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# Association between placenta previa and risk of hypertensive disorders of pregnancy: a meta-analysis based on 7 cohort studies

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**Abstract. – OBJECTIVE: The aim of this research is to evaluate the association between placenta previa and hypertensive disorders of pregnancy (HDP).**

**MATERIALS AND METHODS: A computerized literature search was carried out on PubMed to collect relevant articles on the association between placenta previa and HDP before November 2013. Pooled relative risk (RR) and 95% confidence intervals (CIs) were used to assess the strength of the associations.**

**RESULTS: A total of 7 cohort studies were identified according to the inclusion criteria. Overall, a significantly inverse correlation between placenta previa and HDP was found when all study results were pooled into the meta-analysis (RR = 0.55, 95% CI: 0.32-0.97). For subgroup analyses, the same results were found in pregnancy-induced hypertension (PIH) group (RR = 0.36, 95% CI: 0.23-0.57) but not in other HDPs group (RR = 0.94, 95% CI: 0.44-2.00).**

**CONCLUSIONS: This meta-analysis suggested a reduced risk for PIH in women with placenta previa.**

*Key Words:*
Hypertensive disorders, Pregnancy-induced hypertension, Preeclampsia, Placenta previa, Pregnancy, Meta-analysis.

## Introduction

Hypertensive disorders of pregnancy (HDP) are the main causes of maternal and perinatal morbidity and mortality[1]. HDP is comprised of chronic hypertension, gestational hypertension, preeclampsia and eclampsia, while gestational hypertension and preeclampsia were also referred as pregnancy-induced hypertension (PIH)[2]. The mechanisms of HDP have not yet been fully elucidated. However, growing evidence supports that the placenta plays a critical role in the pathogenesis of preeclampsia[3-5]. It is now commonly accepted that reduced uteroplacental perfusion and placental ischemia/hypoxia, which develops as a result of abnormal cytotrophoblast invasion of spiral arterioles, trigger a cascade of events leading to the maternal disorder[6-9]. In the placenta previa (PP), the blood supply and oxygenation of a placenta implanted in the lower uterine segment are thought to be increased compared with those in a placenta implanted in the upper uterine segment[10]. As the increased blood supply may improve the situation of placental ischaemia, we speculated that the risk of hypertensive disorders is lower in placenta previa compared with normally implanted placenta.

Early in 1958, Bieniarz[11] reported an inverse association between lower placental implantation in the uterus and hypertension in later pregnancy. After twenty years, Nicolaides et al[12] showed that low implantation of the placenta might protect against the development of pregnancy-induced hypertension and was associated with improved values in tests of placental function. Subsequently, several retrospective studies based on a large cohort of population have further confirmed this hypothesis by the controlling the confounding factors such as parity, preterm or term delivery, cigarette smoking, maternal age, race, maternal height and weight at delivery[10,13,14]. However, some other studies did not show the same consequence. Two retrospective cohort studies[15,16] reported the 1.5 odds ratio (OR) (95% confidence interval (CI) = 0.9-2.5) and 0.88 OR (95% CI = 0.64-1.20) respectively, which did not show the inverse relation.

Recently, two case-control studies[17,18] have demonstrated a strong inverse relation between placenta previa and preeclampsia. To obtain an overall quantitative estimation of the association between placenta previa and HDP, a meta-analysis was performed.



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## Materials and Methods

### Searching Method

The basis diagnosis of the placenta previa included complete, partial and marginal praevia and low-lying placenta[19]. According to these criteria, we searched related literatures in PubMed database before November 2013 using the following key words: "hypertension," "preeclampsia," or "eclampsia" combined with "placenta previa". Furthermore, we screened the reference lists from all relevant articles to identify additional studies. There were no restrictions regarding language or country.

### Inclusion/Exclusion Criteria

Eligible studies had to meet all of the following criteria: (1) cohort study on the association between placenta previa and HDP; (3) with relative risk estimates and respective variance, or the relevant information needed to calculate them. Studies were excluded when they were: (1) not a cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

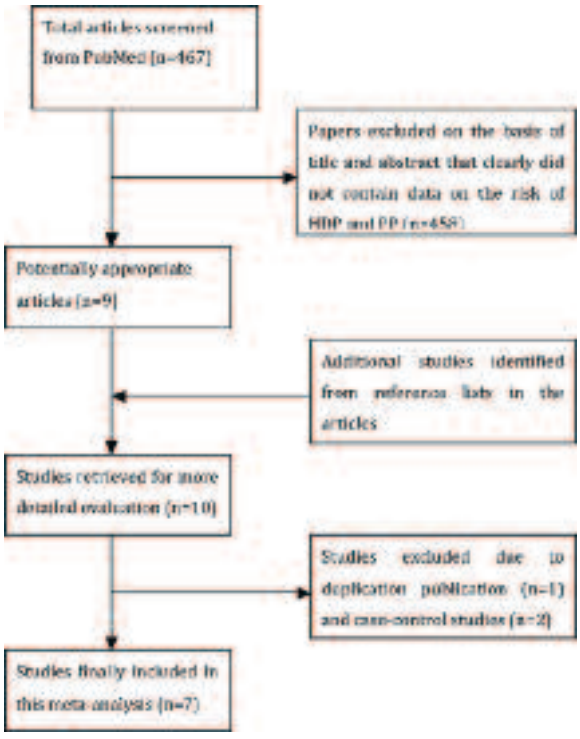


**Figure 1.** Literature screening and exclusion.

### Data Extraction

For all included studies, we extracted the following information: the name of the first author, year of publication, the country in which the study was conducted, study design, study period, number of subjects, risk estimates with corresponding 95% (CIs) and adjustment.

### Statistical Analysis

Pooled relative risks (RRs) and 95% CIs were used to assess the strength of the associations. For simplicity, we took the OR for cohort studies as the estimate of RR. Heterogeneity among studies was examined using Q-test and $I^2$ score[20]. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel-Haenszel) or random effect model (Der-Simonian and Laird) was selected to summarize the pooled RR[21]. The significance of the pooled RR was determined by the z test. Publication bias was assessed using the funnel plotand Egger's test[22,23]. $p$ value less than 0.05 was considered statistically significant. All statistical analyses were conducted using Stata 12.0 software (Stata-Corp, College Station, TX, USA).

## Results

### Study Selection

The process of study selection was shown in Figure 1. Ten potentially relevant studies were retrieved for further evaluation[9,11-17,24,25]. Three studies were excluded as they were case-control studies and one of them was a duplication[17,18,25]. Thus, a total of 7 studies were included in this meta-analysis. Table I listed the main characteristics of each study included in this meta-analysis. Among the 7 cohort studies, four studies offered adjusted RRs, one study offered crude RR, and two studies did not offer RR.

### Quantitative Synthesis

The RRs of hypertension disorders in patients with placenta previa in all seven studies were shown in Figure 2. A reduced risk for HDP was observed in the women with placenta previa (RR = 0.55, 95% CI: 0.32-0.97). There was statistically significant heterogeneity across the studies ($p < 0.001$, $I^2 = 86.1\%$). In 7 included studies, 3 studies were defined as gestational hypertension (BP ≥140/90 mmHg) with or without proteinuria, 1 study was preeclampsia, and 3 studies were general HDP that included gestational hyperten-

**Table I.** Comparison of measured variables before and after intervention in BAL fluid.

| Reference | Country | Study design | Study period | Definition of hypertension | Total number of subjects | Adjustment | Hypertensive disorder | | No Hypertensive disorder | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Placenta previa | No previa | Placenta previa | No previa |
| Nicolaides et al. 1982[10] | British | Cohort | 1973-1981 | PIH | 24750 | N | 6 | 3744 | 195 | 20805 |
| Leiberman et al. 1991[8] | Israel | RCC | 1972-1986 | HDP | 106866 | Parity, preterm or term delivery | 12 | 5867 | 479 | 100508 |
| Jelsema et al. 1991[23] | USA | Cohort | N | PE | 6576 | Maternal weight, parity, gestational age | 4 | 536 | 117 | 5919 |
| Ananth et al. 1997[11] | Canada | RCC | 1980-1993 | PIH | 121082 | Parity, Cigarette smoking | 24 | 14142 | 392 | 106549 |
| Wang et al. 1999[12] | Malaysia | RCC | 1989-1998 | PIH | 258444 | Maternal age, race (Chines, Malay, Indians), diabetes mellitus, maternal height and weight at delivery and maturity | 3 | 1902 | 123 | 23816 |
| Huang et al. 2007[13] | Taipei | RCC | 1990-2003 | HDP | 37702 | Maternal age, parity, previous induced abortion, previous cesarean deliveries, prepregnancy body mass index, years of education, previous fetal death, previous preterm birth, previous placenta previa, marital status, amniocentesis, conception methods, presence of uterine fibroids, uterine malformation, employment during pregnancy, smoking during pregnancy, and fetal sex | 16 | 640 | 441 | 36605 |
| Rosenberg et al. 2011[14] | Israel | RCC | 1988-2009 | HDP | 185476 | N | 41 | 11082 | 730 | 173623 |

HDP: hypertensive disorder of pregnancy, PIH: pregnancy-induced hypertension, PE: preeclampsia, N: not offered, RCC: Retrospective cohort study.

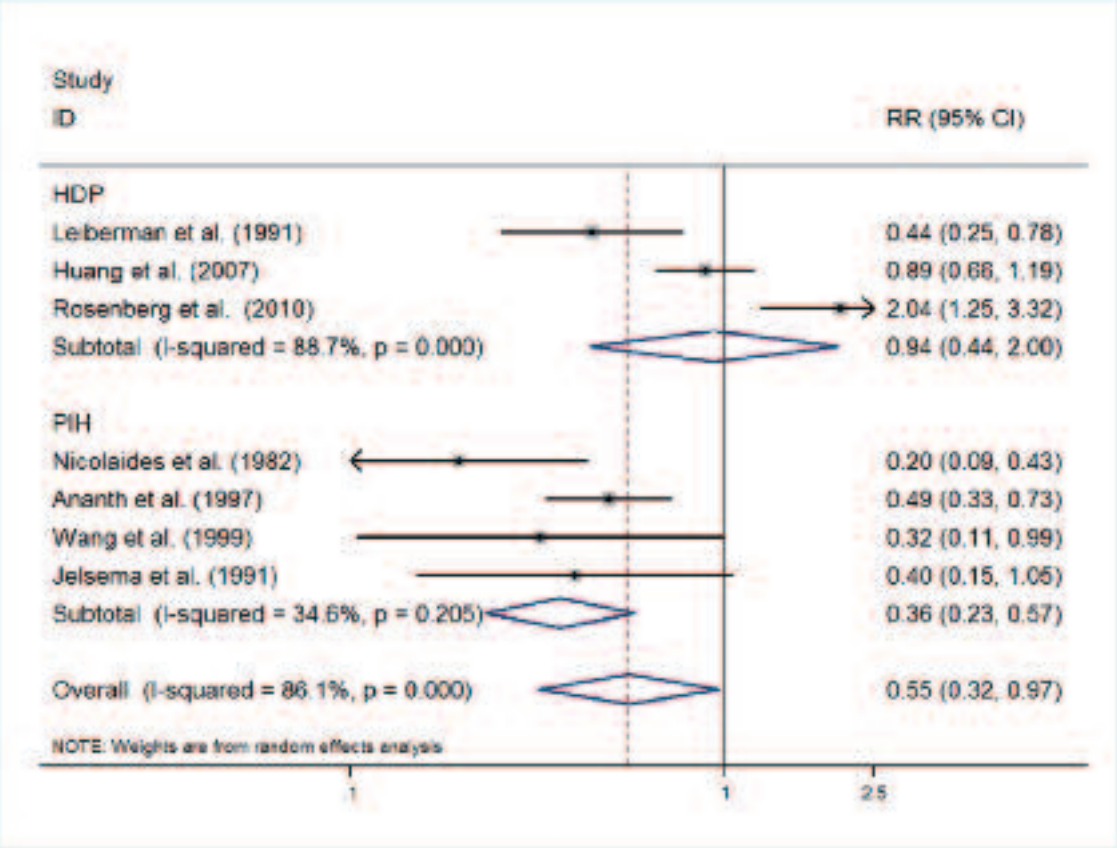


**Figure 2.** The forest plot of all selected studies on the association between placenta previa and HDP

sion, preeclampsia/eclampsia/superimposed hypertension, and chronic hypertension. We categorized 4 studies (the former two) as PIH subgroup and defined another 3 studies as other HDP subgroup, and the subgroup analyses for PIH and other HDP were conducted. The RR in other HDP group was 0.94 (95% CI, 0.44-2.00), and that in PIH group was 0.36 (95% CI, 0.23-0.57) (Figure 2). A strong inverse relation between placenta previa and PIH was observed. When we pooled the adjusted RRs into analyses (Figure 3), the risk estimate was 0.68 (95% CI: 0.35-1.00), which also showed an inverse relation between placenta previa and HDP.

### *Sensitive Analysis and Bias Diagnosis*

To compare the difference and evaluate the sensitivity of this meta-analyses, we used both models (the fixed effect model and random effect model) to evaluate the stability of the meta-analysis. All results were not materially altered (data not shown). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are credible.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (data not shown). Then, the Egger's test was used to provide the statistical evidence of funnel plot symmetry. There was no evidence of publication bias in overall analysis ($p$ for Egger's test = 0.329).

## Discussion

Some studies have focused on the association between placenta previa and the risk of hypertensive disorders. However, the results were not consistent. Cobo et al[26] reported a severe preeclampsia case that occurred in a patient with placenta previa. Jelsema et al[24] reported the association between decreased occurrence of preeclampsia and placenta previa and a strong association between placenta previa and premature delivery. Therefore, we conducted this meta-analysis to demonstrate the association between placenta previa and the risk of hypertensive disorders based on 7 indi-

vidual cohort studies. In the study, we found a protective relation between placenta previa and hypertensive disorders (RR = 0.55, 95% CI: 0.32-0.97), even after controlling confounding factors such as parity, preterm or term delivery. In subgroup analysis, we observed a strong inverse correlation between placenta previa and PIH (RR = 0.36, 95% CI: 0.23-0.57).

PIH is associated with an increase in the prevalence of cardiovascular disease risk in later life of Japanese women[27]. A recent study[28] reported that almost half of early-onset preeclampsia women will develop hypertension, as opposed to 39% and 25% of women in the PIH and late-onset preeclampsia groups, respectively. The factors including extremes of maternal age, nulliparity, prior history of pregnancy-induced hypertension, and high body mass index are found to be associated with PIH[29], while cigarette smoking during pregnancy is a protective factor for PIH[30]. In the present meta-analysis, we observed a reduced risk of HDP especially PIH in the women with placenta previa, suggesting that placenta previa is another protective factor for HDP. Considering the previous studies[31], several possible interpretations may be used to explain this finding. First of all, the placenta implanted in the lower uterine may contribute to the venous drainage and reduce the risk of toxemia. Secondly, the improved blood supply and oxygenation of the placenta implanted in the lower uterine segment may have a role in the prevention of PIH[10,13]. In addition, abnormal or incomplete invasion of endometrial arterioles by trophoblastic cells in the early development of the placenta may result in later placental ischemia and induce endothelial damage and PIH[32]. Although some researchers[33,34] have found no association or a positive association between placenta previa and the frequency of PIH, this meta-analysis validated the inverse correlation between placenta previa and HDP (particularly PIH) in 7 large cohorts of population. We speculate that the discrepancy among previous studies may be caused by many factors, such as different population properties, size of subjects, etc. However, we are confident that the finding form this meta-analysis is more convincing than any single study.

However, this meta-analysis may have a couple of limitations. Firstly, the time span of this meta-analysis is very long and the diagnosis criteria for HDP used in every study may be different. Secondly, the confounding factors were not corrected in 4 studies while the given confounding factors in other 3 studies were inconsistent. Nevertheless, the inverse relation between placenta previa and HDP was also observed when the adjusted RRs were used, which may reduce the influence of above limitations.

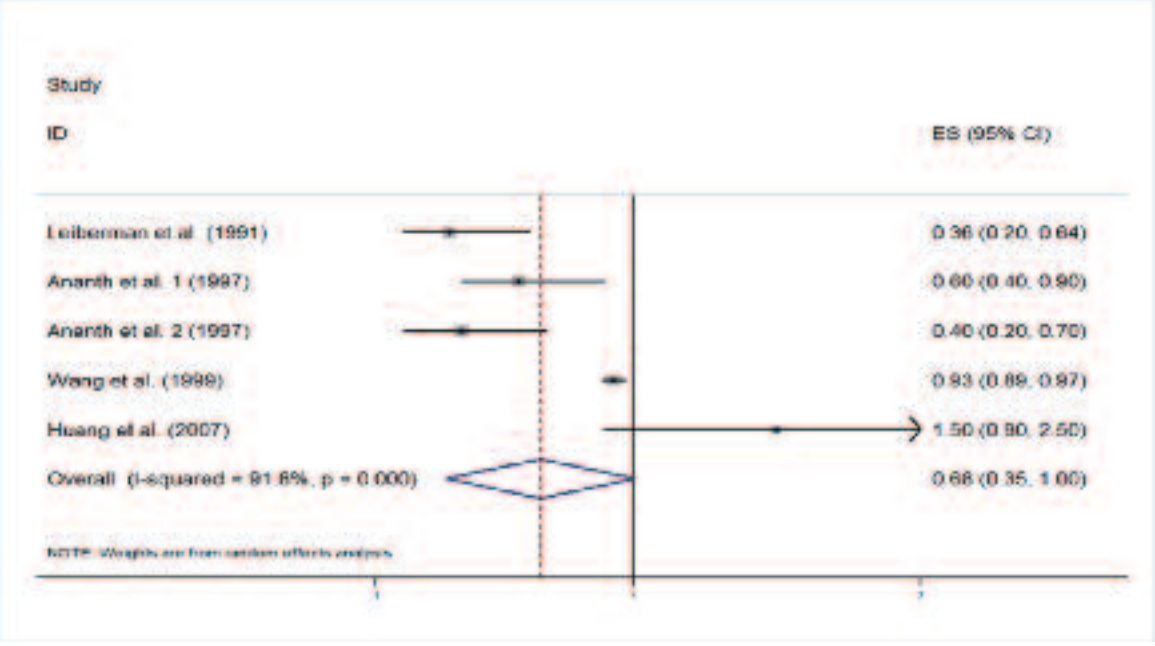


**Figure 3.** The forest plot of all studies with adjusted RRs on the association between placenta previa and HDP.

## Conclusions

This meta-analysis provides quantitative evidence for the inverse correlation between placenta previa and HDP/PIH. However, the precise reason for this correlation requires further investigation.

### Acknowledgements

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

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