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Review

Gestational diabetes mellitus in HIV-infected pregnant women: A systematic review and meta-analysis

Belete Biadgo [a,*], Sintayehu Ambachew [a], Molla Abebe [a], Mulugeta Melku [b]

[a] Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

[b] Department of Hematology and Immunohematology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

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ABSTRACT

Background: Impaired glucose metabolism during pregnancy can result in a significant adverse pregnancy-outcomes. Previous studies have reported the contribution of ART to the impaired glucose tolerance and gestational diabetes mellitus (GDM) in HIV-infected pregnant women.

Methods: PRISMA guideline was followed for this systematic review and meta-analysis. The STATA version 11 was employed to compute the pooled prevalence of GDM using the random effect model and 95% confidence interval. Subgroup analysis was conducted by geographical regions. Visual inspection of the funnel plot and Egger's regression test statistic were used to show the publication bias.

Results: A total of 13,517 articles were identified, of which 21 publications met the inclusion criteria. The pooled prevalence of GDM among HIV-infected pregnant women was 4.42% (95% CI: 3.48; 5.35). According to the subgroup analysis, the pooled prevalence of GDM among HIV-infected pregnant women was 7.1% (95%CI: 3.38; 10.76) in Asia, 5.83% (95% CI: 2.61; 9.04) in Europe, 3.58% (95% CI: 2.67; 4.50) in America and 3.19% (95% CI: −2.89; 9.27) in Africa.

Conclusion: The pooled prevalence of GDM among HIV-infected pregnant women is expectedly high. Therefore, early screening of HIV-infected pregnant women for GDM is vital to reduce its complications related to pregnancy.

Protocol registration number: International Prospective Register of Systematic Reviews CRD42018090735.

Abbreviations: ADA, American Diabetes Association; ART, Antiretroviral therapy; CI, Confidence Interval; DIPSI, Diabetes in Pregnancy Study Group of India; GDM, Gestational Diabetes Mellitus; HAART, Highly active Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; MeSH, Medical Subject Headings; PIs, Protease Inhibitors; NDDG, National Diabetes Data Group; NGG, National German Guidelines; OGTT, Oral Glucose Tolerance Test; IADPSG, International Association of Diabetes and Pregnancy Study Group

* Corresponding author.
E-mail address: beletebiadigo@yahoo.com (B. Biadgo).

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Contents

1. Background

Gestational diabetes mellitus (GDM) is a glucose tolerance disorder, which is diagnosed during pregnancy for the first time. It is a common medical complications during pregnancy and affects an estimated 14% of the pregnancies [1]. It is a neglected contributor to the continuing high rate of maternal and neonatal mortality if insufficiently managed [2]. According to the global estimates, the median prevalence of GDM in North America and Europe is 7% and 5.8%, respectively [2]. Moreover, in Africa, its prevalence is estimated to be 8.9% [3].

It has been speculated that antiretroviral therapy (ART) induces glucose metabolism abnormalities which likely increases the rate of GDM in women infected with Human Immunodeficiency Virus (HIV) [4]. HIV-infected women taking protease inhibitors (PIs) are three times more likely to develop diabetes mellitus (DM) than women not taking PIs as part of their Highly Active Antiretroviral Therapy (HAART) [5]. The introduction of ART has revolutionized the care of HIV–infected pregnant women. However, their impact on the mechanism of glucose metabolism disorder in pregnancy is not well understood. A previous study reported a high incidence of GDM in HIV-infected pregnant women and PIs were contributing as a significant independent risk factors [6].

The overall prevalence of all disorders of glucose metabolism in patients on ART has been reported to be 23–25% [7,8] and associated with undesirable obstetric outcomes [9]. A study has demonstrated intra-class differences in the effect of PIs on glucose metabolism [10]. A recent meta-analysis showed no significant association between HIV-positivity and GDM [4]. As increased use of ART has transformed HIV into a chronic condition, individuals who are currently HIV-positive are likely to live a healthy and productive life, leading to increasing numbers of pregnancies among HIV-positive women in countries with access to medical care [11,12].

The rate GDM varies considerably in different studies and is likely to depend on different contributing factors, like the type of ART used, antenatal care, the diagnostic criteria for GDM and screening policy, and the ethnicity of the studied population [6,13,14]. Many evidence supported the importance of diagnosing hyperglycemia in pregnancy [15,16]. However, there is no consensus on the diagnostic criteria used for the diagnosis of GDM worldwide; and this may, at least in part, affect the prevalence of GDM in different countries.

The high rate of GDM among HIV-infected women suggests that screening of this group for GDM has utmost importance, and it also needs further study. As the global burden of diabetes during pregnancy continues to rise, addressing challenges in diagnosis, prevention and treatment are imperative to prevent maternal mortality and morbidity. However, to our knowledge, there is no systematic review and meta-analysis in the literature that estimates the pooled prevalence of GDM among HIV-infected women. Thus, this review provides empirical evidence necessary for researchers, policy-makers, and public health stakeholders to derive health-promoting policies, allocate resources, and set priorities for monitoring future trends. Therefore, the aim of this review was to estimate the pooled prevalence of GDM among HIV-infected pregnant women globally.

2. Methods

2.1. Design and protocol registration

This protocol was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P 2015 Guidelines) [17]. It has been registered in the PROSPERO, international prospective register of systematic reviews, with registration identification number of CRD 42018090735.

2.2. Study selection and eligibility criteria

2.2.1. Inclusion criteria

The review included studies that were conducted and published on GDM among HIV-infected pregnant women. We have included studies reported the prevalence of GDM among HIV-infected women, used Oral Glucose Tolerance Test (OGTT) to diagnose GDM and published in the English language.

2.2.2. Exclusion criteria

Studies where the diagnosis of GDM was based on non-fasting blood glucose measurements and non-original research articles were excluded.

2.3. Information source and search strategy

Relevant published articles were searched in Pub Med/Medline, HINARI, SCOPUS, EMBASE and Web of Sciences electronic databases. Also, Google Scholar and Google were searched for grey literature studies published during the entire temporal spectrum covered by those databases up to April 2018. The search terms were developed in accordance with the Medical Subject Headings [18] using a combination of key terms: [Gestational Diabetes Mellitus) OR Gestational Diabetes Mellitus [MeSH Terms]) OR GDM) OR GDM [MeSH Terms])] AND [Human Immunodeficiency Virus) OR Human Immunodeficiency Virus [MeSH Terms]) OR HIV) OR HIV [MeSH Terms])] AND [Pregnant women) OR Pregnant women [MeSH Terms]. Reference lists of retrieved articles were probed to identify any studies that were not retrieved from electronic databases. Content experts were contacted to get additional studies that were not retrieved by electronic database searching and reference list scrutinizing.

2.4. Outcomes of interest

The main outcome of interest of this systematic review was the prevalence of GDM among HIV-infected pregnant women worldwide. The prevalence was calculated by dividing the total number of GDM cases by the total number of study participants and the results have been stratified by geographic location.

2.5. Data extraction and quality appraisal

The relevant data from each selected study has been extracted and summarized in an Excel spreadsheet. All articles retrieved through search strategy were imported into Endnote X7 (Thomson Reuters, New York, USA). After excluding duplicate articles, titles and abstracts were independently screened for inclusion in full-text appraisal by two groups of authors; group one (BB, SA) and group two (MM, MA). Similarly, the two groups of authors were independently appraised the full texts of the studies; and in case of discrepancies, it was resolved through discussion and consensus.

For articles deemed relevant, the following variables were collected: name of the first author, year of publication, study year, study region/country, diagnostic criteria, and method of diagnosis, ART regimen, study design, the total number of participants and number of participants with GDM. When authors found multiple publications in the same dataset, the articles reported the prevalence of GDM in extractable form were used. Moreover, for prospective cohort and cross-sectional studies that reported the outcomes of interest, baseline data were used for our systematic review and meta-analysis. The quality of articles were assessed using Joana Brigg's Institute (JBI) critical appraisal checklist for simple prevalence [19] and analytical cross-sectional studies [20] having nine and eight checklist items, respectively. Studies with an overall quality assessment score of $\geq$50% on the quality scale were considered of good quality.

2.6. Data analysis and synthesis

The data were extracted using Microsoft Excel, and then exported into STATA version 11 (Stata Corp LLC, Texas, USA) for analysis. The magnitude of heterogeneity between studies was quantitatively measured by the index of heterogeneity (I^2 statistics). The I^2 values of 25%, 50%, and 75% were assumed to represent low, medium and high heterogeneity, respectively. The significance of heterogeneity was determined by the p-value of I^2 statistics, and a p-value of <0.05 was considered as an evidence of heterogeneity. When the value of I^2 was greater than 50%, sensitivity analyses were carried out. Subgroup analyses were done considering the geographic region, diagnostic criteria and ART regimen as a grouping variables. Small study effects or publication bias was evaluated using the visual funnel plot test, and Egger's statistics. A random effect model was used to estimate the pooled prevalence of GDM. The results were presented both in text and forest plot.

3. Results

3.1. Characteristics of studies

A total of 13,517 potential articles were identified through the systematic literature search. After duplicate removed, articles were screened by their title and abstract. Twenty-two articles were found to be eligible for full-text appraisal, of which 21 of them comprising 33,979 study participants were found to be eligible for meta-analysis (Fig. 1).

According to the geographic regions, two articles were from Africa [21,22], ten from America [23–32], five from Europe [6,13,33–35], and four from Asia [36–39]. The JBI quality

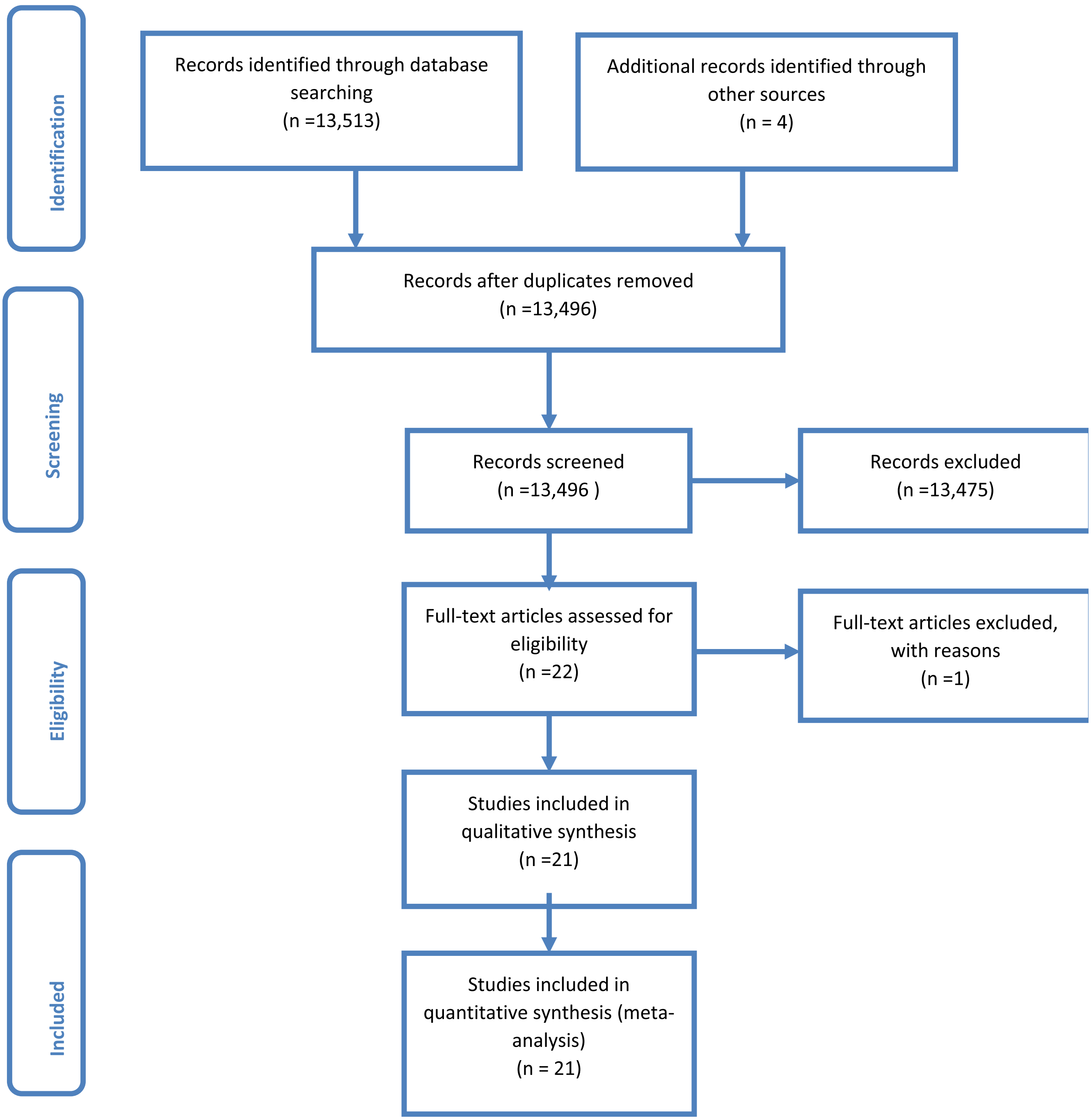

Fig. 1 – Flow chart to describe the selection of studies for a systematic review and meta-analysis of the prevalence of GDM in pregnant women infected with HIV.

appraisal checklist indicated that all of the included studies were of good quality (Table 1).

3.2. *Pooled prevalence of GDM among HIV-infected pregnant women*

The pooled prevalence of GDM among HIV-infected pregnant women was 4.42% (95% CI: 3.48–5.35). According to the subgroup analysis by geographic regions, the pooled prevalence of GDM was 7.1% (95%CI: 3.38, 10.76) in Asia, 5.83% (95% CI: 2.61, 9.04) in Europe, 3.58% (95% CI: 2.67, 4.50) in America and 3.19% (95% CI: −2.89, 9.27) in Africa (Fig. 2). Considering ART regimen as the grouping variable, the pooled prevalence of GDM was 6.05% (95%CI: 3.79, 8.31) and 3.75% (95%CI: 2.68, 4.83) among women who took PIs and combined ART regimens, respectively (Fig. 3). Similarly, a subgroup analysis was done to determine the pooled prevalence of GDM by the diagnostic criteria used to diagnose GDM and it was 7.42% (95%CI: 2.93, 11.91) and 5.71% (95%CI: 2.70, 8.72) according to the American Diabetes Association (ADA) and National Diabetes Data Group (NDDG) criteria,

Table 1 – The characteristics and outcomes of studies included in the *meta*-analysis (n = 21).

Authors name, (References)	Year of publication	Geographic region	Study design	Diagnostic criteria used	Type of ART medication	Mean age	Sample size	GDM (%)	Study quality
Jao et al. [21]	2013	Africa	Cross-sectional	ADA	Combined ART	30.5	166	6.6	Good
Van der Merwe et al. [22]	2011	Africa	Cohort	–	Combined ART	30.1	1079	0.37	Good
Yudin et al. [23]	2016	America	Cross-sectional	ADA	Combined ART	38.1	142	6.0	Good
Tuomala et al. [24]	2005	America	Cohort	–	Combined ART	32	2543	3.0	Good
McGowan et al. [25]	1999	America	Cross-sectional	–	Combined ART	29	30	3.3	Good
Hitti et al. [26]	2007	America	Cohort	ADA	Protease Inhibitors	29[#]	149	8.72	Good
Ewing et al. [27]	2016	America	Cross-sectional	–	Protease Inhibitors	–	11,858	3.85	Good
Kourtis et al. [28]	2006	America	Cross-sectional	–	Combined ART	–	12,378	2.3	Good
Chmait et al. [29]	2002	America	Cross-sectional	ADA	Protease Inhibitors	–	39	30.77	Good
Beitune et al. [30]	2006	America	Cohort	–	Combined ART	22.5	57	5.26	Good
Watts et al. [31]	2004	America	Cohort	ADA	Combined ART	28.3	1407	2.1	Good
Arab et al. [32]	2017	America	Cohort	–	–	–	1997	4.41	Good
Reitter et al. [40]	2014	Europe	Cohort	NGG	Combined ART	31.1	330	11.4	Good
Gonzalez-Tome et al. [41]	2008	Europe	Cohort	NDDG	Protease Inhibitors	33	609	7.0	Good
Moore et al. [33]	2015	Europe	Cross-sectional	O'Sullivan's	Protease Inhibitors	31	263	2.1	Good
Pinnetti et al. [34]	2009	Europe	Cohort	NDDG	Protease Inhibitors	33	78	7.7	Good
Aebi-Popp et al. [35]	2010	Europe	Cohort	NDDG	Combined ART	32	266	2.6	Good
Rani et al. [36]	2016	Asia	Cross-sectional	DIPSI	Combined ART	–	100	11.0	Good
Wetchittichareon et al. [37]	2013	Asia	Cross-sectional	NDDG	Protease Inhibitors	28.9	109	7.3	Good
Marti et al. [38]	2007	Asia	Cohort	–	Combined ART	30.9	167	8.9	Good
Dadhwal V [39]	2017	Asia	Cross-sectional	DIPSI	Combined ART	25.72	212	3.3	Good

Note: **ADA:** American Diabetes Association; **ART:** Antiretroviral Therapy**;** **DIPSI:** Diabetes in Pregnancy Study Group of India; **NDDG**: National Diabetes Data Group; **NGG:** National German Guidelines; **OGGT**: Oral Glucose Tolerance Test; –: Not reported.

[#] Reported in median age.

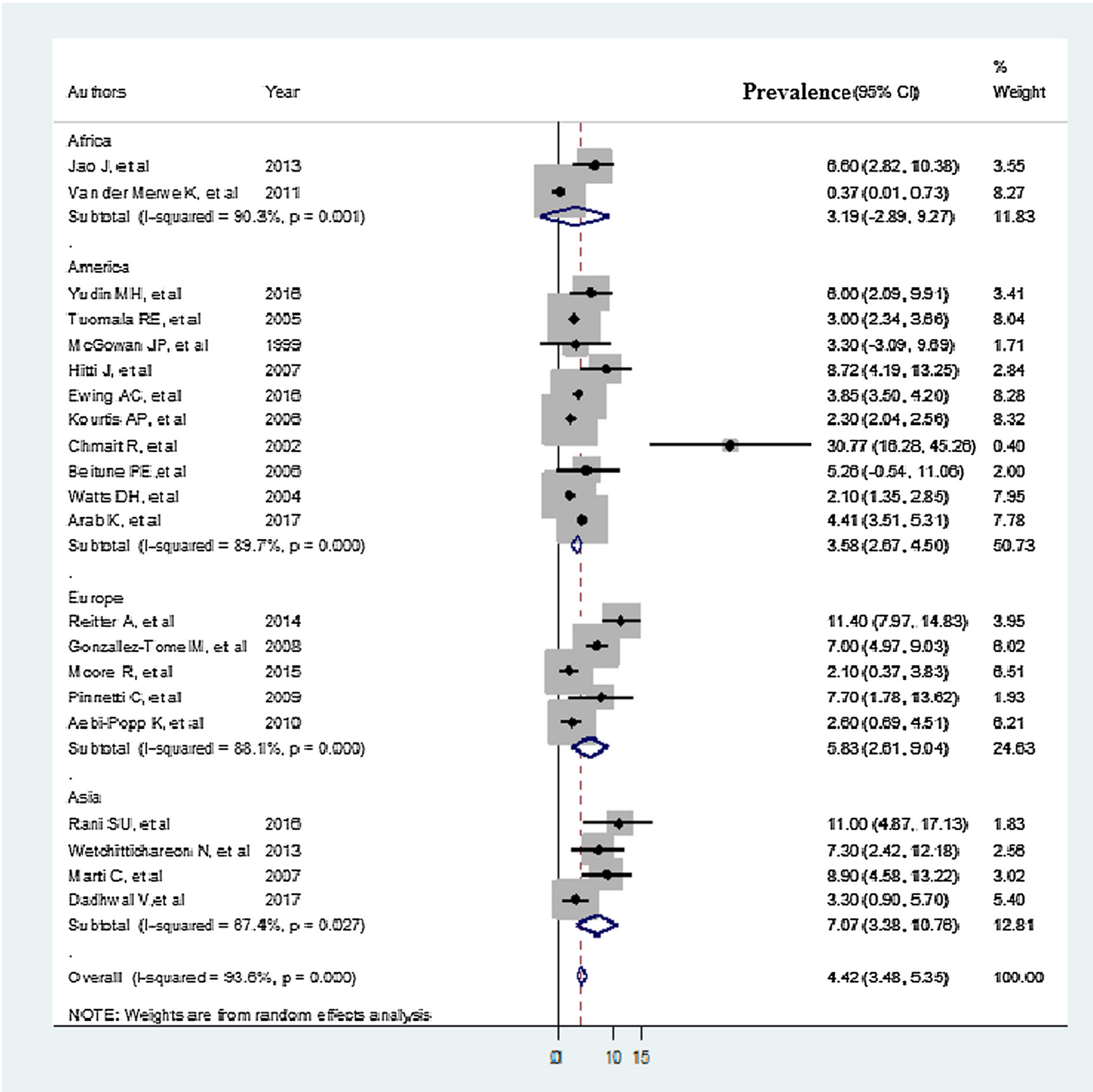

Fig. 2 – Forest plot showing pooled prevalence of GDM among HIV-infected pregnant women by continent-a subgroup analysis.

respectively. Unfortunately, about one-third of the studies did not report the criteria used to diagnose GDM (Fig. 4).

3.3. *Single study influence analysis on the overall estimate of the meta-analysis*

Sensitivity analysis was done to test the effect of each study on the pooled estimate of the prevalence of GDM by excluding each study step-by-step. The result showed that excluded studies did not show much influence in the pooled prevalence of GDM (Supplementary table 1).

3.4. *Publication bias*

The included studies were assessed for potential publication bias visually by funnel plot (Supplementary Fig. 1). The funnel plot seemed to be symmetrical, indicating the absence of publication bias. In addition, Egger's statistics showed that the there was no publication bias (egger's regression coefficient = 1.763 and p-value = 0.11).

4. Discussion

In this systematic review and meta-analysis, the pooled prevalence of GDM among HIV-infected pregnant women was 4.42%. The evidence generated is an input for the researchers to further explore the biological interplay of HIV and GDM, and for policymakers in designing strategies to reduce pregnancy-related morbidity and mortality among HIV-infected pregnant women.

The pooled prevalence of GDM among HIV-infected pregnant women was 4.42% (95% CI: 3.48, 5.35). This result was

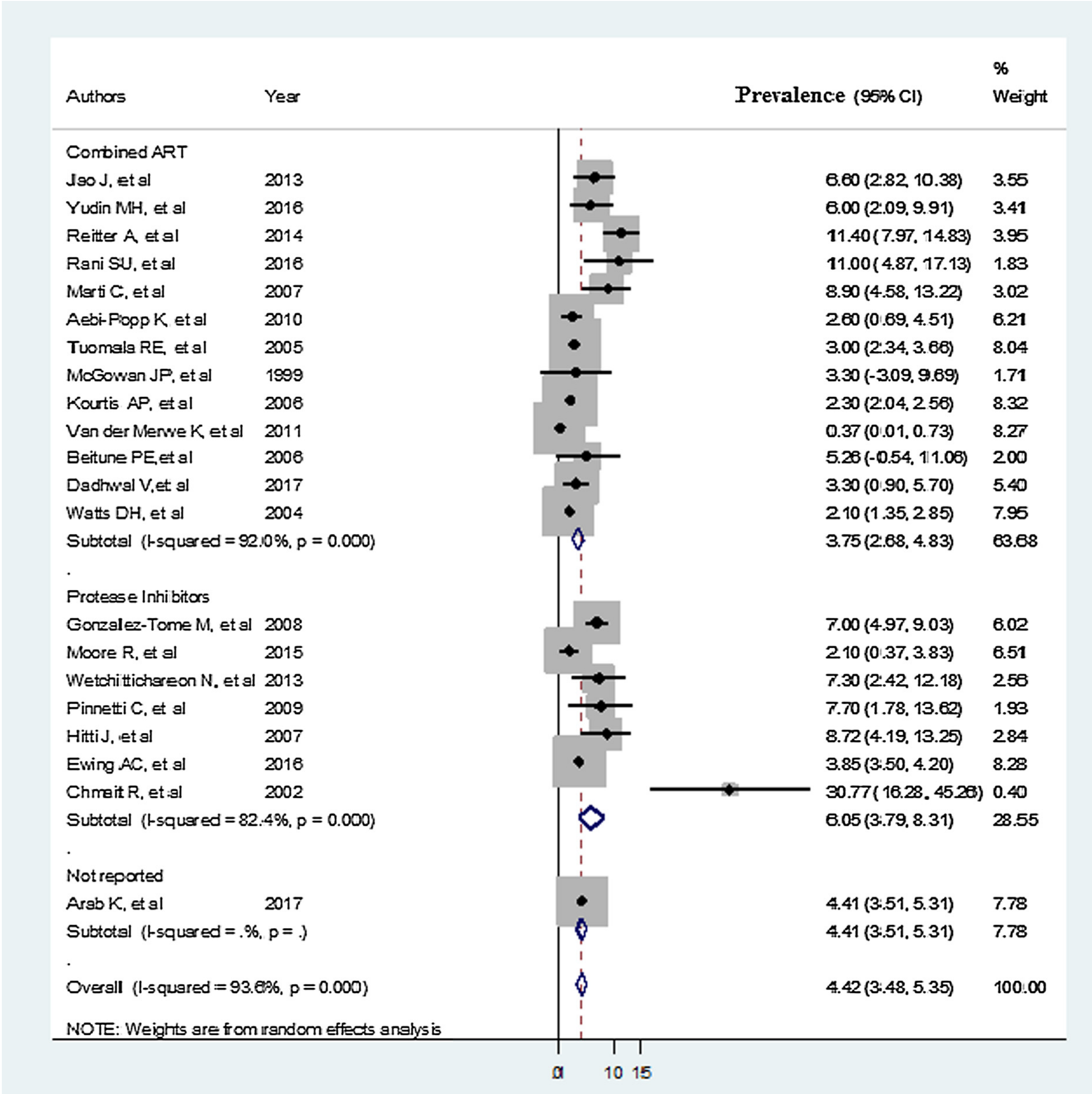

Fig. 3 – Forest plot showing pooled prevalence of GDM among HIV-infected pregnant women by ART regimen-a subgroup analysis.

consistent with GDM among a general population of pregnant women in Europe (2–6%) [42]. On the contrary, the finding was lower than the global GDM prevalence estimated by the World Health Organization (8.5%) [43], the International Federation of Gynecology and Obstetrics (14%) [44], and International Diabetes Federation in 2013 (13.8%) [45] and 2017(14%) [46] among the general population of pregnant women. Moreover, our estimate was lower than a systematic review and meta-analysis estimates of GDM among general pregnant women population in China (14.8%) [47] and Eastern and Southeastern Asian countries (10.1%) [48]. The possible explanation for these discrepancies might be related to the differences in the population studied; lack of consensus on testing methods and diagnostic glycemic thresholds.

The subgroup analysis revealed that the pooled prevalence of GDM among HIV-infected pregnant women was 7.07% (95% CI: 3.38, 10.76) in Asia, 5.83% (95%CI: 2.61, 9.04) in Europe, 3.58% (95%CI: 2.67, 4.50) in America and 3.19% (95%CI: 2.89, 9.27) in Africa. There are evidence in regional differences regarding the distribution of GDM, such as in Africa and Asia; with the prevalence ranging up to 13.9% in Africa and 17.8% in Asia [3,49]. Moreover, the regional variability of DM was reported for the general population in Europe (8.5%) [50], and South-East Asia region (9%) [51] and United States (9.4%) [52] which was higher than the finding of this study. There is no clear reasons for the discrepancies in prevalence across continents, but it has been speculated that it may be due to socioeconomic, ethnic and lifestyle disparities. For

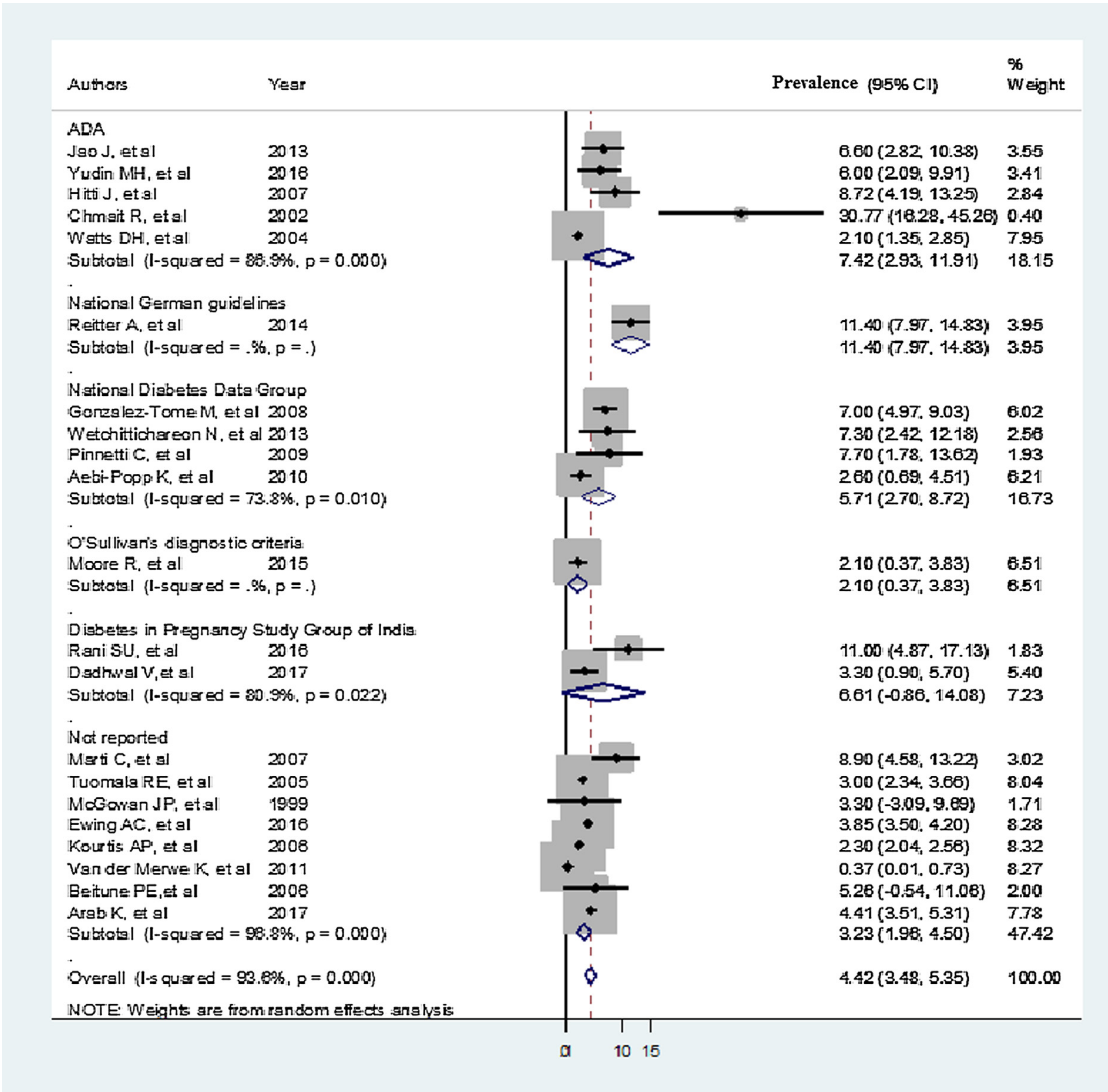

Fig. 4 – Forest plot showing pooled prevalence of GDM among HIV-infected pregnant women by diagnostic criteria-a subgroup analysis.

instance, a higher risk of GDM has been reported in Asian women compared with their Caucasian, African-American, and Hispanic counterparts [53]. The other factors that may contribute to the variation in prevalence across the continents might be the difference in access to the maternal health care facility for the screening of GDM. In most developed countries, improvement in an access and use of ART has transformed HIV into a chronic condition; individuals who are currently HIV-positive are likely to live a healthy and productive life, leading to increasing numbers of pregnancies among HIV-infected women [11,12].

In this review, the pooled estimated prevalence of GDM in Africa, 3.19% (95%CI: 2.89, 9.27), is lower than in other regions. As many African populations are undergoing rapid transformation, the toxic combination of early life undernutrition in uterus and infancy, combined with excessive weight gain in later life may contribute to increased GDM susceptibility [54], and it is expected that the prevalence of GDM in Africa is higher than reported elsewhere. However, due to lack of prevalence data, our estimate was lower in Africa than other continents.

Considering ART regimen as a grouping variable, the pooled prevalence of GDM was 6.05% (95%CI: 3.79, 8.31) and 3.75% (95%CI: 2.68, 4.83) among women who took PIs and combined ART regimens, respectively. We have found a high prevalence of GDM among PIs compared to combined ART users. This finding is supported by previous study which reported that the use of PIs based regimen is linked to glucose intolerance with rate up to 23% [55] and exposure to first-generation PIs increased risk of developing GDM [48]. The possible explanation for this variation is that, the use of PIs was associated with a significantly higher risk of insulin resistance and lipid metabolism in HIV-infected patients due to alteration in the production of some endocrine hormones that are involved in glucose metabolism [56,57].

Moreover, the subgroup analysis was done based on the diagnostic criteria employed for diagnosis of GDM. About one-third of the studies did not report the diagnostic criteria used. According to ADA criteria, the prevalence of GDM, 7.42% (95%CI: 2.93, 11.91), was in line with Germany national guidelines (NGG) of GDM (11.4%). However, according to the NDDG criteria, 5.71% (95%CI: 2.70, 8.72), the finding was lower compared to the NGG of GDM [44]. Worldwide, there is a lack of uniformity on the diagnostic criteria used for the diagnosis of GDM, and this phenomenon affects the prevalence of GDM in different countries. The lack of uniformity in screening methods, definition, and diagnostic criteria for GDM makes it difficult to compare the prevalence of GDM between and within countries. Therefore, it is necessary to develop a standardized approach to allow for comparison of GDM burdens worldwide.

The limitations of this study were: substantial heterogeneity of GDM prevalence across studies, inconsistencies in using diagnostic criteria for GDM; and risk of bias in the original studies which made the comparison of our result to other estimates difficult. Given these limitations, this is the first study that systematically synthesized data on the prevalence of GDM among HIV-infected women in global perspective. In conclusion, the pooled prevalence of GDM among HIV-infected pregnant women was high. Hence, early screening of HIV-infected pregnant women for GDM is crucial to reduce pregnancy-related complications.

Acknowledgement

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Availability of data and materials

All data pertaining to this study are contained and presented in this document.

Authors' contributions

BB involved in the design, selection of articles, data extraction, statistical analysis and manuscript writing. MM involved in designing the protocol, statistical analysis and manuscript writing. SA, MA, and MM also involved in data extraction, analysis, and manuscript editing. All authors read and approved the final draft of the manuscript.

Consent for publication

Not applicable.

Declaration of Competing Interest

The authors declared that there is no competing interest.

Funding Statement

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107800.

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