal pregnancy is lower than in preeclampsia, as the majority of pregnancies are normal, the population prevalence of placental lesions is higher in normal pregnancy. This phenomenon is analogous to fetal aneuploidy, where the risk for trisomy may be higher in women ≥37yrs-old (point prevalence), but the majority of trisomic pregnancies occur in women <37yrs of age (population prevalence).

Strengths and limitations of the systematic review

The quality of the data available for meta-analysis has some limitations due to the small number studies and selection bias of retrospective reviews. However, it is important to note that at least half the studies minimized bias by blinding the operator, and that the majority of these were conducted prospectively. The prevalence of placental histological lesions seems to differ according the gestation at onset of preeclampsia. There was a paucity of data on early-onset preeclampsia, mandating that future studies should report according to a temporal classification of preeclampsia – especially for vascular lesions

Clinical and research implications of study findings

Even with the use of strict histological diagnostic criteria, there is a consistent, increased prevalence of both villous and vascular placental lesions in preeclampsia compared to normal pregnancy. However, the relative prevalence of these placental lesions have been consistently over-estimated by a factor of two to three-

fold because of unblinded study methodology. Future research and clinical evaluations should not only use standardised objective criteria to diagnose placental pathology, but should also be blinded to minimise operator bias. This meta-analysis also highlights the effect of estimating the population prevalence of abnormal placental histology, which is higher in normal pregnancies. Furthermore, others have shown that villous and vascular placental lesions also occur in fetal intrauterine growth restriction (without hypertension), recurrent pregnancy loss and spontaneous preterm birth. These findings imply that the findings of villous and vascular placental lesions are neither sensitive nor specific to the diagnosis of preeclampsia. Impartial scientific observation would demands that we question whether these placental lesions could truly play an etiological role in the development of preeclampsia – or whether they are a consequence of the disease process [23, 24, 25] .

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Conflict of interest

The authors have no conflict of interest to declare.

Author (year)	Study design	Blinding	Total number	Proportion of PE	Gestation at delivery (weeks)*	Summary of findings
Kos M (2005)[4]	Retrospective	Unblinded	329	85%	36.4 (3.5)	No significant difference in the ischemic changes between placentas from preeclampsia cases and the control group.
Ogge G (2011)[5]	Retrospective	Unblinded	8307	11%	24.7 - 42.1	Maternal underperfusion lesions are more frequent in early- than in late-onset PE. The more severe the vascular lesions, the earlier the presentation and severity of the disease.
Maloney KF (2012)[6]	Retrospective	Unblinded	278	26%	36.1 PIH# 34.1 PE#	Malperfusion lesions are more common in the hypertensive group, with no statistically significant difference between the different clinical types of hypertensive disease.
Devisme L (2013)[7]	Retrospective	Unblinded	346	50%	31.6 (4.0)	Placental lesions due to hypoxia or ischemia were the lesions were most strongly associated with preeclampsia.
Vinnars MT (2010)[8]	Retrospective	Blinded	314	50%	35#	Histological signs of ischemia were seen in placentas from pregnancies affected preeclampsia and they correlated with the severity of the disease regardless of gestational age.
Van Der Merwe JL (2010)[9]	Prospective	Blinded	100	50%	30.9 (2.5) Early PE 38.5 (2.1) Late PE	Early- and late-onset preeclampsia show clear histopathological differences. Differences were less between late-onset preeclampsia and normal term placentas.
Pathak S (2011)[10]	Prospective	Blinded	959	3%	39.5 (1.39)	Specific placental lesions are significantly more common in complicated pregnancies. Placentas may present normal features even in severely complicated pregnancy.
Ruiz-Quinonez G (2014)[11]	Prospective	Blinded	144	31%	39 (1) Mild PE 37 (4) Severe PE	Placental hypermaturity is more frequent in PE patients.

Table 1. Summary of the studies included which reported villous and vascular placental lesions in normotensive pregnancies and those complicated by preeclampsia (PE) or pregnancy induced hypertension (PIH). * Mean (SD) or range, # SD not supplied.

Table 2. Summary of the pooled prevalence and odds ratios (95% CI) in all, blinded and unblinded studies that reported villous and vascular placental lesions in normotensive pregnancies and those complicated by preeclampsia (PE).

	Pooled prevalence in PE (95% CI)	Pooled prevalence in controls (95% CI)	Pooled OR (95% CI)
Villous lesions			
All studies	45.2% (24.4%-66.9%).	14.6% (7.6-23.5%)	5.79 (2.66-12.59)
Unblinded studies	48.2% (19.1%-77.9%)	11.6% (6.4-18.1%)	7.59 (2.16-26.62)
Blinded studies	42.0% (13.3%-74.2%)	18.5% (1.4-48.7%)	4.28 (1.16-15.76)
Vascular lesions			
All studies	38.2% (12.1%-68.7%)	5.9% (1.0-14.6%)	14.0 (7.43-26.37)
Unblinded studies	37.3% (3.1%-82.4%)	8.1% (4.5-13.2%)	20.34 (11.53-35.89)
Blinded studies	38.9% (24.1%-54.8%)	9.8% (0.7-27.8%)	7.08 (2.55-19.61

Figure legends

Figure 1. Flow of study identification.

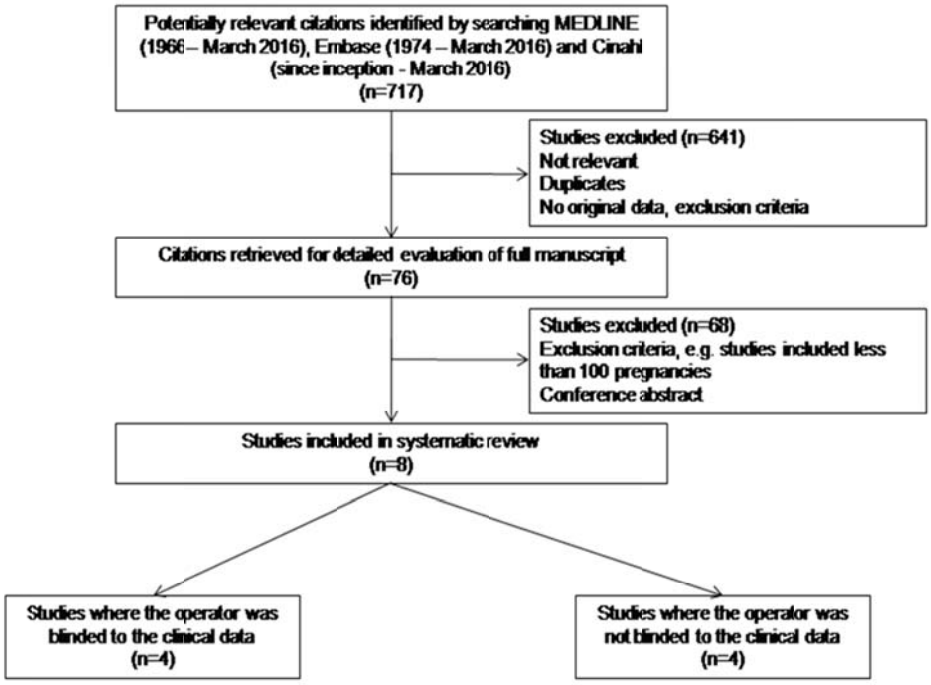


Figure 2. Bar chart showing quality criteria of articles included in systematic review, assessed using checklist of Strengthening the Reporting of Observational Studies in Epidemiology

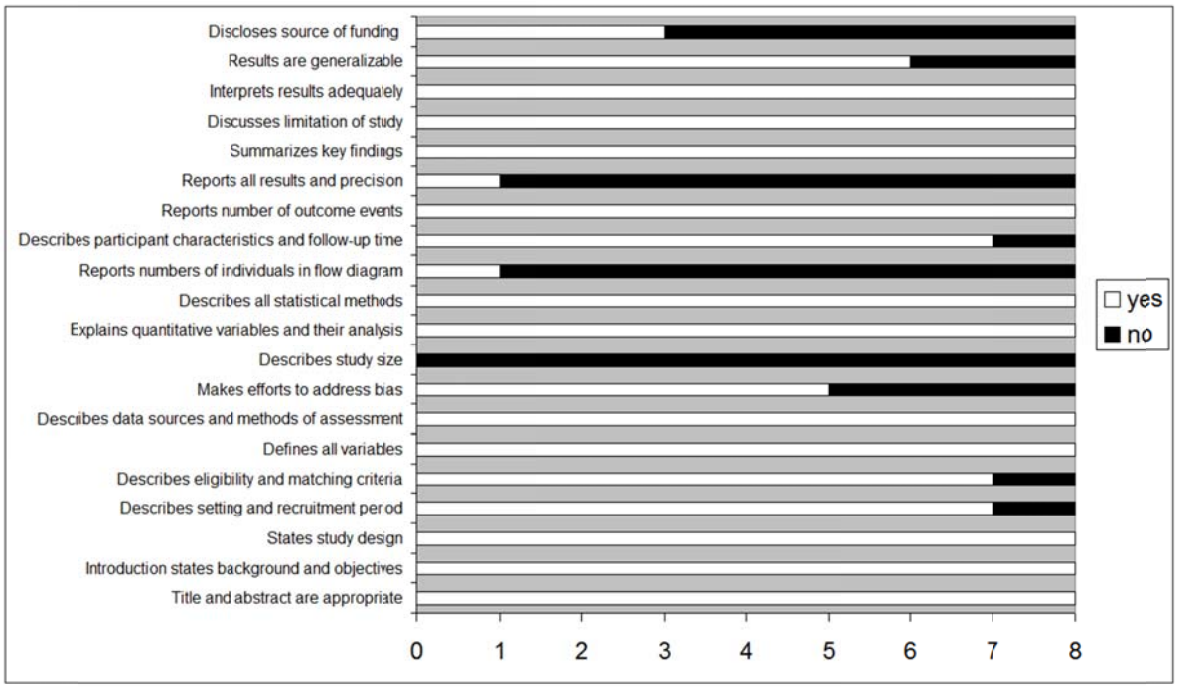
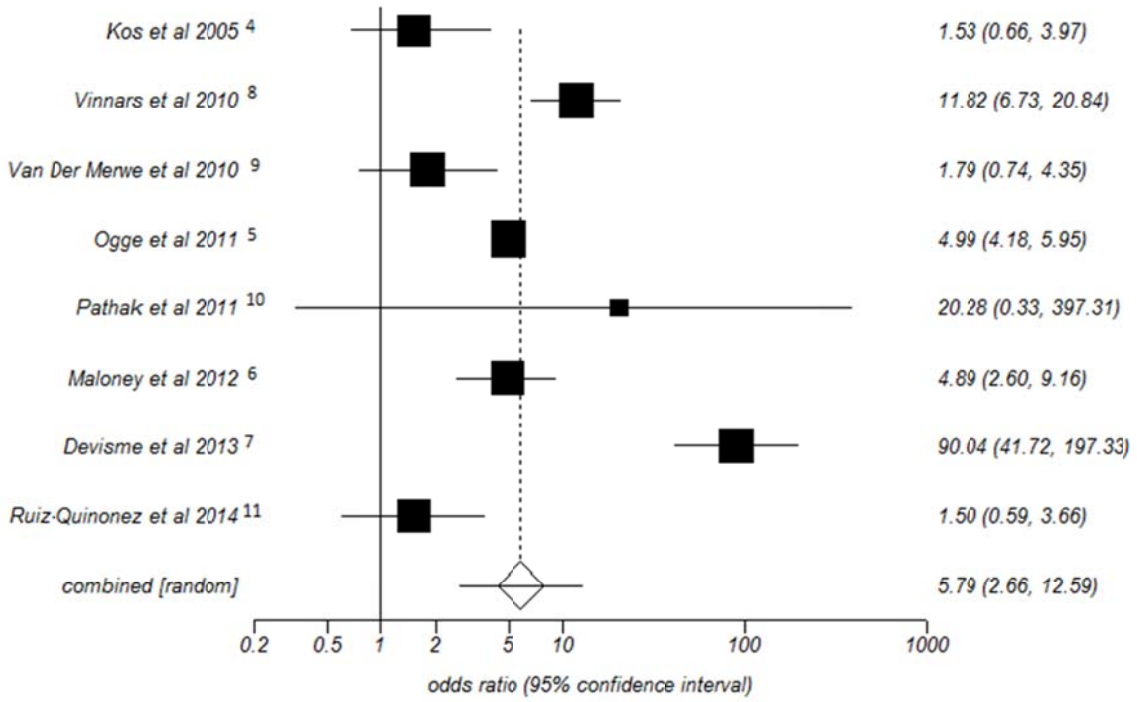
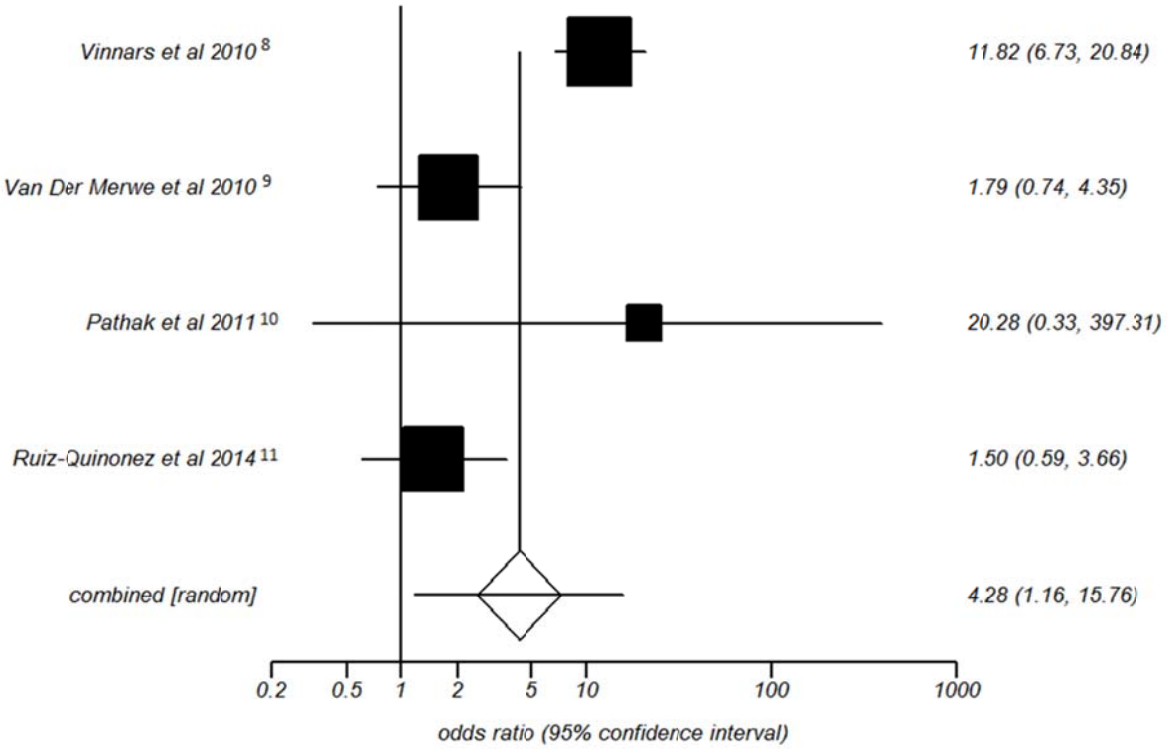


Figure 3: Forest plot, random-effects model of the odds ratio of villous lesions in the pregnancies complicated by preeclampsia and normotensive controls (Figure 3a), and where the operator was blinded (Figure 3b) and unblinded (Figure 3c). Only the first author is given for each study. The squares represent the studies included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimates for each single study, the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.





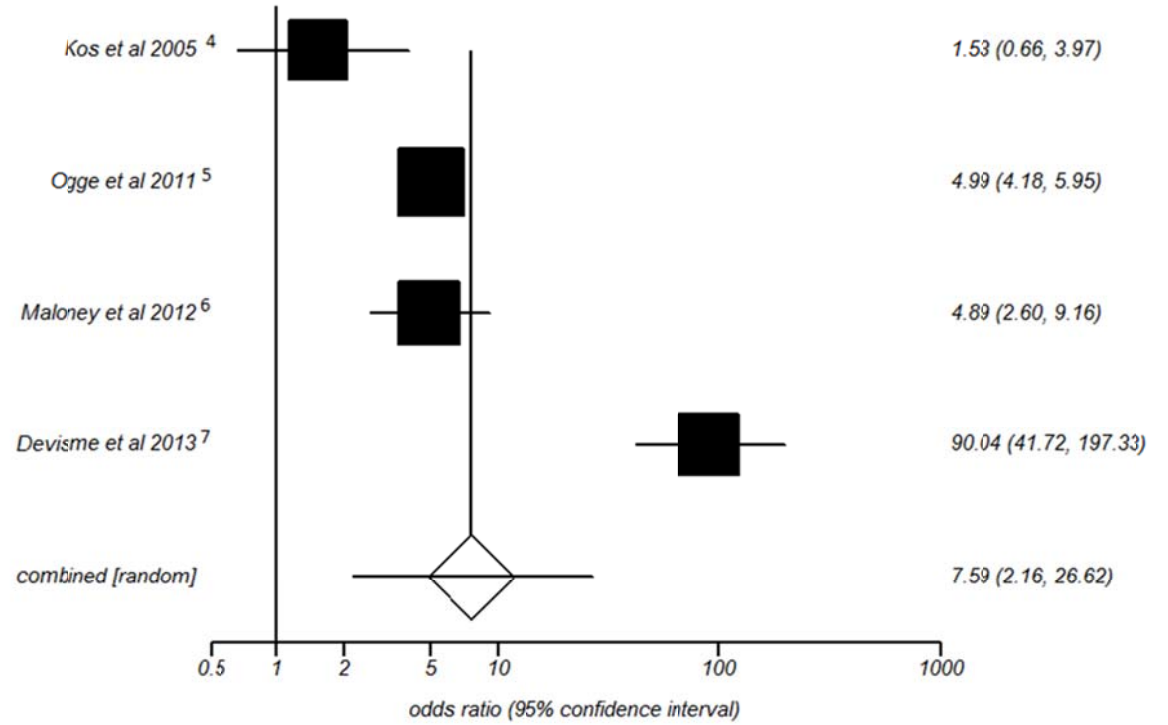
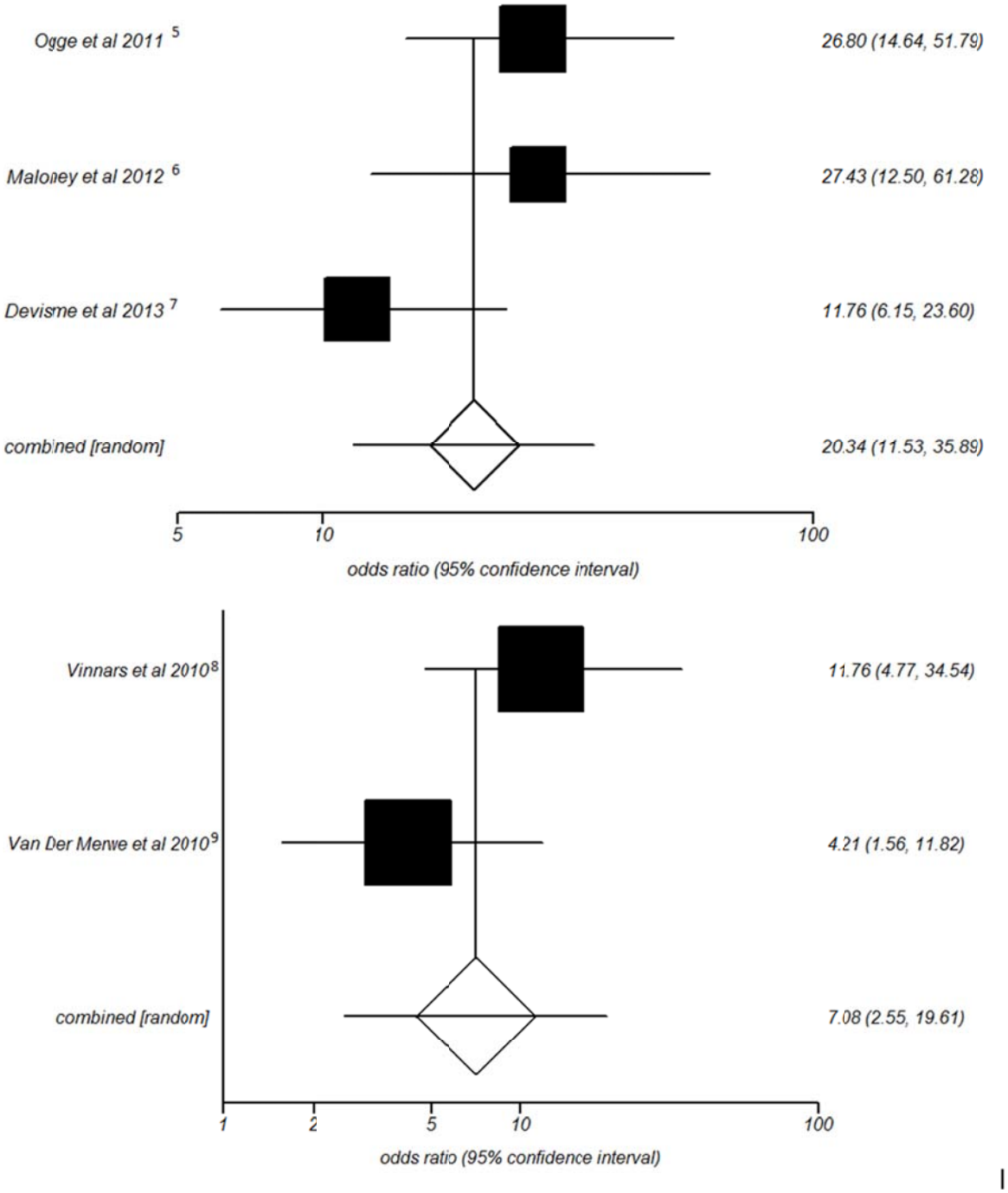
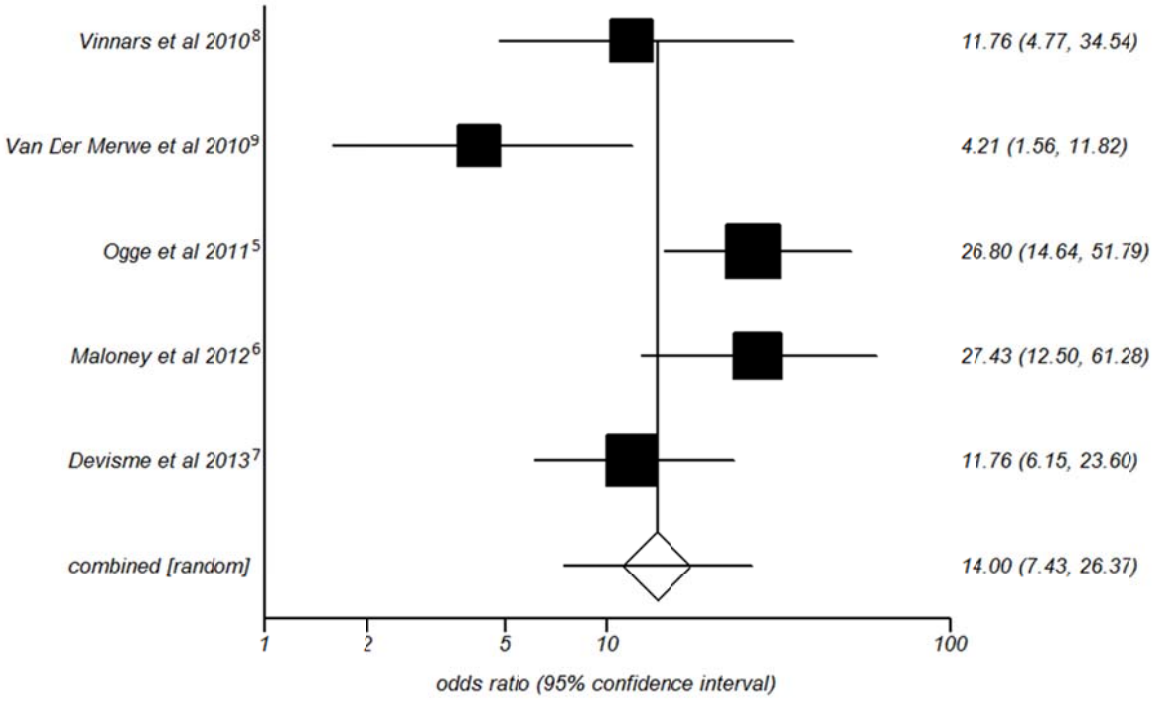


Figure 4: Forest plot, random-effects model of the odds ratio of vascular lesions in the pregnancies complicated by preeclampsia and normotensive controls (Figure 4a), and where the operator was blinded (Figure 4b) and unblinded (Figure 4c). Only the first author is given for each study. The squares represent the studies included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimates for each single study, the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.





Supplementary Figure 1: Forest plot, random-effects model of the odds ratio of villous lesions in the pregnancies complicated by preeclampsia and normotensive controls, in studies where the cases and controls were gestational age matched. Only the first author is given for each study. The squares represent the studies included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimates for each single study, the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.

Supplementary Figure 2: Forest plot, random-effects model of the odds ratio of villous lesions in the pregnancies complicated by late-onset preeclampsia and normotensive controls. Only the first author is given for each study. The squares represent the studies

included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimated for each single study, the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.

Supplementary Figure 3: Forest plot, random-effects model of the odds ratio of vascular lesions in the pregnancies complicated by preeclampsia and normotensive controls, in studies where the cases and controls were gestational age matched. Only the first author is given for each study. The squares represent the studies included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimates for each single study, the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.