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Prof. Dr. Sergio Machado and Dr. Saurabh Chandan,
Editor in Chief
World Journal of Meta-analysis

Dear Prof. and Dr,

RESUBMISSION OF MANUSCRIPT TO *World Journal of Meta-analysis*

We are pleased to enclose herewith a revised manuscript entitled “**Prevalence of anxiety among gestational diabetes mellitus patients: a systematic review and meta-analysis**” by Ching et al. to the *World Journal of Meta-analysis* for publication.

The changes are in blue fonts. We hope the revised manuscript will better suit the *World Journal of Meta-analysis* and we thank you for your continued interest in our research.

Thank you for your kind attention.

“WITH KNOWLEDGE WE SERVE”

Ching SM

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Peer-review report

Reviewer #1:

1. This study pooled data from existing literature to determine the pool estimates for the prevalence of anxiety among women diagnosed with gestational diabetes mellitus (GDM). This study is a meaningful meta-study and has been well described overall. However, there are some changes that need to be made. My opinion is as follows. 1. (Introduction) In the introduction section, the author should describe the trends in pre-study on GDM and depression and anxiety.

Responses: Thank you for your comment. We have edited as suggested in Introduction. To read as:

Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing over the past decades^{1,2}. Globally, GDM has been reported as a leading cause of morbidity and mortality among both the infant and their mother^{3,4}. Mothers with GDM are at increased risk of getting pregnancy complications such as preterm delivery, preeclampsia, abnormal birth weight and metabolic and electrolyte disorders⁵. Studies also indicated that GDM may persist after postpartum and subsequently develop into overt diabetes mellitus, and it was estimated that the risk for developing diabetes mellitus after GDM increased linearly with the duration of follow-up ranged from 19.72% at 10 years. The estimated risks for type-2 diabetes mellitus ranged from 19.7% at 10 year to 39.0% at 30 years⁶. Neonates born to GDM mothers are at higher risk of suffering from adverse neonatal outcomes such as abnormal birth weight, congenital anomalies, hypoglycaemia and longer duration in neonatal intensive care unit for further investigation⁷⁻⁹.

Previous studies showed that the prevalence of depression among mothers with GDM have ranged from 25.9 to 56.7%^{10,11} and the prevalence of anxiety was from a range of 4.8 to 57.7% (1-4)^{12,13}. Anxiety is a normal reaction to stress which involves both psychological and physical reactions. It becomes clinically significant when the anxiety grows out of proportion to the situation and causes functional impairment. Anxiety disorders are among the most common mental illness, and are characterized by feelings of tension, worried thoughts and physical changes such as increased blood pressure. People with anxiety disorders usually have recurring intrusive thoughts or concerns. They may avoid certain situations out of worry. They may also have physical symptoms such as sweating, trembling, dizziness or a rapid heartbeat¹⁴. With a remarkable increase in lifetime prevalence, anxiety has become a public health burden worldwide, causing increased use of mental health services and loss of productivity¹⁵. In particular, anxiety is a common psychiatric condition that affects up to one-fifth of pregnant mothers¹⁶ and is significantly associated with postpartum depression (odds ratio=2.6, 95% CI=2.0, 3.5) and reduced odds of breastfeeding (odds ratio=0.63, 95% CI=0.5, 0.7)¹⁷. Thus, anxiety and related mental conditions could pose negative effects on child development¹⁸. A high state of anxiety is found in 15.8% of pregnant women, while 12.5% of women suffer high trait anxiety¹⁹. Similarly, pregnant mothers with GDM were more anxious than pregnant women with others medical problems and or healthy pregnant women²⁰.

2. (Materials and Methods) "(3) Studies were published in English peer-reviewed journal from inception to 31 October 2019." In the Inclusion criteria section, is all studies before 31 October 2019 included?

Responses: Thank you for your comment. All related studies published from inception to 31 October 2019 were eligible to be included. We had made the changes in Literature search section in Methods. To read as:

Literature search

Two investigators (KWL and HCL) independently searched Medline, Cinahl, PubMed and Scopus databases for potential studies published in journals from inception to 31 October 2019. We used following search terms: (Anxiety OR anxiety symptom OR anxiety disorder OR generalized anxiety disorder OR panic disorder OR panic attack OR agoraphobia OR phobia OR specific phobia OR specific phobic disorder OR medication-induced anxiety disorder OR medical condition induced anxiety disorder OR social anxiety disorder) AND (prevalence) AND (gestational diabetes OR GDM OR gestational diabetes mellitus OR diabetes in pregnancy). The search strategies with the

Boolean or phrase operators were shown in the Appendix 1. Studies in English, available in full-text and conducted among humans were searched. Then, we removed duplications using Endnote, after that we screened the title and abstracts for its suitability. Finally, articles with their full text were assessed for eligibility to be recruited into the quantitative analysis.

3. Page 3, line 32: The source for the utilities (eg. Endnote programme X5 version) should be presented.

Responses: We have added the source for the utilities by giving website that access to the software. We had made the changes in Statistical analysis section in Methods. To read as:

Statistical analysis

A random-effects (DerSimonian and Laird Method) meta-analysis method was employed to pool the prevalence estimated from these related studies and was reported with a 95% confidence interval (CI). I^2 index was used to assess the studies heterogeneity (i.e. low is <25%, moderate 25–50%, and high >50%), that indicated the total percent of discrepancy due to variation in the included studies²⁵. For statistical analysis, Open Meta(Analyst) software was used, this software can be accessed and downloaded from <http://www.cebm.brown.edu/openmeta/index.html>²⁶. Funnel plot was generated using The jamovi project computer Software, this software can be retrieved from <https://www.jamovi.org>²⁷.

4. (Quality assessment) Quality assessment is very important in meta-research. A more specific explanation is needed for the checklist of strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Responses: Thank you for your comment. We had made the changes in Quality assessment section in Methods and results. To read as:

Methods section:

Quality assessment

The quality of the individual studies was determined using the checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)²⁴. The aim and use of STROBE is to assess the strengths and weaknesses of the studies reported in the medical literature, STROBE results also helps thought readers to know what was planned, done and found, as well as what is incomplete and inadequate in the reporting of articles. The tool consists of 22 items to help assess the important components found in observational studies. In certain instances where the information provided was insufficient in order to making judgement for a certain item, that item was graded with a '0', rendering the item as having a high risk of bias. Each article's quality was graded as 'good' if the STROBE score was ≥ 14 ; or graded as 'poor' if the STROBE score was <14. Two investigators (NKD and MT) individually assessed the study quality, with differences resolved by discussion with the third and fourth investigators (SMC and FKH). Studies were included in analysis regardless of STROBE score and grade.

Results section:

Quality assessment

We assigned the studies with an overall rating based on STROBE checklist. All three studies received an overall "Good" quality with a score ≥ 14 over 22 (Appendix 4-6). In summarizing the results, we concluded that all studies had methodological issues such as not describing any efforts to address potential sources of bias, how missing data were addressed, and lack of sensitivity analysis.

5. (Statistical analysis) I suggest that the authors present a funnel plot to evaluate the publishing bias. It will help many scholars refer to this study in the future.

Responses: Thank you for your comment. We performed sensitivity test and publication analysis using funnel plot for your perusal. The results of sensitivity test and publication analysis were placed in Appendix 2-3.

Prevalence of anxiety

The overall pooled prevalence of anxiety was 29.5% (95% CI=6.9, 52.0) (Figure 2). The pooled prevalence of anxiety using DASS-21 was higher than prevalence of anxiety using ICD-9/10 (42.4% versus 4.8%). Sensitivity analysis reveals that Beka et al.,¹³ had substantial influences on the overall prevalence which cause prevalence of anxiety increased from 29.5% (95% CI= 6.9, 52.0) to 42.4% (95% CI= 13.2, 71.5). On the other hand, removal of Egan et al., 2017¹² or Lee et al., 2019²⁸ did not cause statistically significant changes to the overall prevalence of anxiety (Appendix 2). Indeed, funnel plot (Appendix 3) suggested that there was publication bias. Nevertheless, we did not exclude any studies from the meta-analysis due to there was only three studies available.

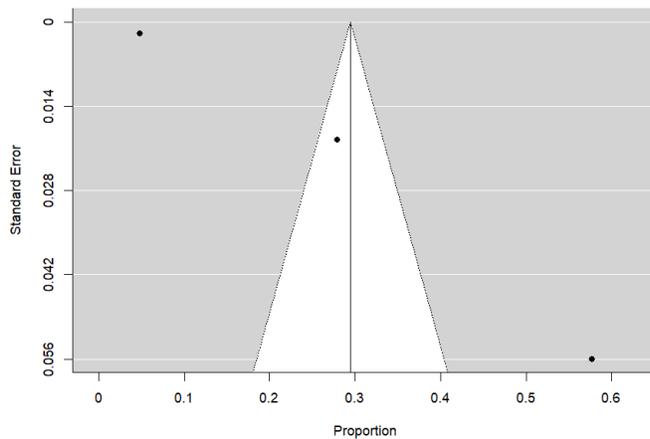
Appendix 2:

Sensitivity analysis for prevalence of anxiety among gestational diabetes mellitus patients using binary random-effects model.

Studies	Estimate	Lower bound	Upper bound	Std. error	P-value
Overall	0.295	0.069	0.520	0.115	0.011
- Beka et al., 2018	0.424	0.132	0.715	0.149	0.004
- Egan et al., 2017	0.163	-0.064	0.390	0.116	0.159
- Lee et al., 2019	0.310	-0.209	0.828	0.264	0.242

Appendix 3:

Funnel plots of studies evaluating prevalence of anxiety among gestational diabetes mellitus patients.



6. (Results) It is thought that there will be a limit to producing meaningful results in meta-research with just three studies. However, if few studies have been reported, I think that analyzing meta-study with three studies is not wrong. However, this should be described in detail as the limitations of the study in the Discussion section.

Responses: Thank you for your comment. We have addressed your concern in the Limitation section as suggested. To read as:

Strength and Limitations

To date, this is the first systematic and meta-analysis on anxiety among patient with GDM. This study clearly indicates that anxiety is prevalent among GDM patients. The finding of this review is consistent with the previous literature pertaining to anxiety among pregnant women experiencing medical complications. However, there are several limitations. [Strict inclusion/exclusion criteria and a paucity of literature on the topic of interest have resulted in the inclusion of only three papers.](#) However, according to Valentine et al., 2010, the minimum number of studies needed to conduct a meta-analysis is two⁵⁸. On top of that, we did sensitivity analysis and funnel plot to show the publication bias. Nevertheless, due care is necessary when interpreting the results as at least 5 studies or more are needed to reasonably and consistently achieve powers from the random-effects meta-analyses that are greater than the studies that contribute to them⁵⁹. Second, the pooled sample size is not large enough to reflect the anxiety prevalence in clinical setting, therefore limiting the generalizability of our study findings.

7. (Results) What does the arrow in Figure 2 mean? In addition, the number of samples from one study (Beka et al., 2018) is so large that it greatly affects the results of meta-analysis. If you had enough previous studies, you can perform a subanalysis. If you analyze without one study (Beka et al., 2018), it is highly likely that the results of the meta-analysis will be derived differently. This should be fully explained as a limitation of the study in the discussion section.

Responses: Thank you for your comment. The arrow showed in forest plot (I^2) represent the symbol for heterogeneity (I^2). In figure 2, we had removed subgroup analysis in view of the limited studies. We agreed with you that Beka et al had a significant impact as the prevalence of overall of anxiety. The overall anxiety had changed from 29.5% to 42.4% based on sensitivity test (Appendix 2), which had function to examine how each individual study affects the overall estimate of the rest of the studies.

8. (Discussion) In the first paragraph, the author overemphasized the results of meta-analysis. As noted earlier (number 7), this meta-analysis has many limitations. A modification is required.

Responses: Thank you for your comment. We have made the modification to the Discussion as well as in the limitation sections. To read as

Discussion

Our systematic review and meta-analysis offer preliminary evidence regarding the prevalence of anxiety among GDM patients. The results indicated that the pooled prevalence of anxiety among GDM patients was 29.5%. ~~(95% CI=6.9, 52.0). In subgroup analysis, the pooled prevalence of anxiety using DASS-21 was 42.4% (95% CI=13.2, 71.5) versus 4.8 (95% CI=4.4, 5.2) using ICD-9/10.~~

Several reasons may have contributed to the high heterogeneity ($I^2=99.12\%$) in the pooled prevalence that was seen in our systematic review and meta-analysis. First, there are differences in terms of the methodological approach used in different studies for the detection of anxiety. The diagnostic method would identify specific anxiety disorders with more stringent criteria, while the screening method served as case identification. Diagnostic versus screening criteria used by different studies for the clinically significant anxiety symptoms were omitted. For instance, Beka et al. (2018) used ICD-9 and ICD-10 to diagnose anxiety disorder while Egan et al. (2017) and Lee et al. (2019) used DASS-21 for screening anxiety symptoms. Unlike ICD, DASS-21 is a screening tool with 21 items which consists of three domain assessing depression, anxiety and stress²⁹. DASS-21 English version has been translated and validated into Malay version by Musa et al.,³⁰. DASS-21 has distinctive cut-off value for severity rating scale; anxiety is detected if anxiety domain score is ≥ 8 (Mild and above)²⁹, however it should be noted that clinically significant anxiety symptoms should be moderate and above in severity scale is considered significant.

Strength and Limitations

To date, this is the first systematic and meta-analysis on anxiety among patient with GDM. This study clearly indicates that anxiety is prevalent among GDM patients. The finding of this review is consistent with the previous literature pertaining to anxiety among pregnant women experiencing medical complications. However, there are several limitations. [Strict inclusion/exclusion criteria and a paucity of literature on the topic of interest have resulted in the inclusion of only three papers.](#) However, according to Valentine et al., 2010, the minimum number of studies needed to conduct a meta-analysis is two⁵⁸. On top of that, we did sensitivity analysis and funnel plot to show the publication bias. Nevertheless, due care is necessary when interpreting the results as at least 5 studies or more are needed to reasonably and consistently achieve powers from the random-effects meta-analyses that are greater than the studies that contribute to them⁵⁹. Second, the pooled sample size is not large enough to reflect the anxiety prevalence in clinical setting, therefore limiting the generalizability of our study findings.

Science Editor: 1 Scientific quality: The manuscript describes a meta-analysis of the prevalence of anxiety among gestational diabetes mellitus patients. The topic is within the scope of the WJMA. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This study pooled data from existing literature to determine the pool estimates for the prevalence of anxiety among women diagnosed with gestational diabetes mellitus, which was a meaningful meta-study and well described. However, there were some changes that need to be made according to the comment; and (3) Format: There is 1 table and 2 figures. A total of 54 references are cited, including 12 references published in the last 3 years. There are 2 self-citations. 2 Language evaluation: Classification: Grade B. The language was edited by Joshua James Stuart. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and PRISMA 2009 Checklist. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by 2 grants. The topic has not previously been published in the WJMA.

5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Responses: We have uploaded the grant approval documents in the submission system for your perusal.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Responses: We have uploaded the original pictures (Figure 1 and Figure 2) in powerpoint for better resolution.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Responses: We have added the DOI number to the revised version of manuscript.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. 6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.

Responses: Thank you for your comment. We have added "Article highlight" section as suggested. To read as:

Article highlight

The systematic review and meta-analysis reporting the pooled prevalence of anxiety among GDM patients is high (29.5%). We suggest that epidemiological studies on anxiety should be conducted urgently as it merits clinical attention. In addition, it is important to identify factors associated with anxiety among women diagnosed with GDM.