



Letter Article

Impact of missingness on clinical trials on the effectiveness of antenatal vitamin D supplementation in gestational diabetes mellitus patients

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Dear Editor,

Gestational diabetes mellitus (GDM) is a vital medical complication of pregnancy in which glucose intolerance is first detected or develops during gestation. GDM is associated with adverse maternal and neonatal outcomes, and contemporarily, several clinical trials have tested their incidence in antenatal vitamin D receiving GDM patients. Considering their clinical significance, these trials' findings pertaining to the above outcomes require cautious interpretation, in terms of the risk of bias due to missingness. Any such bias in randomized controlled trials (RCT) can contaminate the results of a meta-analysis that extracts data from these RCTs. Best known to me, perhaps, no review article has explored the perinatal outcomes in these trials in the context of missingness. Therefore, this letter attempts to draw on it to highlight its importance and briefs the contemporarily available techniques to handle it in a meta-analysis setting. In this letter, missingness refers to the incomplete outcome data of participants who were not observed until the end of the trial, but not the available outcome data the trialists excluded from statistical analysis.

The assessment of the risk of bias in RCTs varies depending on the assessed outcome types (dichotomous or continuous). In the RCTs reporting dichotomous outcomes, their ratio of missingness to the number of events of interest helps compare their risk of bias. The risk of bias increases as this ratio becomes bigger [1]. Using this method, I piloted the missingness associated plausible risk of bias between two relevant RCTs as examples [2,3]. I compared some of the maternal (preterm delivery, pre-eclampsia, polyhydramnios, macrosomia (>4000 gm), and cesarean section) and neonatal (hospitalization, hyperbilirubinemia, and hypoglycemia) outcomes reported in both the trials. Although these trials had few missing data, given their small sample sizes and clinical importance, it seems apropos to include here [2,3]. For the cesarean section, and hyperbilirubinemia and hospitalization of newborns, the risk of bias due to missingness was reasonably low as these ratios had relatively lower values and were

identical among the trials (Table 1). However, for the remaining outcomes, juxtaposed to Jamilian et al. [3] study, these ratios were higher in that by Asemi et al. [2], suggesting a higher risk of bias in the later. For instance, the ratios for newborn hypoglycemia in these studies were 0.30 and 2.50, respectively. The above can also be determined by the risk of occurrence of a binomial outcome. If two hypothetical trials had an identical proportion of missing data, the risk of bias in the results would have been higher in the trial with a lower risk of events [1].

Likewise, the chances of bias can be judged for continuous outcomes, for example; in systematic review articles intending to judge RCTs that tested the changes in gestational weight or body mass index in prenatal vitamin D receiving GDM patients [4]. The influence of missingness of such outcomes increases with the proportion of missing data in these trials [1].

Besides the above considerations, the risk of bias assessment attributable to missingness requires an exploration of their reasons and balance between the compared intervention groups. When these are identical, the trials are likely to be at a lower risk of bias [1]. However, even if the missingness is balanced between the intervention groups, bias may creep in if its reasons are dissimilar [1]. For example, in one of the RCTs discoursed above [2], although the missingness was almost balanced among the treatment arms, the causes were not identical.

In addition to the risk of bias assessment, meta-analytic methods like the available case analysis (ACA) and imputation case analysis are also valuable to explore the impact of missing outcome data. It is based on the assumption that participants are missing at random (MAR), which is conditional on other variables included in the meta-analysis, but not dependent on the outcome [5,6]. However, MAR assumption can't be validated during meta-analysis when the reasons for attrition are not known, and a sensitivity analysis like best-case and worst-case scenario and pattern mixture models might be required [5]. Pattern mixture models quantify the degree of departure from MAR by informative missingness odds ratio for binomial outcomes [6].

Overall, this discourse implies that the evidence from RCTs on dichotomous maternal and neonatal outcomes in prenatal vitamin D supplemented GDM mothers should be judged in conjunction with the above-stated factors of incomplete outcome data. Nevertheless, through this letter, perhaps I have

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only scratched the surface of the context; therefore, a systematic review may be more appropriate for a detailed exploration of the issue.

Table 1 Incomplete outcome data to event ratio for maternal and neonatal outcomes of two trials

Outcome		Author*, year			
		Jamilian et al., 2019* [3]		Asemi et al., 2015## [2]	
		Event (n)	Ratio (missing /event)	Event (n)	Ratio (missing /event)
Maternal outcomes	Preterm delivery	2	1.50	1	5
	Preeclampsia	10	0.30	1	5
	Polyhydramnios	8	0.38	4	1.25
	Macrosomia (>4000gm)	8	0.38	4	1.25
	Cesarean section	29	0.10	26	0.19
Neonatal outcomes	Newborn hyperbilirubinemia	17	0.18	20	0.25
	Newborn hospitalization	15	0.20	20	0.25
	Newborn hypoglycemia	10	0.30	2	2.50

+First author's last name, # no. of missing = 3, ## no. of missing = 5

Abbreviations

GDM: Gestational diabetes mellitus; RCT: Randomized Controlled Trials; ACA: Available Case Analysis; MAR: Missing at Random

Declarations

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Availability of data and materials

Data will be available by emailing sumanta.saha@uq.net.au.

Authors' contributions

Sumanta Saha (SS) is the principal investigator of this manuscript (Letter). SS is responsible for the study concept, design, writing, reviewing, editing, and approving the manuscript in its final form. SS read and approved the final manuscript.

Ethics approval and consent to participate

I conducted the research following the Declaration of Helsinki; however, Letter Article needs no ethics committee approval.

Consent for publication

Not applicable

Competing interest

The author declare that they have no competing interests.

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