Author’s response to reviews

Title: Peri-conceptional or pregnancy exposure of HPV vaccination and the risk of spontaneous abortion: a systematic review and meta-analysis

Authors:

Xin Sun (sunxin@wchscu.cn)
Jing Tan (tanjing84@outlook.com)
Yi-quan Xiong (xiongyq2018@126.com)
Qiao He (15802498951@163.com)
Yan-mei Liu (lymsmile@126.com)
Wen Wang (wangwen83@outlook.com)
Meng Chen (526543200@qq.com)
Kang Zou (zoukang528@hotmail.com)
Xing-hui Liu (xinghuiliu@163.com)

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Author’s response to reviews:

Reviewer 1

Thank you for the opportunity to read and review your paper. It addresses an important subject, and your study appears to have been an interesting one.

We would like to express our great appreciation to you for the efforts you spent on our manuscript.

I have read the manuscript and my comment are:

1. In conclusion part should to be in details such as what the authors recommend about the HPV vaccination base on many studies that the authors have already review and read them. It will be interesting if the authors do that.

Thanks for the comment. We have added our recommendation about the HPV vaccination (“Considering the insufficient evidence, women at childbearing age should preferably avoid
unintended HPV vaccination during pregnancy”) in the conclusion section in revised manuscript (P16, L13-15).

2. I recommended that the authors make it especially for the result of each manuscript, I think it will be easy to understand.

Thanks for the comment. We added some description of the included articles in the results section: “There are four observational studies, included: Kharbanda et al. [12] was conducted within the data from Vaccine Safety Datalink of seven sites in USA between January 2008 and November, 2014; Scheller et al. [2] used nationwide registers to identify the women who had vaccine exposure in Denmark between October 2006 and November 2013; Baril et al. [15] included women registered with the Clinical Practice Research Datalink General Practice OnLine Database in the United Kingdom, who received at least one 2vHPV dose between September 2008 and June 2011; and Panagiotou et al. [14] was a long term follow-up of a randomized, double blinded trial combined with an independent unvaccinated population based cohort in Costa Rica. The other three studies reported combined results of more than one trial, including combined analysis of forty-two (conducted in 40 countries) [16], seven (conducted in 31 countries) [13], and five trials (conducted in multiple countries) [18].” (P8, L18-22; P9, L1-8). Detailed description of each included study was showed in table 1, including study design (observational study or clinical trial), exposure vaccine, vaccination exposure time, comparison, etc.

Reviewer 2

Interesting study well done

Thank you for your comments, we would like to express our great appreciation to you for the efforts you spent on our manuscript.

1. It is advisable to use more database such as SCPOUS, CINHAL and etc.

Thanks for the comment. The three databases, Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), were recommended in Cochrane Handbook for Systematic Reviews of Interventions and Assessing the Methodological Quality of Systematic Reviews (AMSTAR). In our study, by searching these three databases (data of Medline were contained in Pubmed) and checking all reference lists of included articles (P6, L4-8), we believe that there is almost no possibility of missing relevant researches. Hence, other databases, such as SCPOUS and CINHAL were not included in the literature search section.

2. Assessing the heterogeneity is still unclear in the text
Thanks for the comment. We have rewritten the heterogeneity assessing as: “Between-study heterogeneity was estimated by the clinical features of included studies and the Cochran chi-square test and I2 statistic” (P7, L16-17). In the result section, we showed heterogeneity (I2) following every pooled result and heterogeneity was also showed in tables 2, 3, and figures 1, 2. When there was only one study, the heterogeneity was not presented. According to the study design and characteristics of pregnant women, potential heterogeneity may exist. However, considering the limited studies included and the insignificant statistic heterogeneity in most of pooled results, we just conducted two subgroup analyses to explore heterogeneity: (1) different sources of data (clinical trials vs. databases) and (2) different type of data (raw data vs. adjusted data) (P7, L21-22).

3. It is mentioned " Sensitivity analyses were conducted to examine the association between exposure of HPV vaccination and spontaneous abortion by using alternative effect measures (odds ratio, OR vs. RR), and statistical models (random-effects model vs. fixed-effects model). " but seem unclear!!

Thanks for the comment. We apologize for the not clear expression in the manuscript and the description of sensitivity analyses has been revised in the manuscript: “Sensitivity analyses were conducted to explore the robustness of our findings using different effect measures (when original effect size was RR, OR was used to instead of RR), and statistical models (when original statistical model was fixed-effects model, random-effects model was used to instead of fixed-effects model)”(P8, L1-4).

4. Authors state " The results showed 2vHPV vaccination during Pre-90 days to pregnancy end, Pre-45 days to pregnancy end, and during pregnancy, did not increase the risk of spontaneous abortion with pooled RRs of 1.15 (95% CI: 0.95-1.39, I 2 = 0.0%), 1.28 (95% CI: 0.96-1.70, I 2 = 0.0%), and 0.85 (95% CI: 0.45-1.61), respectively (Table 2, Figure 3).” But I think the interpretation of this results seems wrong, the risk increased however for the last one no however statistically is not significant. but need more clinical explanation.

Thanks for the comment. We have revised this inappropriate interpretation of our result in the manuscript: “The results showed 2vHPV vaccination during Pre-90 days to pregnancy end and Pre-45 days to pregnancy end, seem to increase the risk of spontaneous abortion, but without statistical significance ( pooled RR 1.15, 95% CI: 0.95-1.39, I 2 = 0.0% and pooled RR 1.28, 95% CI: 0.96-1.70, I 2 = 0.0%). However, 2vHPV vaccination during pregnancy was not associated with spontaneous abortion (pooled RR 0.85, 95% CI: 0.45-1.61), respectively” (P9, L11-17).

5. My main question is that how does vaccine increase the risk of SA? unfortunately this paper neither in introduction nor in discussion explain about this direction and possible cause and effect

Thanks for the comment. The potential mechanism between HPV vaccines and SA is still unclear and has not been established. We added a paragraph about the potential mechanism in
“Although the association between HPV vaccination and spontaneous abortion has aroused great interest in recent years, the potential mechanism is rare known. One explanation is that spontaneous abortion may be caused by repeated antigen exposure [31, 32]. Another explanation is that the ASO4 adjuvant in vaccine may alter the maternal immune system during early pregnancy, and then increase the risk of spontaneous abortion [14, 33]. However, these two potential mechanisms are controversial, and need further exploration [12, 14].”

(P15, L1-7)