Review Article

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Prevalence of Gestational Diabetes Mellitus in Nepal: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Gestational diabetes mellitus is a condition of glucose intolerance during pregnancy. The burden of Gestational diabetes mellitus is ever increasing including a lower middle-income country like Nepal.

Methods: This meta-analysis was conducted in accordance to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Databases of "Embase", "Google Scholar", "Scopus", "Web of Science" were searched for observational studies in Nepal from 2000 to July 2021. Random effect model was used to estimate the pooled prevalence subgroup analysis.

Results: This systematic review and meta-analysis analyzed 9 studies with a total of 20865 participants. Pooled prevalence of gestational diabetes mellitus was 2.61% (95% CI: 1.25- 5.37). From subgroup analysis, the prevalence of Gestational diabetes mellitus according to the diagnostic criteria were: International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria 6.56% (95% CI: 4.79-8.92), World Health Organization (WHO) criteria 4.81% (95% CI: 3.79-6.08), Diabetes in Pregnancy Study Group of India (DIPSI) criteria 4.71% (95% CI: 3.06-7.18), Carpenter and Coustan criteria (CC) 1.08% (95% CI: 0.43-2.71); prevalence according to the publication time: before 2015 1.20% (95% CI: 3.64-6.41), in and after 2015 4.84% (95% CI: 0.42-3.39); prevalence according to the place: within Kathmandu valley 2.70% (95% CI: 1.17-6.08), outside Kathmandu valley 2.28% (95% CI: 0.26-17.15).

Conclusion: Our study revealed the increasing prevalence of GDM in Nepal. Further large observational studies at local levels are essential to measure the actual burden, risk factors and potential preventive measures for Gestational diabetes mellitus.

Keywords: Diabetes in pregnancy; gestational diabetes mellitus; meta-analysis; Nepal; prevalence.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of carbohydrate intolerance diagnosed for the first time during pregnancy, irrespective of gestational age and parity.[1] Pregnancy is a diabetogenic state associated with hyperinsulinemia and insulin resistance due to placental hormones.[2] The high-risk factors for GDM are age more than 30 years, marked obesity, previous history of GDM, family history of type 2 diabetes mellitus (T2DM) and poor obstetrical outcome in the past.[3] In 2017, about 18.4 million women affected by some form of hyperglycemia in pregnancy were diagnosed with GDM.[4] GDM has now become an important issue of public health concern.[5]

GDM is responsible for maternal, fetal as well as, neonatal complications. Maternal complications include recurrent genitourinary infections, preterm labor, premature rupture of membrane, post-partum hemorrhage. Around 10-30% of pregnant women with GDM develop pre-eclampsia. The risk of developing T2DM in later life in women with history of GDM is around seven times than those without GDM.[6] Fetal consequences are hyperglycemia, macrosomia, shoulder dystocia, increased incidence of abortion, intrauterine death, still birth. Neonatal complications include respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia and neonatal macrosomia.[7, 8] They also have an increased risk of developing childhood obesity and/or metabolic syndrome.[7, 9]

Nepal is composed of 77 districts, 7 provinces and

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approximately 30 million residents.[10] Various studies have shown the increasing prevalence of GDM in Nepal. However, a systematic calculation of the burden of GDM in Nepal is still lacking. Therefore, this systematic review and meta-analysis was conducted to estimate the prevalence of GDM in Nepal.

METHODS

This systematic review and meta-analysis with pre-defined methodology was registered in PROSPERO (CRD42021270618). We used the Preferred Reporting Items for Systemic review and Meta-Analysis (PRISMA) statement in conjugation with the PRISMA checklist and flow diagram, for manuscript format development.[11]

LITERATURE SEARCH

We searched the online databases of "Embase", "Google Scholar", "Scopus", and "Web of Science" to identify all the relevant published articles from 2000 to July 2021. For literature search the keywords were "Gestational diabetes mellitus", "Diabetes in pregnancy", "Prevalence", "Epidemiology" and "Nepal" and search was conducted using suitable Boolean operators. Authors of some studies were contacted via email and ResearchGate for the retrieval of full texts and clarification of doubts wherever required. A detail of the literature search is shown in the Supplementary file (Appendix 1).

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Cross-sectional studies aimed at finding the prevalence of GDM in Nepal in any age group of pregnant females in any setting.

GDM diagnosed using standard criteria.

Sample size more than 100.

Studies published in English language from 2000 till July 2021.

EXCLUSION CRITERIA

Studies other than cross sectional study.

Review articles, conference papers, letter to the editor, case reports.

Articles published in a language other than English.

Not accessible/irretrievable full texts.

Studies with insufficient information and incomplete outcomes of interest.

STUDY SELECTION

Literature search was performed utilising the aforementioned search strategy. After screening through titles and abstracts, key articles were identified by consensus. Full articles were obtained for all studies meeting the inclusion criteria for further assessment. Bibliographies of selected articles were also searched to identify relevant studies. The final list of included studies had the concurrence of all authors.

DATA ABSTRACTION

Studies obtained from the electronic databases, supplementary sources, and manual searching were exported to Endnote reference software version 20.2 (Thomson Reuters, Stamford, CT, USA) in the compatible formats. Duplicate articles were screened first by Endnote and then manually. Duplicates were then recorded and removed. For multiple publications of the same data in more than one journal, the most inclusive, comprehensive studies, with larger sample size, and the most recent ones were considered for review.

Data abstraction was done in Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA). The data items extracted from each study were author, journal, study duration, year of publication, study site, mean age/ age group, diagnostic criteria, sample size, cases and prevalence of GDM.

QUALITY ASSESSMENT

To evaluate the quality of the studies included in this review, the modified Newcastle-Ottawa Scale[12, 13] for cross-sectional studies was used. Critical appraisal was conducted by two reviewers (PP and KP) independently of each other. Cohen's kappa was used to determine interrater reliability and assess the level of agreement between two authors in the quality assessment of the studies. The mean score of two authors was taken for the final decision, and articles with a score ≥5 out of 10 were included in the analysis. The details of the quality assessment have been mentioned in the Supplementary file (Appendix 2 and 3).

STATISTICAL ANALYSIS

Prevalence estimates of gestational diabetes mellitus were calculated by pooling the study-specific estimates with its 95% confidence interval using the Der Simonian and Laird's random effect model.[14] Heterogeneity was assessed across studies using I^2 index (0% to 40%: not important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity) indicating the percent of total discrepancy due to studies variation.[15] Sub-group

analyses were performed to examine the effects of study publication year, diagnostic criteria and study site on the prevalence of GDM.

Publication bias was assessed using a funnel plot in which log-transformed prevalence rates were plotted against Standard Error and Egger test. A p-value < 0.05 was considered suggestive of statistically significant publication bias. The 'meta' package (version 4.18-2) and 'metafor' package (version 3.0-2) in R statistical software and R Studio as Integrated Development Environment were used for the meta-analysis.[16]

RESULTS

STUDY SELECTION

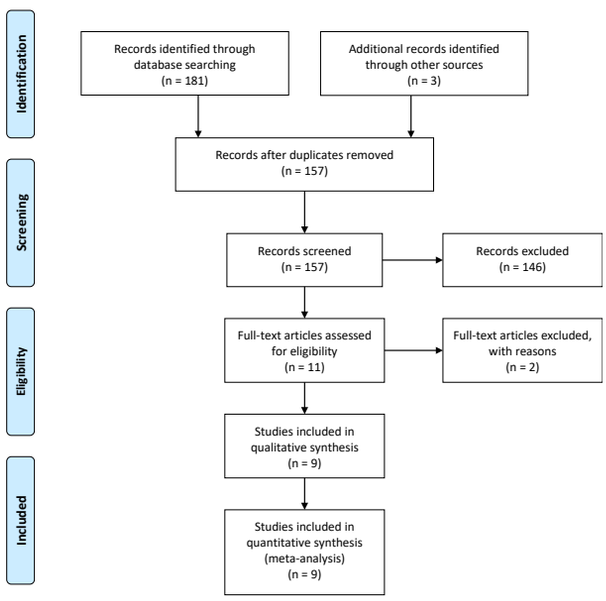

Figure 1. PRISMA flow diagram for study selection

The initial electronic search identified 184 articles. After adjustment of duplicates, 157 articles remained. Of these, 146 articles were excluded after reading their titles and abstracts as they did not meet the inclusion criteria. Eleven full text articles were reviewed for eligibility and finally nine were included for systematic review. The PRISMA diagram detailing the selection process is shown in Figure 1.

QUALITY ASSESSMENT

A risk-of-bias assessment of all the included studies was carried out using the Newcastle Ottawa Scale for cross-sectional studies. All the articles scored more than 5 during quality assessment and were included in the analysis. The value of Cohen's Kappa was found to be 0.534, which can be considered to be "moderate agreement". illustrated in the Supplementary file (Appendix 3).

STUDY CHARACTERISTICS

Altogether 9 articles were included in this review, all of which were cross-sectional study. The total study population consisted of 20865 participants. The study population ranged from 256 (Joshi et al.) to 13382 (Sharma et al.). The studies were conducted in 7 different districts: one from Solukhumbu, Dhading and Kailali, two from Lalitpur, five from Kathmandu and one from Kavre district of Nepal. This has been illustrated in Figure 2. The year of publication of the studies ranged from 2011 (Shrestha A. et al.) to 2020 (Shrestha B. et al.). The diagnostic criteria used by the studies were Carpenter and Coustan (CC),[17] World Health Organization (WHO) 1999,[18] WHO 2013,[18] International Association of Diabetes and Pregnancy Study Groups (IADPSG),[19] Diabetes in Pregnancy Study Group of India (DIPSI)[20] and American Diabetes Association (ADA) criteria.[21] The cutoff values of serum glucose in these criteria are highlighted in Table 1. For studies reporting prevalence using two or more diagnostic criteria, one with the highest prevalence was considered in the meta-analysis. A detailed description of the characteristics of individual studies is shown in Table 2.

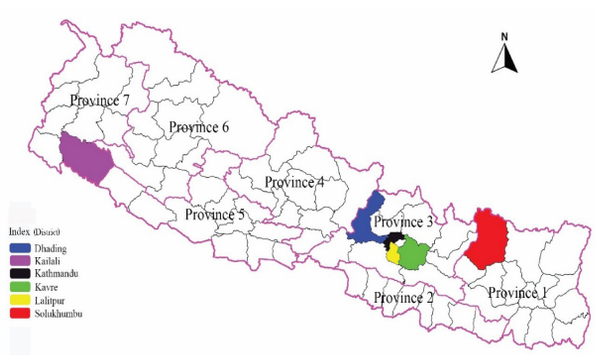

Figure 2. Districts included in the studies

Table 1. Diagnostic criteria for GDM

Criteria	**CC** (Assuming a prior non-fasting 50gm GCT ≥135mg/dl) 100 gm OGTT Serum glucose level (mg/dl)	**WHO 1999** 75gm OGTT Serum glucose level (mg/dl)	**WHO 2013** 75gm OGTT Serum glucose level (mg/dl)	**IADPSG** 75gm OGTT serum glucose level (mg/dl)	**DIPSI** 75gm OGTT Serum glucose level (mg/dl)	**ADA** 75gm OGTT Serum glucose level (mg/dl)
Fasting	≥ 95	≥ 126	≥ 92-125	≥ 92	Not required	≥ 95
1 hr.	≥ 180	Not required	≥ 180	≥ 180	Not required	≥ 180
2 hr.	≥ 155	≥ 140	≥ 153-199	≥ 153	≥ 140	≥ 155
3 hr.	≥ 140	Not required	Not required		Not required	
Criteria for GDM diagnosis	Two or more values raised above cutoff	One value raised above cutoff is sufficient	One or more value raised above cutoff	At least one value raised above cutoff	Single value raised above cutoff	Two or more values raised above cutoff

Table 2. Study Characteristics of Included Articles

Study	Study Duration	Year of Publication	Study Design	Study Site	Mean Age (Age Group)	Diagnostic Criteria	Study Population	GDM Cases	Prevalence %
Thapa P et al.[22]	2009-2010	2015	Cross sectional	Solukhumbu, Kailali, Dhading	23.3 ± 4.4	WHO, IADPSG	564	14(WHO) 37(IADPSG)	2.48 (WHO), 6.56 (IADPSG)
Sharma P.K. et al.[23]	2005-2007	2010	Cross sectional	Lalitpur	20 to 40	Carpenter and Coustan	13,382	53	0.4
Joshi R. et al.[24]	2008-2009	2017	Cross sectional	Lalitpur	NA	WHO, ADA	256	16(WHO), 10(ADA)	6.25, 3.9
Bajracharya A. et al.[25]	2013	2014	Cross sectional	Kathmandu	30.02±3.513 (20 to 35)	Carpenter and Coustan	2845	45	1.58
Tamrakar P.[26]	2013	2014	Cross sectional	Kathmandu	25.64 ± 4.06	WHO	510	22	4.31
Shrestha B. et al.[27]	2016-2017	2018	Cross sectional	Kathmandu	NA	WHO	600	27	4.5
Shrestha B. et al.[28]	2019	2020	Cross sectional	Kathmandu	GDM positive women=26.56(±5.02); GDM negative = 25.9(±4.66)	WHO, DIPSI	425	19 (WHO), 20 (DIPSI)	4.47, 4.71
Shrestha A. et al.[29]	2009-2010	2011	Cross sectional	Kavre	15 to 40	Carpenter and Coustan	1598	12	0.75
Basnet T. et al.[30]	2014-2015	2018	Cross sectional	Kathmandu	25.83±4.34(17 to 43)	Carpenter and Coustan	685	17 (Cutoff 140mg/dl), 20 (cutoff 130 mg/dl)	2.48, 2.91

POOLED PREVALENCE OF GESTATIONAL DIABETES MELLITUS

The pooled prevalence of gestational diabetes mellitus was 2.61% (95% CI: 1.25- 5.37), based on 9 articles in a sample of 20865 participants, irrespective of the diagnostic criteria used. Higgins I^2 = 97.12% showed the presence of considerable heterogeneity between individual studies. The graphical display of the pooled prevalence of gestational diabetes is presented in Figure 3.

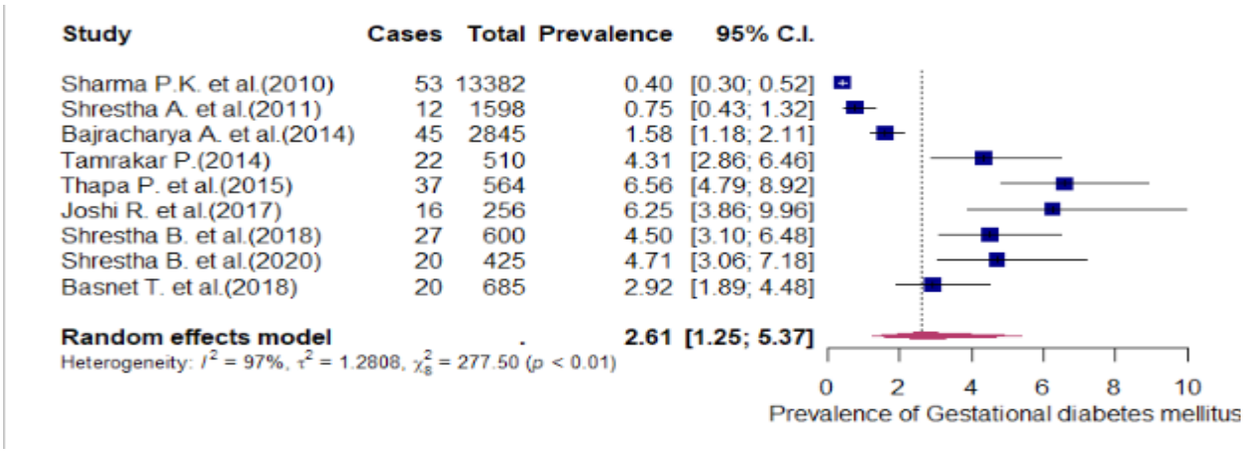

Figure 3. Forest Plot with 95% CI for the Pooled Prevalence of GDM

SUB-GROUP ANALYSIS

Subgroup analyses on the basis of criteria used to diagnose GDM, publication time (published before 2015 or published after 2015) and study site (inside Kathmandu valley or outside Kathmandu valley) were carried out to find the prevalence of GDM. When analysed by criteria used to diagnose GDM, the highest prevalence was found using IADPSG criteria (6.56%, 95% CI: 4.79-8.92), followed by WHO criteria (4.81%, 95% CI: 3.79-6.08), and DIPSI criteria (4.71%, 95% CI: 3.06-7.18) while the lowest prevalence was seen in the studies utilising Carpenter and Coustan criteria (1.08%, 95% CI: 0.43-2.71). The higher prevalence of GDM using WHO criteria compared to Carpenter and Coustan criteria was statistically significant (p < 0.001).

A subgroup analysis according to publication time revealed higher prevalence of GDM in studies published in and after 2015 (4.84%, 95% CI: 3.64-6.41) compared to the studies published before 2015 (1.20%, 95% CI: 0.42-3.39) which is statistically significant (p < 0.001).

Furthermore, the prevalence of GDM was higher among the participants of the Kathmandu valley (2.70%, 95% CI: 1.17-6.08) than outside the Kathmandu valley (2.28%, 95% CI: 0.26-17.15) which is not statistically significant (p=0.89).

PUBLICATION BIAS

Egger's regression asymmetry test was statistically insignificant (p = 0.5584) which is interpreted as no publication bias. As there are less than 10 studies included in the meta-analysis, funnel plot asymmetry does not give sufficient power to the test and may not detect real asymmetry. However, the funnel plot visualizing publication bias amongst the 9 studies used for meta-analysis is shown in Figure 4. Publication bias for subgroup analysis was not possible due to a smaller number of studies.

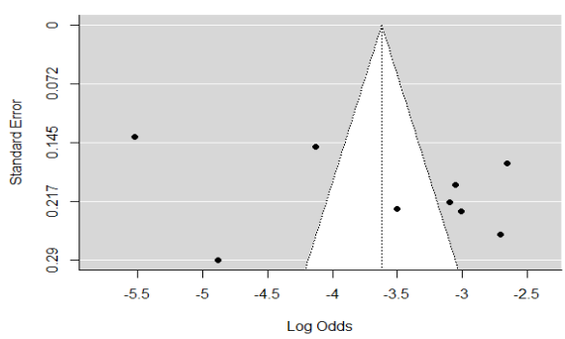

Figure 4. Funnel Plot for Publication Bias

DISCUSSION

This is the first systematic review and meta-analysis with an aim of finding the prevalence of GDM in Nepalese population. The pooled prevalence was calculated using Der Simonian and Laird's random effects model.

The study by Gandevani et al. showed that the worldwide prevalence of GDM, regardless of screening threshold category, was 4.4%.[31] A study conducted by Lee et al. showed 11.5% prevalence of GDM in Asia.[32] Similarly, a study by Nguyen et al. showed a 10.1% prevalence of GDM in Eastern and Southeastern Asia.[33] The prevalence of GDM in neighboring countries was 10.13% in India,[34] 9.7% in Bangladesh,[35] 14.8% in China[36] and 11.8% in Pakistan.[37] According to our meta-analysis, the pooled prevalence of GDM in Nepal was 2.61%, ranging from 0.40% to 6.25%. This pooled prevalence of GDM in Nepal is considerably lower in comparison to the regional and worldwide prevalence.

All the studies in this meta-analysis are hospital based. The study of Lee et al. showed similar prevalence of GDM between hospital and community settings (12.1% vs 11.1%).[32] So, based on this evidence even if GDM is

screened in a community setting of Nepal there might be similar or even low burden of GDM as compared to this hospital-based burden. This is also supported by facts such as having lower odds of overweight/obesity and comparatively early age at marriage in rural Nepal which are protective factors for reducing the risk of GDM[38].

In Nepal, only 56.5 percent of pregnant women attend at least 4 Antenatal Clinic (ANC) visits and 65.6 percent of deliveries happen in hospital. [39] This signifies the low health seeking behavior of pregnant females in Nepal. Since GDM screening and diagnosis in the included studies were out carried in ANC clinic , the lower percentage of pregnant women attending ANC clinics might have resulted into lower screening and diagnosis and hence a low prevalence of GDM. The percentage of pregnant women visiting health care settings should be larger to obtain information on true burden of GDM. If the true prevalence of GDM in Nepal is as low as determined by the meta-analysis, a lot of pregnant mothers might be unaware regarding GDM or just diabetes mellitus in general. A poor level of knowledge of pregnant Nepalese women regarding diabetes mellitus has been described in the literature.[40]

A considerable heterogeneity (I2 = 97.12%) was observed in the overall prevalence of GDM in our analysis. This may be due to different diagnostic criteria used in different places; for example, IADPSG criteria uses a fasting blood glucose cutoff of ≥92mg/dl for 75gm OGTT to diagnose GDM. The evidence suggests there is positive correlation between sample size and the prevalence.[41] In our meta-analysis there was one study with a large sample size[23] which gave larger weight to the prevalence of GDM. This may also have contributed to the high heterogeneity in the result.

From subgroup analysis, a higher prevalence of GDM was noted in Kathmandu valley (2.70%) compared to outside the valley (2.28%). However, the difference was not statistically significant (p = 0.89). The high prevalence within the valley can be explained by the presence of risk factors such as sedentary lifestyle,[42] marriage and parity at higher ages,[43] and better health seeking facilities. In addition to this, the studies from outside the valley demonstrated a wide range of prevalence. The study by Thapa et al. in pregnant women of rural areas has revealed higher prevalence of gestational diabetes mellitus in particular. Abundance of behavioral risk factors such as insufficient physical activity, inadequate fruits and vegetable intake among pregnant women as well as transforming lifestyle along with increasing urbanization in rural Nepal could be the reason behind the higher prevalence in these areas.[22, 44]

Similarly, the prevalence of GDM before 2015 was 1.20% and in and after 2015 was 4.84% which is statistically significant (p < 0.001). The increasing burden of diabetes including GDM in recent years in Nepal is attributed to the local social and cultural factors such as increasing urbanization and changes in food and lifestyle-related behaviors.[45] Similar rise of GDM cases are observed in many South Asian nations probably due to rise in incidence of T2DM and obesity, which are major contributing factors for GDM.[46]

Our meta-analysis indicated that the prevalence of GDM also differed according to the diagnostic criteria used; 6.56% from IADPSG criteria, 4.81% from WHO criteria, 4.71% from DIPSI criteria and 1.08% from Carpenter and Coustan criteria. The reason for highest prevalence of GDM by IADPSG criteria is because of low cutoff for fasting blood glucose (≥92 mg/dl IADPSG vs ≥126mg/dl WHO criteria).

Also, our study suggests that the prevalence of GDM diagnosed using one-step WHO criteria was approximately 4 times more than that from the two and step Carpenter and Coustan criteria which is statistically significant (p < 0.001). Literature suggest that one-step diagnostic criteria for GDM, despite being simple and less expensive, overestimates the prevalence.[47] The 75g two-hour glucose test is more practical and convenient compared with the 100g three-hour test in Nepal because of topographical inaccessibility to hospitals as, in many parts of the country, the pregnant women have to walk hours just to reach the hospital. Furthermore, it appears to be more sensitive in predicting the complications of pregnancy like gestational hypertension, preeclampsia and macrosomia than the 100g three-hour test.[48] The increased sensitivity can be explained by the fact that only one elevated glucose value is needed to diagnose GDM in 75g two-hour test compared to 100g three-hour test which requires two abnormal glucose values.[49] However, literature suggests that two-step screening method is more accurate and could accordingly reduce personal and societal costs despite its inconvenience for patients and increased workload for healthcare professionals.[50]

In Nepal, there is no national guideline or diagnostic criteria for the diagnosis and treatment of GDM. One of the tertiary centers of Nepal; Tribhuvan University Teaching Hospital utilizes the two-step approach by Carpenter and Coustan criteria for diagnosing GDM. However, WHO criteria, DIPSI criteria, and IADPSG criteria are followed throughout Nepal depending on the place and patients' preference. This has led to discrepancy in the estimation of total GDM burden within the country. Therefore, it is imperative to make a standard diagnostic criterion to measure the actual burden of GDM all over the country. Moreover,

awareness should be raised from the grass root level to alert pregnant mothers regarding the consequences of GDM and the role of antenatal screening and treatment in reducing the maternal and fetal complications.

Our study was not free of limitations. As, the included studies with conducted in hospital-based settings and are from widely population non-homogenous resulting in high heterogeneity. So, the pooled prevalence might be less meaningful and erratic. Additional analysis could not be performed because risk factors such as body mass index, family history of GDM, level of physical activity, and dietary intake were not properly assessed by the studies. Also, as all the studies were hospital-based that were conducted in a few districts which may not represent the real status of entire country. Considering these limitations, the results should be interpreted wisely by the clinicians.

CONCLUSIONS

As per our meta-analysis, the overall prevalence of GDM in Nepal is 2.61 percent, with the highest prevalence using IADPSG criteria (6.56%, 95% CI: 4.79-8.92) and lowest using Carpenter and Coustan criteria (1.08%, 95% CI: 0.43-2.71). The prevalence of GDM is in increasing trends (1.20% before 2015 and 4.84% from 2015). Further studies at provincial and local levels of the country should be conducted to measure the actual burden of GDM and speculate the potential risk factors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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