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Human Immunodeficiency Virus and risk of pre-eclampsia and eclampsia in pregnant women: A meta-analysis on cohort studies

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ABSTRACT

Maternal HIV infection is related to several perinatal adverse outcomes. This study is aimed at establishing whether maternal HIV infection is associated with the development of pre-eclampsia (PE) and eclampsia. We comprehensively searched MEDLINE/PubMed, Web of Science, SCOPUS and Embase databases for relevant studies published up to 20 November 2018, without time and language restrictions. We have limited our literature searches to observational studies in humans. We applied a random-effects model to calculate the relative risks (RR) and 95% confidence intervals (CI) for the *meta*-analyses. We also systematically reviewed eligible studies to determine the effects of HIV infection on imbalance of angiogenic and anti-angiogenic factors, which are effective in increased risk of PE or eclampsia. We identified a total of 11,186 publications, out of which 22 eligible studies (11 prospective and 11 retrospective cohort studies) comprising 90,514 HIV-positive and 66,085,278 HIV-negative pregnant women were included in meta-analysis. Results of the *meta*-analyses suggested that maternal HIV infection is not significantly associated with the development of PE (RR, 1.04; 95%CI, 0.89–1.21) and eclampsia (RR, 1.05; 95%CI, 0.63–1.75). Six studies were included to understand the effects of HIV infection on imbalance of angiogenic and anti-angiogenic factors. All six studies demonstrated that HIV infection had no significant effect on expression levels of these factors in pre-eclamptic and normotensive pregnant women. Our study showed that maternal HIV infection was not significantly associated with increased or reduced risks of pre-eclampsia and eclampsia. More well-designed studies with large sample size and well defined outcomes are recommended to confirm or refute the present findings.

1. Introduction

Pre-eclampsia (PE) occurs in 3–8% of pregnancies worldwide and is one of the leading causes of maternal and neonatal mortality and morbidity. Eclampsia is a severe complication of PE, which is characterized by endothelial dysfunction, elevated blood pressure, incomplete placentation, overemphasized immune responses, seizures, and proteinuria [1]. PE is responsible for more than 60,000 maternal and 500,000 fetal deaths per year worldwide and is one of the risk factors for preterm birth, intrauterine growth restriction, and placental abruption [2,3]. Despite extensive research, the specific etiology of PE or eclampsia is unclear and is assumed to be multi-factorial [4]. Although it is showed that PE could be initiated by abnormal placentation resulted from imbalance between angiogenic (Vascular endothelial growth factor [VEGF] and placental growth factor [PlGF]) and anti-angiogenic (soluble endoglin [sEng] and soluble fms-like tyrosine kinase-1 [sFlt-1 or sVEGFR-1]) factors during pregnancy [5,6]. Pregnant women with PE often show an elevated expression of anti-angiogenic

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factors [6].

In recent years, several studies suggested that inflammation resulting from infections could play an important role in the development of PE [1,7]. However, earlier evidence suggest that the role of Human Immunodeficiency Virus (HIV) infection in the development of PE is contradicting [1]. In fact, PE is characterized by excessive up-regulation of generalized maternal inflammatory response, while HIV-positive patients are immune-compromised. Therefore it can be hypothesized that HIV infection can result in lower incidence of PE [8].

According to World Health Organization (WHO) fact sheet on HIV/AIDS, in 2017, there were 36.9 million people living with HIV infection. Women and girls of reproductive age comprise approximately half of the HIV-infected population worldwide, and 1.1 million of them were pregnant women. The global weekly incidence of young women aged 15–24 years to be infected with HIV is estimated as 7000 [9]. HIV infection is related to a great number of documented maternal complications and deaths [10,11]. Moreover it is indicated that HIV infection could cause several cardiovascular complications such as chronic arterial injury, endothelial damage, and atherosclerosis [6]. Some reports in the past two decades suggested that HIV pregnant women have a lower risk of developing gestational hypertension disorders like PE, although some other studies conflict this observation. In light of these conflicting reports, we have performed a systematic review and meta-analysis study as an attempt to better understand the association between HIV infection and the development of PE and eclampsia.

2. Materials and methods

The MOOSE and PRISMA guidelines were followed to conduct and report the present study [12,13]. The protocol followed for this meta-analysis is accessible in PROSPERO (CRD42018110636). The exposure for the study was HIV infection and the main outcome of interest was the development of PE or Eclampsia in infected pregnant women and healthy controls. The studies considered for this meta-analysis were observational studies with clearly defined comparison group (HIV-negative and HIV-positive pregnant women). Moreover in this systematic review, we assessed the results of studies that evaluated the effects of HIV infection on expression levels of angiogenic and anti-angiogenic factors in pre-eclamptic and healthy control pregnant women. We excluded studies that did not evaluate PE or Eclampsia as an outcome, studies that reported ambiguous eligibility criteria, those with no HIV-negative pregnant participants as the control group, and those with insufficient data to determine relative risk (RR) and 95% confidence intervals (CI). We also excluded articles without original data (review, systematic reviews, editorials, or letters).

2.1. Data sources and search strategy

To identify the relevant studies, two independent investigators searched the databases of PubMed/MEDLINE, Web of Sciences, Scopus, EMBASE, and Google Scholar up to 20 November 2018, using a combination of the following search terms: (“Human Immunodeficiency Virus” OR “HIV infection” OR “AIDS”) AND (“pre-eclampsia” OR “eclampsia” OR “gestosis” OR “pregnancy hypertension”). The above mentioned keywords were also combined with terms such as “sFlt-1”, “sEng”, “PlGF”, and “VEGF” to further broaden the scope to include angiogenic and anti-angiogenic factors in the systematic review. We restricted our literature search to human-subjects’ studies. To enhance the search sensitivity, we manually searched the bibliographies of all the included studies and any relevant review articles.

2.2. Data extraction

After deleting the duplicates and any irrelevant studies by title and abstract screening, two independent reviewers further examined the remaining studies for exclusion and inclusion criteria as specified in our review protocol. The data extracted from each included study was assessed for the risk of bias using the Newcastle–Ottawa scale [14]. Similar to our previous cohort studies [15–17], a maximum of nine scores were defined. These include selection of HIV-positive and HIV-negative pregnant women (0–4 points), comparability of subjects (0–2 points), and tools to evaluate the outcome of interest (0–3 points). Each study is awarded a maximum of one score for any numbered item within the selection and outcome categories, and a maximum of two scores for comparability. Studies with a total score of 0–3, 4–6, and 7–9 points were specified as poor, moderate, and high quality, respectively. All uncertainties in the above steps were deliberated by through discussion and agreement with the principal investigators (A.R. and S.M.R).

2.3. Data synthesis and statistical analysis

All analyses were done using Stata software version 12 (Stata Corp., College Station, TX). Dichotomous outcome data was extracted from individual studies, and relative risks (RRs) and 95% CIs (all studies included had cohort design) were calculated using random-effects models. The Cochrane’s Q-test and I^2 tests were used to assess the heterogeneity between studies [18]. The degree of heterogeneity was categorized as none ($< 25\%$), low (25–49%), moderate (50–74%), or high ($\geq 75\%$) [18]. Prespecified subgroup analysis was performed considering the type of study (retrospective or prospective cohort) and geographical area (continents). Meta-regression analysis was performed regarding the year of publication. Publication bias was assessed through the Begg’s and Egger’s methods for asymmetry [19]. A P-value of < 0.05 was considered as statistically significant. Results are presented as forest plots and the association between HIV infection and PE is illustrated by the RR and 95% CI.

2.4. Role of the funding source

There is no funding source for this study. The corresponding authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Study characteristics

The described electronic and manual searches yielded 11,186 articles, of which 22 articles [8,20–40] comprising 90,514 HIV-positive and 66,085,278 HIV-negative pregnant women met the inclusion criteria of meta-analysis. Six other studies were included in the systematic review to assess the effects of HIV infection on the expression levels of angiogenic and anti-angiogenic factors and its relevance to the development of PE (Fig. 1). The articles included in the meta-analysis span across ten countries with studies conducted in a cohort design (11 prospective and 11 retrospective). Six studies comprising 74,323 HIV-positive and 57,285,308 HIV-negative pregnant women were also included. No randomized controlled trials were identified. One case-control study [41] was identified, but excluded as the study started with pre-eclamptic women. The study characteristics, methods used to define the outcome, and quality assessment ratings are presented in Table 1.

3.2. Results for PE

As mentioned previously, the current analysis included 22 articles comprising 66,175,792 participants. The incidence of PE was 4.33% (3926/90,514) and 3.98% (2,630,569/66,085,278) in HIV positive and HIV-negative pregnant women, respectively. Results of the meta-analysis suggest that HIV infection was not correlated to the development of PE as the study showed no significant association between these factors (RR, 1.04; 95% CI, 0.89–1.21). A substantial heterogeneity

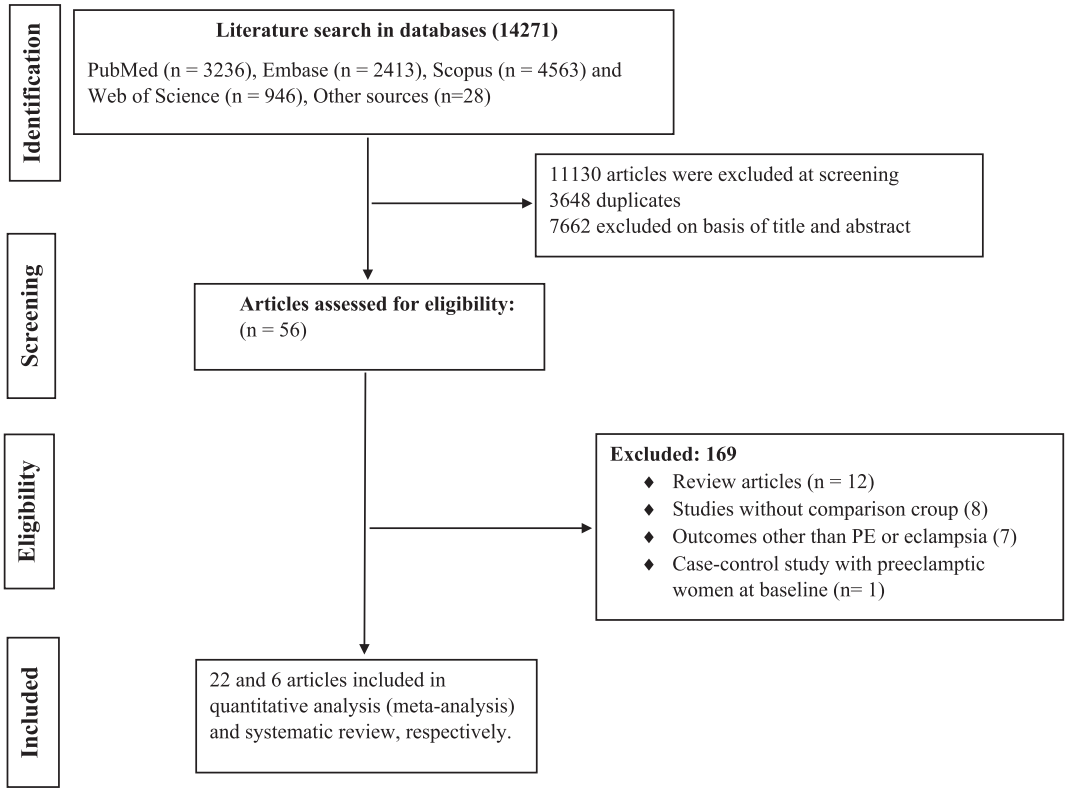

Fig. 1. Flow chart showing the process of study selection.

($\chi2 = 103.8$; $I^2 = 79.8\%$) was observed between the studies. A positive association was also not observed in two sets of studies involving prospective cohort (RR, 0.93; 95% CI, 0.63–1.37; $\chi2 = 59.37$; $I^2 = 83.2\%$) and retrospective cohort (RR, 0.98; 95% CI, 0.75–1.3; $\chi2 = 34.6$; $I^2 = 71.2\%$) study designs (Fig. 2). Moreover, a similar non-significant results were observed in sub-group analyses performed in different geographical regions; America (RR, 0.95; 95% CI, 0.83–1.08; $\chi2 = 22.7$; $I^2 = 69.3\%$), Europe (RR, 1.39; 95% CI, 0.6–3.2; $\chi2 = 24.6$; $I^2 = 83.8\%$) and Africa (RR, 1.01; 95% CI, 0.75–1.45; $\chi2 = 16.6$; $I^2 = 58\%$) (Supplementary Fig. 1), Asia (RR, 0.75; 95% CI, 0.21–2.7). As shown in Fig. 3, *meta*-regression analysis indicated a decreasing trend of RR from 1990 to 2018. There was no significant publication bias (*P* value = 0.37) in the studies on association between HIV infection and risk of developing PE (Supplementary Fig. 2).

Table 1
Main characteristics of studies investigating the association between HIV infection and pre-eclampsia and eclampsia.

First author	Publish Year	Country	PE criteria	Total pregnant women	HIV infected women			Non HIV infected women		
					N	With PE	With EC	N	With PE	With EC
Minkoff et al. [19]	1990	USA	NM	203	85	1	NM	118	4	NM
Geary et al. [20]	1995	USA	NM	1395	279	13	NM	1116	69	NM
Wimalasundera et al. [21]	2002	UK	Higgins and de Swiet	428	214	9	NM	214	12	NM
de Groot et al. [22]	2003	South Africa	ACOG	251	81	35	6	170	61	29
Frank et al. [2 3]	2004	South Africa	Davey and MacGillivray	2600	704	21	2	1896	58	6
Mattar et al. [24]	2001	Brazil	ACOG	1831	123	1	NM	1708	182	NM
Suy et al. [25]	2006	Spain	ACOG	8768	82	9	NM	8688	260	NM
Bodkin et al. [26]	2006	South Africa	NM	313	212	36	6	101	10	1
Kourtis et al. [27]	2006	USA	ACOG	8,797,145	12,378	956	NM	8,784,767	624,284	NM
Boer et al. [28]	2007	Netherlands	ISSHP	339	143	3	NM	196	2	NM
Haeri et al. [29]	2009	USA	ACOG	453	151	9	NM	302	36	NM
Singh et al. [30]	2009	India	ACOG	150	50	3	NM	100	8	NM
Waweru et al. [31]	2009	Kenya	NM	114	57	10	NM	57	7	NM
Boyajian et al. [32]	2012	Canada	ACOG	364	91	3	NM	273	14	NM
Ngene et al. [33]	2013	South Africa	NM	73	31	1	3	42	6	13
Hall et al. [7]	2014	South Africa	ACOG	2230	1093	35	NM	1173	57	NM
Landi et al. [34]	2014	Italy	ISSHP	266	126	3	NM	140	14	NM
Eon et al. [35]	2014	Nigeria	NM	210	105	2	NM	105	0	NM
Sansone et al. [36]	2016	Italy	ACOG	84,725	453	46	18	84,272	3416	1680
Olayide et al. [37]	2016	Nigeria	ACOG	766	55	0	NM	711	76	NM
Prophet et al. [38]	2018	USA	ACOG	57,271,569	72,842	2550	1239	57,198,827	2,001,955	686,385
Sebitloane et al. [39]	2017	South Africa	ACOG	1461	1159	180	NM	302	65	NM

Abbreviations: PE, Pre-eclampsia; EC, eclampsia; NM, not mentioned; ACOG, American College of Obstetricians and Gynecologists, ISHHP, International Society for the Studies of Hypertension in Pregnancy.

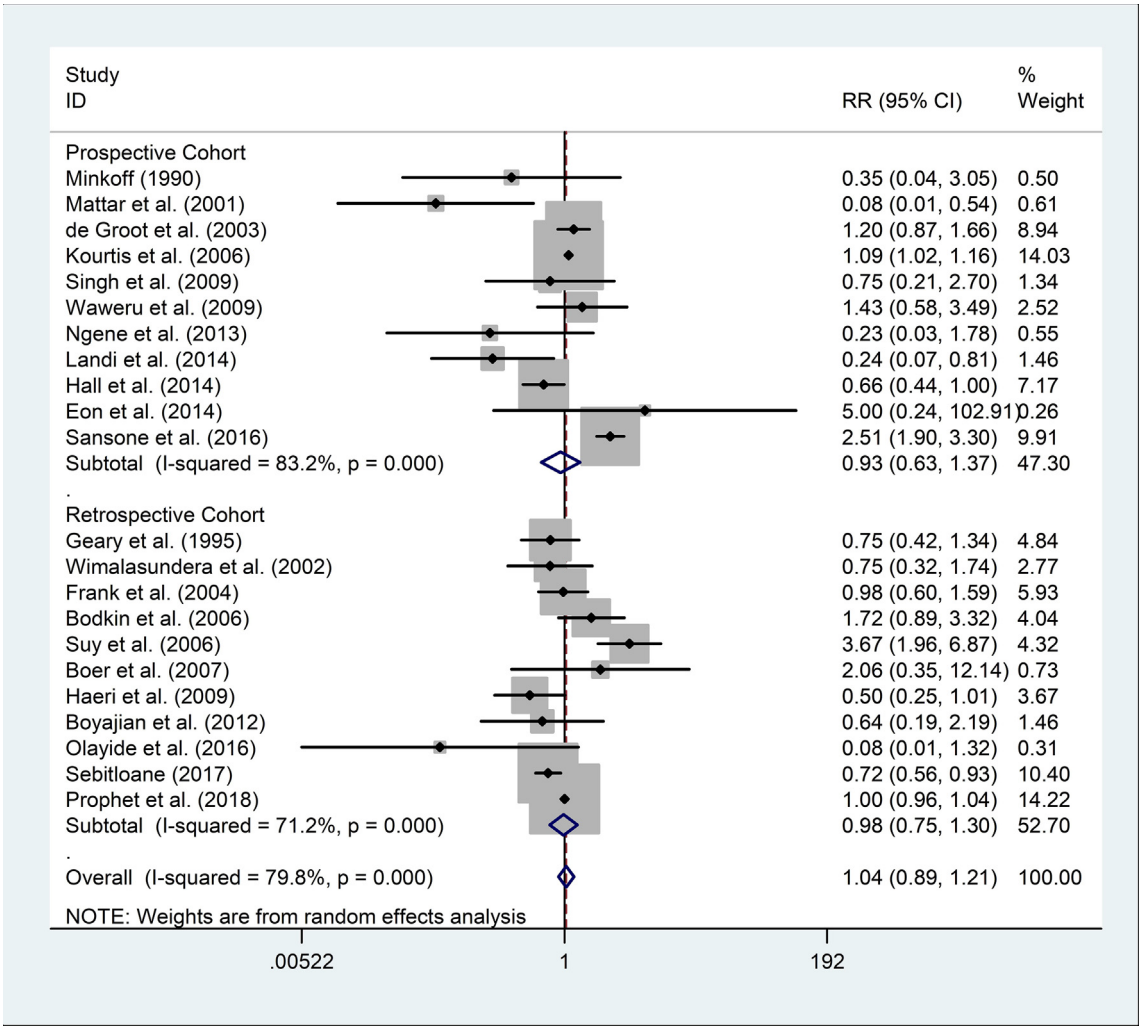

Fig. 2. Forest plot for the association between HIV infection and Pre-eclampsia. Subgroups are based on prospective or retrospective cohorts. The center of each square represents the relative risk (RR), the area of the square is the weighted percentage in the meta-analysis and the horizontal line indicates the 95% CI. % weight: weight of each study compared with all the studies.

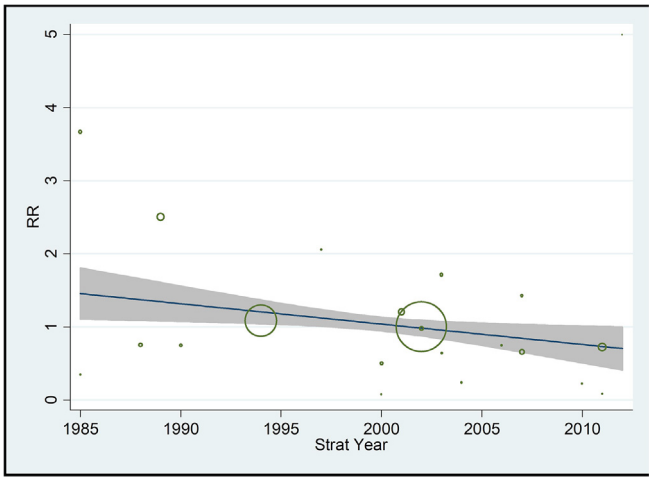

Fig. 3. Meta-regression regarding the effects of implementation year on the pooled relative risk (RR) of the association between HIV infection and Pre-eclampsia showing decreasing trend over the time.

3.3. Results for eclampsia

To evaluate the association between HIV infection and risk of eclampsia, six articles containing 57,359,631 pregnant women were included for meta-analysis. Among the six studies chosen for meta-analysis, four were performed in South Africa, one study in Italy, and one study in Unites States. The incidence of eclampsia in HIV positive pregnant women (1.71%; 1274/74,323) was slightly higher than HIV negative pregnant women 1.2% (688,114/57,285,308). Similar to PE, meta-analysis results indicated that there is no significant association regarding the maternal HIV infection and risk of eclampsia (RR, 1.05; 95% CI, 0.63–1.75). Heterogeneity between studies ($\chi 2 = 17$; $I^2 = 70.6\%$) was marginally high. In subgroup analysis, a significant association was observed in retrospective cohorts (RR, 1.42; 95% CI, 1.34–1.5; $\chi 2 = 0.74$; $I^2 = 0\%$), while prospective cohorts showed no such association (RR, 0.69; 95% CI, 0.19–2.56; $\chi 2 = 16.5$; $I^2 = 87.9\%$) (Fig. 4). Furthermore, subgroup analysis based on geographical regions (continents) resulted in no significant risk from four studies in South Africa (RR, 0.55; 95% CI, 0.27–1.13; $\chi 2 = 3.8$; $I^2 = 22.9\%$), but significant association was observed in studies performed in Italy (RR, 1.99; 95% CI, 1.26–3.14) and United states (RR, 1.42; 95% CI, 1.34–1.5) (Supplementary Fig. 3). There was no significant publication bias (P value = 0.81) in the studies with respect to association between HIV infection and risk of eclampsia (Supplementary Fig. 4).

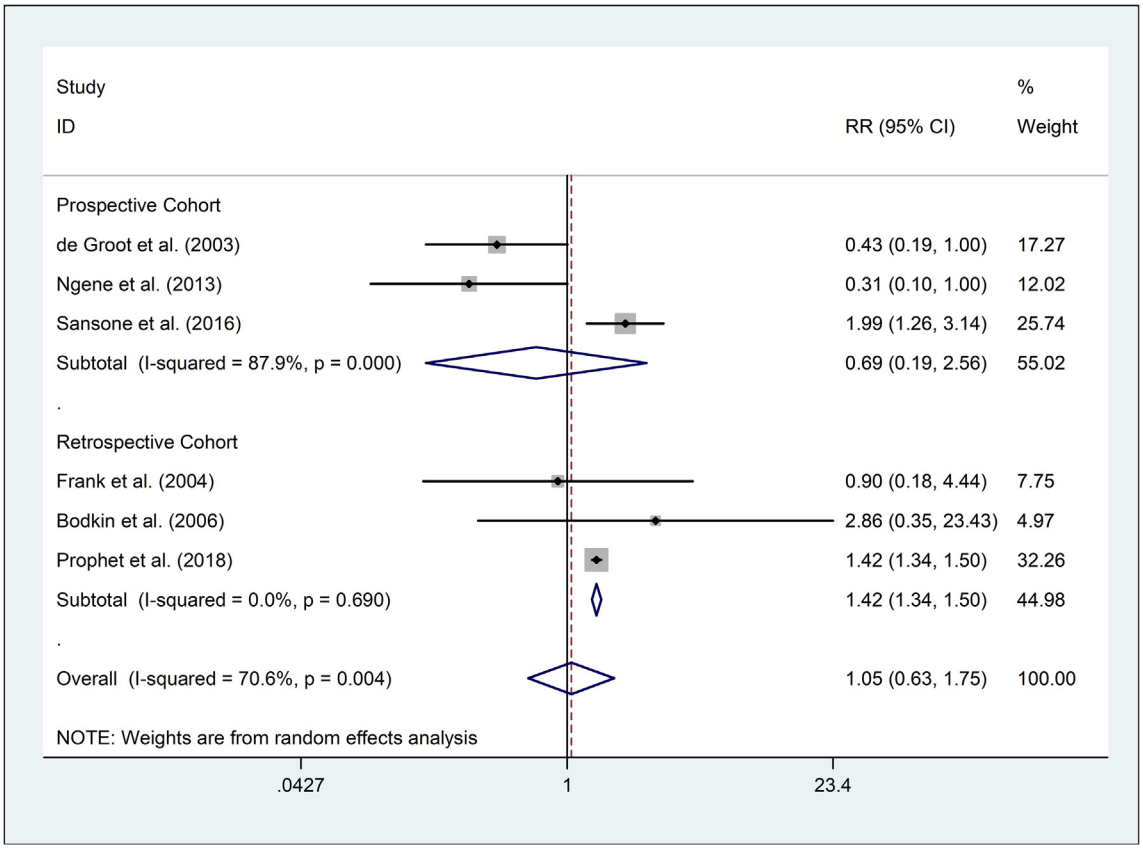

Fig. 4. Forest plot for the association between HIV infection and eclampsia. Subgroups are based on prospective or retrospective cohorts.

3.4. Results for effect of HIV on angiogenic and anti-angiogenic factors

To determine the effects of HIV infection on expression levels of angiogenic and anti-angiogenic factors in relation to the development of PE and eclampsia, we systematically reviewed literature for identification of eligible relevant studies. Our attempts yielded six eligible studies [5,6,42–45], all performed in South Africa from 2013 and later. All these studies suggested that anti-angiogenic factors are associated with the development of PE, but HIV infection does not alter the expression level of these factors in both normotensive and pre-eclamptic women. Study characteristics, measures of evaluated angiogenic and anti-angiogenic factors, and a summary of interpretation on results of these studies are presented in Supplementary Table 1.

4. Discussion

The results from the present study indicated that HIV infection was not significantly associated to the incidence of PE or eclampsia. Our meta-analysis indicated that any associated RR had a decreasing trend during the time from 1990 to 2018. These observations are in line with previous meta-analysis by Conde-Agudelo et al. who indicated that HIV infections either treated or left untreated were not associated with the risk of developing PE (Treated HIV patients: pooled OR, 0.76; 95% CI, 0.46–1.26. Untreated HIV patients: pooled OR, 0.97; 95% CI, 0.67–1.39) [46]. Also our findings are in agreements with a recent meta-analysis conducted by Browne et al., who reported that HIV infection is not associated with the development of hypertensive disorders during pregnancy [47]. Our results contradict with the findings from Calvert and Ronsmans study that reported a significant association between HIV and hypertensive disorders during pregnancy (RR,1.46; 95% CI, 1.03–2.05) [48]. These differences can be attributed to the differences in sample size, nature of the study, and criteria applied for evaluating the outcome in both the studies.

The current study is largest and the most complete study to date that evaluates the association between HIV infection and PE or eclampsia. An analysis of study subgroups involving retrospective or prospective cohorts, and different continents did not result in a significant association of HIV infection and PE. Nonetheless, HIV infection was significantly associated to eclampsia in retrospective cohorts included in the current study and in two other large studies performed in high income countries (Italy and USA) [37,40], and thus call for more well-designed studies with more participants and well defined outcomes.

Almost 19 million women are infected with HIV worldwide, and majority of them are of childbearing age. According to a 2017 estimate, there were 1.1 million pregnant women living with HIV. The current study results report that the incidence rates of PE as 4.33% (47,630 patients) and eclampsia as 1.71% (18,810 patients) for HIV-positive pregnant women. This accounts for a significant public health concern as PE and eclampsia are leading causes of maternal mortality especially in low-income African countries, and any further increase in PE rates could aggravate the disease burden in HIV-infected women.

The underlying mechanisms of HIV infection leading to PE and eclampsia is not clearly known. One possible hypothesis states that the immune suppression resulting from HIV infection may adversely impact the equilibrium between angiogenic and anti-angiogenic factors leading to PE. However, the current systematic study indicated no such association of HIV infection and expression of angiogenic and anti-angiogenic factors in normotensive and pre-eclamptic women (Supplementary Table 1). Prescription of highly active antiretroviral therapy (HAART) and subsequent immune restoration of patients could be another plausible factor for the development of hypertensive disorders including PE and eclampsia. HAART may also increases the risk of PE due to its direct toxicity on the liver [49]. New guidelines by WHO recommend that all HIV-positive pregnant women receive HAART to prevent transmission of HIV to the children. Accordingly 80% of the pregnant women living with HIV received HAART

treatments in 2017 [9]. There are some evidences suggesting that the use of HAART in pregnancy can lead to higher risk of adverse maternal and fetal outcomes, including PE, preterm birth, low birth weight, small for gestational age, and gestational diabetes mellitus [22,26,33,50]. Wimalasundera et al. reported that women living with HIV who did not receive HAART during pregnancy had significantly lower rates of PE than those who received HAART [22]. A cohort study on 1500 HIV positive pregnant women by Machado et al. indicated that the women receiving HAART at conception were at high risk of developing PE by more than 2-fold than women who received no such treatment (AOR 2.3, 95% CI 1.1–4.9) [51]. However, a cohort study in USA by Kourtis et al. reported that there was no difference in incidence of PE before and after initiation of HAART [28]. Another recent systematic review demonstrated that there was no increased risk for PE in women living with HIV receiving either HAART or ART monotherapy in comparison with pregnant women without HIV infection [52]. Another possible mechanism of the maternal HIV causing PE or eclampsia could be the direct effect of HIV infection on the placental growth or chronic inflammation and immune activation leading to disruption of immunological processes in pregnancy [10]. These mechanisms that are associated with preterm birth in maternal HIV patients need to be further investigated for their role in the development of PE or eclampsia.

Our systematic review and meta-analysis has several strengths. Using a comprehensive literature search (with no language or geographical restrictions) from four international databases, a large sample size of cohort studies, and a well-defined study outcome criteria, our study is designed to generate the best possible evidence to assess the effect of maternal HIV-infection on the development of PE and eclampsia. We strictly applied the eligibility criteria to reduce misclassification bias and used random-effects model for heterogeneity. We further applied some subgroup analyses to explore the source of heterogeneity and effects of different factors on estimates of RR. Furthermore, we performed a systematic review to determine the effects of HIV infection on angiogenic and anti-angiogenic factors that are associated with the development of PE. However, the current study also has some limitations. First, it is possible that some papers published in local journals might be missing from our literature search, although we searched main global databases, and references of the related papers. Second, it is to be noted that the majority of studies included in the review lacks data on viral load and CD4 cell counts, and therefore misses evaluation of the effects of these important confounders on the risk of developing PE. It is indicated that CD4+ cell counts are lower in woman with PE as compared to healthy controls [53]. Third, the studies included were limited to few countries and further studies expanding the geographical areas could be needed for more accurate results.

In conclusion, our findings showed no significant association between HIV infection and PE. However a significant relationship of HIV infection to eclampsia was found in retrospective cohorts and in groups involving high income countries. We think caution must be taken when drawing conclusions from these results and more studies with higher sample size and well defined outcomes are necessary to obtain the reliable conclusions regarding the effects of HIV infection and the development of PE and eclampsia.

Notes

Author's Contribution

All authors conceived the study. M.N.S, S.K, M.S, S.A, A.H.H and R.H searched databases and collected the data. M.N.S, S.M.R, Y.F, and A.R analysed and interpreted the data. M.N.S, M.J and S.E drafted the manuscript. A.R, S.M.R. and V.K.R.V, critically revised the manuscript. All the authors commented on the drafts of the manuscript and approved the final version of the article.

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None.

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.preghy.2019.07.008.

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