

## REVIEW

# Gestational diabetes mellitus (GDM) and adverse pregnancy outcome in South Asia: A systematic review

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## Abstract

**Introduction:** The prevalence of gestational diabetes mellitus (GDM) is increasing in developing countries including the South Asian Nations. The current study aimed to examine the association of GDM with adverse pregnancy outcomes from foetal and maternal perspectives in South Asia.

**Methods:** A systematic review was conducted including primary studies published since January 2020 from South Asian countries. Following electronic databases were searched to locate the articles: MEDLINE, EMBASE and EMCARE. Data were extracted using a customized extraction tool and methodological quality of the included studies was assessed using modified Effective Public Health Practice Project (EPHPP) quality assessment tool. Narrative synthesis was performed as statistical pooling was not possible due to the heterogeneous nature of the studies.

**Results:** Eight studies were included in the review. Overall, the review found a positive correlation between GDM and adverse foetal outcomes such as macrosomia, neonatal hyperglycaemia, intrauterine growth retardation (IUGR), stillbirths and low birthweight (LBW), but the findings were not conclusive. GDM was also positively associated with preeclampsia but the association between GDM and C-section delivery was not conclusive.

**Conclusion:** Policymakers, public health practitioners and researchers in South Asia should take in to account the link between GDM and adverse pregnancy outcomes while designing interventions to promote maternal health in South Asia. Researchers should focus on conducting longitudinal studies in future to clearly understand the epidemiology and pathobiology of this issue.

## KEYWORDS

adverse pregnancy outcomes, GDM, gestational diabetes mellitus, South Asia, systematic review

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## 1 | INTRODUCTION

Gestational diabetes mellitus (GDM) can be defined as glucose intolerance of varying degree started at or detected during pregnancy. GDM is known as one of the leading causes of maternal and infant mortality.<sup>1,2</sup> Studies have detected several risk factors of GDM including overweight, obesity, advanced maternal age and family history of diabetes.<sup>3-5</sup>

Globally, the prevalence of GDM is increasing in recent years and affects 1%–14% of all pregnancies.<sup>6</sup> GDM was previously considered to be a major public health problem in developed countries, but it is now a growing problem in developing countries as well. Most of the countries in the South Asian region are no exception to this with an increasing trend in the prevalence of GDM reported in these countries.<sup>7</sup> Evidence suggests that the prevalence of GDM is 11% higher among women from Indian subcontinent than those from Europe.<sup>8</sup> Among Asian countries, the highest prevalence rate is reported in China and India.<sup>9</sup> It is postulated that increased population density followed by the emergence of agriculture, regular famines and the retarded growth with thin physique characterization has elevated the general susceptibility to diabetes in Indian sub-continent.<sup>10</sup>

Along with the increasing probability of being diagnosed with Type 2 diabetes mellitus after pregnancy, GDM is indicated to be closely associated with different adverse pregnancy outcomes both at the foetal and maternal level including an increased risk of caesarean-section (C-section) delivery, preeclampsia, macrosomia and intrauterine growth retardation (IUGR).<sup>11-13</sup> GDM is also associated with newborns delayed brain maturity and neurobehavioral abnormalities including comparatively lower intelligence than normal babies, language impairments, poor attention and impulsivity.<sup>14</sup> Therefore, it is very important that GDM is managed properly to avoid different adverse pregnancy outcomes associated with it.

Evidence suggests that the prevalence of adverse pregnancy outcomes such as preeclampsia, C-section delivery, macrosomia, low birthweight, still births and IUGR is high in South Asian countries.<sup>15-18</sup> For example, Poudel et al. (2020)<sup>17</sup> reported that the pooled stillbirth rate in India, Bangladesh, Nepal and Pakistan was 25.15 per 1,000 births. Another study reported that, the prevalence of C-section delivery is around 13% in South Asian countries.<sup>19</sup> Although several studies have pointed the association between GDM and adverse pregnancy outcomes, it is important that these findings are synthesized systematically to provide concrete evidence for policymakers and practitioners in South Asia. This study aimed to synthesize the evidence on the association between GDM and adverse pregnancy outcomes in South Asian countries.

## 2 | METHODS

### 2.1 | Data sources

We followed PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for conducting this review.<sup>20</sup> A systematic search of electronic databases such as MEDLINE,

EMBASE and EMCARE was performed to identify the primary studies published since January 2020 from India, Bangladesh, Pakistan, Nepal, Bhutan, Sri Lanka, Maldives and Afghanistan. A combination of both MeSH terms and keywords was used to search the relevant articles such as: 'Gestational diabetes mellitus', 'GDM', 'Neonatal hyperglycemia', 'Macrosomia', 'Stillbirth', 'Preeclampsia', 'Caesarean Section', 'Intrauterine growth retardation', 'Low birth weight', 'India', 'Bangladesh', 'Pakistan', 'Nepal', 'Bhutan', 'Sri Lanka', 'Maldives' and 'Afghanistan'. A Boolean searching technique was employed where 'AND', 'OR' and 'NOT' were used to unite different search terms.

### 2.2 | Study selection

Selection of the articles was based on the predefined inclusion/exclusion criteria (Table 1). The search and screening process of the articles were conducted independently by two researchers (SKM and KK). The consistency was ensured by a third researcher (RDG). The full-text screening and selection were done by all three researchers. Any discrepancy was solved by consensus among the group.

### 2.3 | Data extraction and quality assessment

Data from each of the selected studies were extracted using a data extraction template. Information such as title, authors, publication year, country, study design, study population and key findings were extracted from each article and presented in the extraction form in Microsoft excel 2013.

**TABLE 1** Inclusion and exclusion criteria for study selection

<b>Inclusion criteria</b>
1) Studies investigated the role of gestational diabetes mellitus and adverse pregnancy outcomes
2) Primary studies
3) Conducted in South Asian countries, that is, India, Bangladesh, Pakistan, Nepal, Bhutan, Sri Lanka, Maldives and Afghanistan
4) Published in English literature
5) Peer-reviewed articles
6) Published since January 2020
<b>Exclusion criteria</b>
1) Studies did not investigate the role of gestational diabetes mellitus and adverse pregnancy outcomes
2) Not primary studies
3) Conducted in places other than South Asian countries, that is, India, Bangladesh, Pakistan, Nepal, Bhutan, Sri Lanka, Maldives and Afghanistan
4) Published in language other than English
5) Not peer-reviewed articles

Methodological quality of the selected articles was assessed using modified Effective Public Health Practice Project (EPHPP) quality assessment tool.<sup>21</sup> Selected studies were evaluated against four methodological domains: study design and appropriateness of the outcome measure, sample representativeness, data analysis and interpretation. In each individual study, for every domain, a score was assigned: 1 (weak), 2 (moderate) or 3 (strong). The score was then combined to get the total methodological quality score assigned to an individual article. A score of 4–6, 7–9 and 10–12 were graded as weak, moderate and strong respectively.<sup>21</sup>

## 2.4 | Data synthesis

Data synthesis involved systematic collating, combining and summarizing the findings of the selected literatures to answer the research question of the review.<sup>22</sup> Data analysis can be accomplished either using statistical pooling or where it is inappropriate by best evidence synthesis approach. Considering the heterogeneous nature of the included studies, the findings of the included studies were analysed as best evidence synthesis instead of statistical pooling.

## 3 | RESULTS

### 3.1 | Literature selection

A total of 157 articles were identified through initial searching of the electronic databases, of which 10 articles were excluded as duplicate records (Table 1). From the remaining 147 articles, screening of the title and abstracts based on the inclusion criteria resulted in exclusion of 125 articles. A total of 22 articles underwent full-text screening, of which 14 articles were excluded based on the following

reasons: not investigating the role of GDM on adverse pregnancy outcome and not a primary study. Eight articles were included in the final analysis (Figure 1).

### 3.2 | Characteristics of included studies

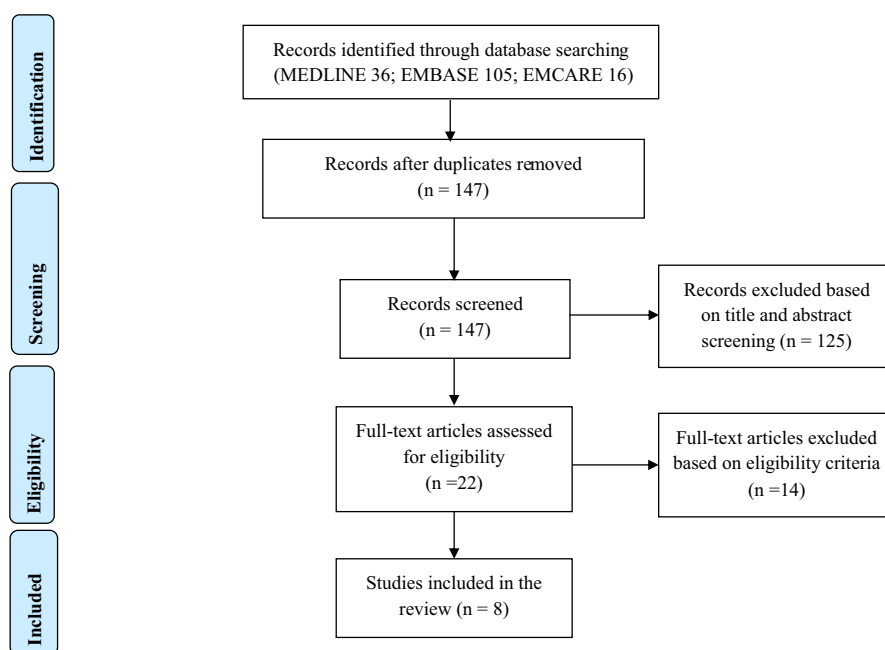
Characteristics of included studies are shown in Table 2. Among the eight studies included,<sup>8,9,23–28</sup> six studies<sup>8,24–28</sup> utilized prospective observational study design while the remaining two studies<sup>9,23</sup> used a retrospective study design. All the studies selected were primary studies carried out in South Asian countries. Five studies were conducted in India,<sup>8,9,26–28</sup> one in Pakistan,<sup>23</sup> one in Bangladesh<sup>24</sup> and one in Sri Lanka.<sup>25</sup> All the studies were conducted in hospital settings except one study which was carried out in rural areas of Assam, India.<sup>26</sup> In five studies, GDM was diagnosed in accordance with the WHO criteria and was measured performing an oral glucose tolerance test (OGTT),<sup>9,23,25–27</sup> while in other studies (n = 3), patient recall were used.<sup>8,24,28</sup>

### 3.3 | Methodological qualities of included studies

Methodological quality of the included studies was ranked against the predefined criteria and six<sup>8,9,23,25,27,28</sup> of the eight studies were classified as of moderate quality while two studies<sup>24,26</sup> were of weak methodological quality.

### 3.4 | Narrative synthesis

Narrative synthesis of the selected articles was performed since the findings are very heterogeneous in nature. Overall, selected studies



**FIGURE 1** PRISMA flow diagram of the study selection process for inclusion in the review

TABLE 2 Characteristics of included studies

Study	Title	Country	Study setting	Study design	Study population/subject/participants	Methodological quality
Akhter et al. (1996) <sup>23</sup>	Diabetes in Pregnancy in Pakistani Women: Prevalence and Complications in an Indigenous South Asian Community	Pakistan	Aga Khan University Hospital in Karachi, Pakistan	Retrospective study	6,830 pregnant women	Moderate
Islam et al. (2016) <sup>24</sup>	Morbidities and Mortalities Among Infant of Diabetic Mother in a Newly Established SCANU of a Tertiary Care Hospital, Bangladesh	Bangladesh	Mymensingh Medical College Hospital (MMCH), Bangladesh	Prospective observational study	A total 50 infant of diabetic mother (IDM) patients who were admitted during Jan and Mar 2015 were recruited in the study.	Weak
Jayawardane et al. (2016) <sup>25</sup>	Hyperglycemia in pregnancy among South Asian women: A single tertiary care center experience from Colombo, Sri Lanka	Sri Lanka	A tertiary care referral centre, Colombo, Sri Lanka	Prospective observational study	Data from first trimester to delivery of 572 were analysed	Moderate
Mahanta et al. (2014) <sup>26</sup>	Maternal and foetal outcome of gestational diabetes mellitus in a rural block of Assam, India	India	Rural areas in Dibrugarh District of Assam, India	Prospective observational study	A total of 930 antenatal women coming during Jun to August 2011 to subcentres, outreach areas, tea-garden hospitals, state dispensaries, primary health centres and community health centres were included in the study.	Weak
Misra and Das (2017) <sup>6</sup>	Neonatal Outcome in Early and Late Gestational Diabetes Mellitus	India	A neonatal intensive care unit of a tertiary hospital in Kolkata, India	Prospective observational study	A total of 2,554 mothers delivered in the hospital were included in the study	Moderate
Saxena et al. (2011) <sup>9</sup>	Pregnancy Outcome of Women with Gestational Diabetes in a Tertiary Level Hospital of North India	India	A tertiary-level hospital of North India	A retrospective analytical record-based study	100 pregnant women (50 diabetic and 50 normoglycaemic)	Moderate
Shefali et al. (2006) <sup>27</sup>	Pregnancy Outcomes in Pre-gestational and Gestational Diabetic Women in Comparison to Non-diabetic Women—A Prospective Study in Asian Indian Mothers (CURES-35)	India	Dr. Mohan's Diabetes Specialities Centre, a tertiary care centre for diabetes in Chennai in southern India	Prospective observational study	225 patients were included from the health centre while 30 non-diabetic controls were recruited from the ongoing population-based study, the Chennai Urban Rural Epidemiology Study (CURES).	Moderate
Wahi et al. (2011) <sup>28</sup>	Prevalence of Gestational Diabetes Mellitus (GDM) and its Outcomes in Jammu Region	India	Department of Gynaecology and Obstetrics, SMGS Hospital and Department of General Medicine, Government Medical College and Hospital, Jammu	Prospective observational study	A total of 272 subjects at 24th to 28th weeks of gestation were evaluated for the GDM and outcome of GDM	Moderate

TABLE 3 Association between gestational diabetes mellitus and adverse pregnancy outcomes

Gestational diabetes mellitus							
Study	Neonatal hyperglycaemia	Macrosomia	Stillbirth	IUGR	LBW	Preeclampsia	Caesarean section
Akhter et al. (1996) <sup>23</sup>	NA	13% of the foetus was suffering from macrosomia	NA	IUGR was 7.1% of GDM affected women	NA	Prevalence of preeclampsia was 19.1% among the GDM patients	C-section rate was 25.9% among the GDM patients
Islam et al. (2016) <sup>24</sup>	Neonatal hyperglycaemia was found among 40% infants of infant with diabetic mother (IDM)	Macrosomia was presented among 24% of the mother with IDM	NA	NA	NA	NA	NA
Jayawardane et al. (2016) <sup>25</sup>	NA	Relatively lower among GDM compared to Hyperglycaemia in early pregnancy (HIEP) group (18.7% vs. 33.7%, $p < .01$ )	NA	NA	No significant difference observed in LBW prevalence among groups ( $p = .76$ )	Prevalence of hypertension in pregnancy was higher among GDM group compared to those with Hyperglycaemia in early pregnancy	No significant difference was observed among groups in terms of prevalence of C-section
Mahanta et al. (2014) <sup>26</sup>	NA	Macrosomia was higher among GDM group compared to the non-GDM group (32% vs. 0.7%)	NA	NA	NA	Pregnancy-induced hypertension was higher among GDM group (OR: 2.82)	NA
Misra and Das (2017) <sup>8</sup>	NA	Macrosomia was not significant (only 4% in the GDM group)	NA	NA	LBW was prevalent in the GDM group (21.8%)	Prevalence of pregnancy-induced hypertension was 20.8% among GDM group	NA
Saxena et al. (2011) <sup>9</sup>	NA	The prevalence of macrosomia was significantly higher in GDM group (28% vs. 0%, $p = .001$ )	NA	IUGR was significantly different between two groups	NA	Pregnancy-induced hypertension was significantly higher among GDM group (40% vs. 10%, $p = .001$ )	C-section delivery was significantly higher in GDM group (42% vs. 0%, $p = .001$ )
Shefali et al. (2006) <sup>27</sup>	NA	Macrosomia was highly prevalent among the GDM patients compared to the non-diabetic group (27.6% vs. 7.1%, $p = .04$ )	NA	NA	Prevalence of LBW was significantly lower among the GDM group compared to the non-diabetic group (8.2% vs. 14.3%)	NA	NA
Wahi et al. (2011) <sup>28</sup>	NA	Macrosomia was highly prevalent among the GDM patients compared to the non-diabetic group (16.2% vs. 5.7%, $p = .02$ )	Stillbirth was significantly higher among GDM group (4.8% vs. 0%, $p = .02$ )	NA	LBW was relatively higher in control group but not statistically significant (14.2% vs. 8.2%)	Gestational hypertension was higher among the GDM group (6.4% vs. 0%, $p < .01$ )	NA

revealed that GDM has a role in adverse pregnancy outcomes both among the foetus such as neonatal hyperglycaemia, macrosomia, stillbirths, intrauterine growth retardation (IUGR) and low birth-weight (LBW) and mothers such as preeclampsia and C-section. The findings are shown in Table 3.

### 3.4.1 | GDM and neonatal hyperglycaemia

Islam et al.<sup>24</sup> presented the role of GDM on neonatal hyperglycaemia. The authors reported that 40% of the GDM mothers have an infant with hyperglycaemia in neonatal period. However, the study did not report the values in any control group making it difficult to draw any concrete conclusions.

### 3.4.2 | GDM and macrosomia

All the studies<sup>8,9,23-28</sup> investigated the role of GDM on macrosomia. Six studies<sup>8,9,25-28</sup> showed that higher percentage of pregnant women with GDM have a foetal outcome of macrosomia compared to women with no GDM. Akhter et al.<sup>23</sup> and Islam et al.<sup>24</sup> reported that macrosomia was highly prevalent among GDM mother, although the findings were inconclusive due to lack of a control group.

### 3.4.3 | GDM and LBW

Four<sup>8,25,27,28</sup> of the eight studies reported the association between GDM and LBW. However, discrepant findings were reported. Although Misra and Das<sup>8</sup> reported the prevalence of LBW among the GDM group, the study did not report the association in relation to that of any control group. On the contrary, Jayawardane et al.<sup>25</sup> and Wahi et al.<sup>28</sup> reported that there was no significant association between GDM and LBW. Shefali et al.<sup>27</sup> found that prevalence of LBW was higher among the control group compared to the GDM group.

### 3.4.4 | GDM and intrauterine growth retardation (IUGR)

Role of GDM on IUGR was measured by two studies<sup>9,23</sup> but the findings were not conclusive. Akhter et al.<sup>23</sup> found that 7.1% of the GDM women have IUGR but did not report anything regarding the control group; thus, making it difficult to draw any conclusion. Saxena et al.<sup>9</sup> also did not find any conclusive evidence on the association between GDM and IUGR.

### 3.4.5 | GDM and stillbirths

Only Wahi et al.<sup>28</sup> investigated the association between GDM and adverse pregnancy outcomes in the form of stillbirths. The study

reported that prevalence of GDM was significantly higher among the GDM group ( $p = .02$ ) compared to the control group.

### 3.4.6 | GDM and preeclampsia

Six of the eight studies investigated the association between GDM and preeclampsia or pregnancy-induced hypertension. Irrespective of the study setting, all the studies reported a positive association between GDM and preeclampsia. Although Akhter et al.<sup>23</sup> and Misra and Das<sup>8</sup> did not report the result in comparison to a control group, they reported that prevalence of preeclampsia was very high (20.8%) among the pregnant women with GDM. On the other hand, Jayawardane et al.,<sup>25</sup> Mahanta et al.,<sup>26</sup> Saxena et al.<sup>9</sup> and Wahi et al.<sup>28</sup> reported the association between GDM and preeclampsia in comparison to a control group and reported that GDM group had significantly higher occurrence of preeclampsia compared to that of the control group.

### 3.4.7 | GDM and C-section delivery

Three studies<sup>9,23,25</sup> investigated the role of GDM on C-section delivery. While Saxena et al.<sup>9</sup> reported a positive association between GDM and C-section delivery, the other two studies<sup>23,25</sup> did not find any significant association.

## 4 | DISCUSSION

This systematic review was aimed at finding the role of GDM on adverse pregnancy outcomes at both foetal and maternal level. Most of the studies included in the review followed a prospective observational design and were carried out in hospital settings in India. Overall, the study findings revealed that GDM was associated with foetal macrosomia. While some studies identified the association of GDM on other adverse foetal outcomes such as neonatal hyperglycaemia, LBW, stillbirths and IUGR, the evidence was not conclusive. Although the association between GDM and preeclampsia or pregnancy-induced hypertension among pregnant mothers was identified, it is difficult to conclude the associations between GDM and C-section delivery.

Consistent with the findings of the present review, other studies have affirmed that untreated GDM is often linked to foetal macrosomia (children with birthweight greater than 4,000 grams).<sup>29,30</sup> The major reason behind the increased risk of macrosomia among pregnant mother with GDM is the enhanced insulin resistance of the mother<sup>31</sup> due to a higher amount of glucose passing through the placenta into foetal circulation. Consequently, this extra amount of glucose is stored as body fat in the foetus and causes macrosomia.<sup>32</sup>

Similar to the findings from our review, other studies have reported positive correlation among GDM, stillbirths and

LBW.<sup>33,34</sup> The leading causes of stillbirths related to GDM are reported to be abnormalities of placenta, congenital malformations and IUGR.<sup>35</sup> Foetal anaerobic metabolism with hypoxia and acidosis resulting from hyperglycaemia is a common metabolic cause of diabetes-related stillbirth.<sup>36</sup>

Women with GDM can give birth to neonates with different metabolic disorders. Neonatal hypoglycaemia is one of them which results from hyperinsulinism leading to neurodevelopmental outcomes.<sup>37</sup> Therefore, if GDM can be controlled, the prevalence rate of neonatal hypoglycaemia can also be controlled as they are interrelated.

Other studies have confirmed the correlation between GDM and adverse outcomes of the pregnant mothers such as preeclampsia and C-section delivery.<sup>38-40</sup> Preeclampsia is a common pregnancy-related complication induced by GDM, characterized by high blood pressure resulted from increased insulin resistance.<sup>41</sup> Hypertensive disorders can be increased two- to threefold in pregnancies due to high blood glucose level.<sup>42</sup> However, several other maternal factors are also associated with preeclampsia including maternal cardiovascular disease, renal disease, overweight and obesity.<sup>43</sup> A strong positive association was found between GDM and C-section delivery in a study from China among pregnant women in Chengdu, Sichuan province.<sup>44</sup> However, in our systematic review, although one study reported positive association, two studies did not find any positive association between C-section delivery and GDM. More studies are required to have a conclusive evidence on this.

As the review highlights the importance of GDM in increasing the prevalence of adverse pregnancy outcomes, it is important that policymakers and practitioners emphasize more on the preventive measures of GDM not only for the sake of GDM alone but also to prevent adverse pregnancy outcomes simultaneously. There are not many direct causes of adverse pregnancy outcomes that are documented; therefore, controlling GDM can indirectly act as a preventive measure for adverse pregnancy outcomes as well. It is important that national and regional policies regarding the prevention and management of GDM also incorporate policies that embed GDM management for adverse pregnancy outcomes. Regional collaborations between different stakeholders need to be strengthened with shared understanding, planning and implementation to address the problem. For example, using the platform of the South Asian Association for Regional Cooperation (SAARC) in active engagement among policymakers and practitioners from these countries can be of value in this regard. The findings of the present review are also important from the clinicians' perspectives of this region. As the review reports positive correlation between GDM and adverse pregnancy outcomes, it is important that clinicians also consider the possibilities of any adverse pregnancy outcomes while recommending the treatment regimens for GDM patients.

To the authors' knowledge, as no other recent systematic reviews have been conducted summarizing the role of GDM on adverse pregnancy outcomes focusing in South Asia.<sup>45</sup> This review

is particularly important as it provides synthesized evidence from South Asian countries for policymakers and clinical as well as public health practitioners to enact effective initiatives to address the issue.

However, one should be cautious while interpreting the findings of the research as the quality of the included studies was relatively moderate<sup>8,9,23,25,27,28</sup> to poor.<sup>24,26</sup> Moreover, most of the included studies followed a prospective observational design and reported differences in the prevalence of adverse outcomes between GDM and non-GDM group, but they did not report a causative association between GDM and adverse pregnancy outcomes. There was significant heterogeneity among selected studies in terms of participants' age, BMI, dietary patterns, study design and the methods of diagnostic criteria and this could have affected the reliability and validity of the findings. It is to be noted that there were limited studies on the association between GDM and pregnancy outcomes in some of the South Asian countries including Afghanistan, Maldives and Bhutan.

## 5 | CONCLUSION

Overall, the findings from the current systematic review suggests a positive association between GDM and adverse pregnancy outcomes in South Asian countries. The review provides valuable information for policymakers and practitioners to undertake effective initiatives to address the issue and to improve the GDM-related care for reproductive aged women. The findings also indicate the need to undertake longitudinal studies to better understand the causative link between GDM and adverse pregnancy outcomes in South Asian countries.

### CONFLICT OF INTEREST

The authors report that there is no conflict of interest to disclose.

### AUTHOR CONTRIBUTIONS

SKM and KK conceptualized and designed the study. SKM, RDG, SA and KK conducted the formal analysis for the study. SKM, RDG, SA, KK and AAS contributed to writing the first draft of the manuscript. SP commented extensively on the draft of the manuscript to finalize. All authors read and approved the final version of the manuscript.

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