Author's response to reviews

Title: Risk factors for ectopic pregnancy: a multi-center case-control study

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Author's response to reviews: see over
Dear Dr Sherif Shazly and Mr Jason Pepito,

Thank you very much for having our manuscript *(Risk factors for ectopic pregnancy: A multi-center case-control study. MS ID: 2023868173158128)* peer reviewed and for giving us the opportunity to revise the manuscript for further consideration for publication in *BMC Pregnancy and Childbirth*.

We are very much encouraged by the positive comments of the reviewers and editors who have also pointed out the problems and deficiencies in the manuscript, and grateful to you for recognizing the value of our work. We have made extensive efforts to revise our manuscript. According to the reviewers’ suggestion, we have stated the necessary of the present study, and outlined the difference with the previous studies. In addition, the results section has also been re-segmented depends on the tables, and added with more detail information for each table according to the reviewer’s suggestion. At the end of this manuscript, we have made a comprehensive conclusion on the overall results with clinical implications of the current findings, rather than concentrates on IVF-ET only. We believed that the publication of our work would advance the understanding of the risk factors for ectopic pregnancy among the general population, and optimizing medical services. Enclosed please find the cover letter containing detailed responses to the reviewers, the clean revised manuscript, the revised manuscript with Track Changes, and the revised tables and figures with the updated information.

What’s more, Institute of Embryo-Fetal Original Adult Disease Affiliated to Shanghai Jiao Tong University School of Medicine has recently been founded, and Cheng Li and Jian Zhang are the researchers of this institute. We would like to add this affiliation in the manuscript. And we would like to note that Dr. Jun Qiu is not the corresponding author of this manuscript. Please allow us to remove the contact information of Dr. Jun Qiu.

We are very pleased to see that the Editors/Reviewers’ comments have helped to make significant improvements to the quality of our manuscript. We hope that the revised manuscript will now be satisfactory to be accepted for publication in the *BMC*
Thank you for your time and consideration. We are looking forward to hearing from you soon.

Kind regards,

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Response to the reviewers

General Note:

The reviewers’ comments were copied from BMC Pregnancy and Childbirth Editor Decision Letter without changes. Our responses addressing individual comments and critiques are intercalated below.

Reviewer 1: Dr. Eva Malacova

Thank you for acknowledging the value of our work and for the constructive comments. Herein, we would address each comment via a point-by-point response.

Major Revision:

1. I was surprised to read in the background section “…there are no relevant studies on the risk factors for EP in the region of Shanghai, China.” This statement seems to suggest that there are no published studies, yet the same authors have recently published a similar study which investigated the risk factors for ectopic pregnancy in women with planned pregnancy. This study was neither referenced nor mentioned in the current manuscript.


Given the strong similarity between the previous and current study, the authors
should cite their previous work, both in the background and discussion sections. However, given their two published studies on the risk factors for ectopic pregnancy in women with planned pregnancy, and on contraceptive use and the risk of ectopic pregnancy, it is unclear what knowledge gap would be left in the area of risk factors and ectopic pregnancy?

Response: Thanks for your suggestion. The study “risk factors for ectopic pregnancy in women with planned pregnancy” was actually conducted by us previously. As you suggested, this information has been mentioned in the both background and discussion. As we explained in the revision, the previous study was just conducted among women with planned pregnancy in only one hospital in Shanghai. The present study was designed in five hospitals covering the population across urban and rural areas of Shanghai with a relatively good representation of the population, in order to comprehensively evaluate all the risk factors for EP among the general population rather than those with planned pregnancy. (see page 5, line 2-7; page 12, line 13-15)

Fertility intention might have a great impact on pregnancy outcome (Weiss NS et al., Am J Public Health, PMID: 3966602). Women without planning to conception often resort to a variety of contraceptive methods, most of which could prevent unwanted pregnancy (intrauterine or ectopic), but if contraception fails, some contraceptive methods, like IUDs, could potentially increase the EP. However, women with planned pregnancy include a certain population of females with a history of infertility and/or assisted reproduction technologies. We hope this could explain the knowledge gap between women with planned pregnancy and on contraception use, when we study the
risk factor for EP.

2. Female sterilization was investigated as one of the risk factors, but not mentioned as a known risk factors in the background, despite the three large studies in this area, which looked at the cumulative risk of EP in previously sterilized women.

Response: Thanks for your careful observation. Female sterilization could actually increase the risk of EP, and has also been confirmed as a risk factor in our study. As you suggested, this factor has been added in the background as a known risk factor. (see page 4, line 10)

3. Age is a well-known risk factor and should be mentioned in the background.

Response: Thank you for this insightful suggestion. Age, as a well-known risk factor, has been added in the background. Reference (Yuk JS et al., Int J Gynaecol Obstet, PMID: 23726169) has also been updated at the end of sentence. (see page 4, line 9)

4. The following sentence (line 14): “However, the study designs of previous researches on these subjects as well as the sample size have resulted in an overall ambiguity…” needs to be clearer and less ambiguous.

Response: Thank you for this insightful comment. As we revised in the manuscript, the previous study focused on women not using contraception at the time of conception to explore the risk factors for EP comprehensively, which failed to evaluate the association between EP and contraceptive using in the current cycle of
conception and might make the results in an overall ambiguity. Because fertility intention might have a great impact on pregnancy outcome when study the risk factors for EP. As to the problem how fertility intention influence the pregnancy outcome, we have explained in question 1 above. However, the previous study showed no problem in the sample size. Herein, we have deleted the relevant comment on the sample size, and apologize for our inappropriate comment. (please see page 4, line 14-19)

5. The results section needs to provide more details for each Table and be better explained and structured.

Response: Thanks for your suggestion on the results description. As your recommendation, the results have been added with more information for each table. And the paragraphs have been re-segmented depends on the tables. (please see page 8-9)

6. The clinical implications of the current findings need to be discussed.

Response: Thank you for your suggestion on the clinical implications. In the revision, we have added the clinical implications at the end of the conclusion, in order to reminder physicians to pay attention to suspected EP cases with exposure to some traditional risk factors and pregnant women following IVF-ET, particularly among tubal infertility cases. (see page 13, line 20-23)

Minor Revision:
7. Were ethics obtained for this study? Please include details.

Response: Yes, as we noted in the manuscript, the study was approved by the Institutional Review Board. We provided the scanning file of IRB approval at the end of this review letter, together with its translation. Due to the approval number containing Chinese characteristics, we did not refer to it in the manuscript.

8. Various typos – please check the spelling.

Response: Thank you for this suggestion. The spelling and typos have been checked to improve the readability.

Reviewer 2

Thank you for spending time on reviewing our manuscript and for your good evaluation and suggestions, which we believe have greatly helped us to improve our manuscript. The response to your comments were shown as follows:

1. Study design and participants: I am unsure why the cases and controls were matched with such a wide age band (5 yrs) as the incidence of ectopic may well be affected by age and there may be some bias attached to this - the authors need to explain the reason for this and why they do not feel that this was a problem. I am unclear why marital status was important.
Response: Thank you for your insightful suggestion. It’s true that the matching criteria of age were a bit wider. When we designed the study, we made the age-matching criteria according to the literature by Victoria LH et al. (Victoria LH et al., JAMA, PMID: 2056626). As age itself might be a risk factor for ectopic pregnancy, thus we made relative wider age-matching criteria. When we finished statistic analysis, if age showed significant between cases and controls, we could use multivariate logistic regression to adjust the age to reach an adjusted odds ratio (AOR). Actually, this study showed no significance between cases and controls (please see table 1). Thus, we believed that 5 years age band is acceptable for this study.

In China, unmarried women are less likely to have intention to give birth; they are more likely to use various contraceptive methods like condoms, emergency contraceptive pills and etc. However, married women are more likely to have intention to give birth, some married women with history of infertility will even refer to assisted reproductive technologies to increase the chance of conception. As contraceptive choice and the assisted reproductive technologies might influence the pregnancy outcome, thus we believed that marital status was important when we recruited subjects.

2. It is also not clear how the sample size was calculated.

Response: According to the OR value of several main factors, reported in literature, we set an α level of 0.05 and a statistical power of 0.8 to estimate the sample size, and
a final of about 200 sample size in each group was calculated. However, this study recruited more than 4800 subjects at five medical centers. Due to the sufficient scale of patients’ visiting annually at all medical centers, we investigated more subjects in order to make the study more confident with a higher statistical power.

3. Oral contraceptives appear to be lumped into one group and should have been split as the risk of ectopic may well be different between the progesterone only and the combined pill. Whilst the authors point this out in the discussion they have not really addressed how this might affect the results.

Response: It’s a good question. However in our study, some participants were lacking of knowledge on the oral contraceptive, so it’s hard for them to recall or provide detail information on the oral contraceptives use (progesterone only pills or the combined pills). As we have discussed in the limitation, “Data collection in this study was based on patients’ self-evaluation; hence, we were unable to obtain additional information on the types of OCPs, sterilization methods, and IUDs for further study”. Thus, some comment on this aspect has been re-discussed in the section of discussion. (see page 11, line 18-22)

4. In the multivariate analysis there is mention of chinese herbs as part of fertility treatment: the details of this as a treatment will only be obvious to those health care professionals used to using chinese herbs and warrants a more detailed explanation of the relevance of this.
Response: As you comment, Chinese herbs as a treatment for infertility are only obvious to those health care professionals used to using Chinese herbs. However in China, there exists part of women who are confident of the efficacy of Chinese herbs to treat the long-term infertility of unknown etiology (Ushiroyama T et al., Am J Chin Med, PMID: 22298444). For example, they used Chinese herbs to increase endometrial thickness, improve the quality of fertility and embryo (Guo J et al., J Tradit Chin Med, PMID: 24992752), and luteal phase defect (Lian F, J Tradit Chin Med, PMID: 1861518). Although there are limited literatures reported the Chinese herbs treatment for infertility in PubMed, we must admit that it was quite popular in China. We just reported this phenomenon truthfully. And finally, we did not find any association between Chinese herbs treatment for infertility and the risk of EP.

5. Conclusion: the conclusion concentrates on IVF-ET only and seems to forget about the other significant results and therefore appears a bit disjointed from the text - rather like it has been plucked from somewhere else. It needs to reflect the original aims of the study not just one significant finding.

Response: It’s a very valuable suggestion for our manuscript. We really missed the other significant results and made the conclusion disjointed. Here, we have re-wrote the conclusion covering all main findings in this study in the revision. (see page 13, line 14-17)
中国福利会国际和平妇幼保健院医学伦理委员会

批件号：国伦理（2011）21号

张健：

你递交的申请《左炔诺孕酮非处方紧急避孕药避孕失败发生输卵管妊娠发病相关因素的研究》具体方案已收悉。经院医学伦理委员会对相关科研项目的有关伦理内容认真讨论，认为该科研项目为总结性研究，以问卷调查形式开展，不涉及患者的隐私及治疗随访，符合医学伦理要求，因此同意你们开展此项科研项目的研究。

合作单位：上海交通大学附属第一人民医院、上海市松江区中心医院、上海市
闵行区中心医院、上海市松江区妇幼保健院

国际和平妇幼保健院医学伦理委员会
2017年11月28日
Dr. Jian Zhang,

We have received the protocol of “Etiological exploration on the risk between Levonorgestrel emergency contraception and ectopic pregnancy” you submitted. After careful consideration of this protocol, this study is a retrospective study via questionnaire-based investigation, without involving in the participants’ privacy and follow-up, and meeting the Ethical requirement of medical study. Thus, we approved the study protocol you submitted.

Cooperative Institution: Shanghai First People's Hospital, Shanghai Jiaotong University; Songjiang Central Hospital; Minhang Central Hospital; Songjiang Maternity and Child Health Hospital

Institutional Review Board

International Peace Maternity and Child Health Hospital

Nov. 28th, 2011