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Authors Reply

Response to the letter regarding "Spontaneous pregnancy following intra-ovarian platelet-rich plasma administration in poor ovarian responders according to the POSEIDON criteria: A cross-sectional study"

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We are pleased that Dr. Hafsa Riaz and colleagues showed interest in our descriptive observational study (1) entitled "Spontaneous pregnancy following intra-ovarian platelet-rich plasma administration in poor ovarian responders according to the POSEIDON criteria: A cross-sectional study". However, we believe that there are several points in the letter to the editor that require clarification.

The letter criticizes our study's conclusion by stating that "The retrospective cross-sectional design without a control arm precludes causal inference: the observed 8.39% spontaneous pregnancy rate cannot be confidently attributed to platelet-rich plasma (PRP)". The nature of our study was observational, and as clearly described in Section 3.2, had a descriptive purpose. Additionally, we did not state a causal claim in our conclusion, nor did we confidently attribute the 8.39% spontaneous pregnancy rate to PRP treatment. More specifically, our conclusion states that "the rate of spontaneous pregnancy following intra-ovarian PRP (IO-PRP) was approximately 8.4%. This ratio seems not to be clinically significant to perform a wait-and-watch plan after IO-PRP instead of other infertility treatments".

Furthermore, the letter notes that our observational study lacks a control arm. Our study was intentionally designed as a descriptive, hypothesis-generating observational analysis, rather than an efficacy trial, target trial emulation, or case-control study. Observational studies with a descriptive aim may only focus on a certain population without including a control arm (2).

Similar to any observational study, selection bias is one of the limitations of this research, and we clearly reported the initial number of participants in our database. Our goal was to provide a real-world description of spontaneous pregnancies in the mentioned population.

Regarding the differences in spontaneous pregnancy rate following IO-PRP with another comparable study, the letter states a range of 4–7%, which has not been mentioned in the cited study. The cited study has mentioned 7.4% as their spontaneous pregnancy rate following IO-PRP therapy (3). Contrary to the claim made in the letter, our study is not directly comparable with that investigation, as we only included participants with a 2-yr follow-up period. Another study did not mention about their follow-up period, except that all the spontaneous pregnancies occurred between cycles 1 and 7 (their supplementary table I), which could be approximated as a follow-up duration of about 7 months.

The letter expresses its concern regarding the clinical relevance of spontaneous pregnancy by stating that "delaying established assisted reproductive technologies in favor of an experimental intervention risks compromising cumulative live birth potential". Thus, it should be clarified that in our study, we did not mention any individual was deprived of assisted reproductive technology (ART) in favor of an experiment during the follow-up period. In our center, all participants were offered ART according to established clinical guidelines, and spontaneous pregnancies occurred among individuals who, for personal reasons, either did not proceed with the scheduled ART or conceived before the planned treatment. Individuals with a short interval between intervention and spontaneous pregnancy (e.g., a few weeks to months) were mostly on the ART waiting list. However, for participants with an interval of more than 6 months between IO-PRP administration and a laboratory-confirmed positive pregnancy test, this delay may be explained by other reasons for discontinuing ART, such as lack of interest in oocyte donation, perceived futility of ART, or failure to attend scheduled interventions for unspecified personal reasons. Given all these considerations, we clearly stated in our conclusion that "this ratio seems not to be clinically significant to perform a wait-and-watch plan after IO-PRP instead of other infertility treatments". This demonstrates that the concern raised in the letter is not aligned with the actual conclusion published in our study.

The statistical analysis was performed using R version 4.4.0 (R Foundation for Statistical Computing). Group comparisons were initially evaluated using appropriate omnibus tests. Post hoc pairwise comparisons were performed only when the overall test indicated statistically significant differences. Tukey's honestly significant difference test and the Games-Howell test were applied following one-way analysis of variance and Welch's analysis of variance, respectively, as both methods inherently control the family-wise error rate across all pairwise comparisons. For non-parametric analyses following the Kruskal-Wallis test, Dunn's test was used, with p-values adjusted for multiple comparisons using the Holm method, as implemented by default in the rstatix package (4). Accordingly, appropriate control for multiple testing was applied throughout the analysis, thereby minimizing the risk of inflated type I error.

Regarding the potential confounding factors, the letter states that concurrent treatments, lifestyle factors, and partner fertility parameters have been ignored in our study. For the concurrent treatments, we explicitly stated in the exclusion criteria that "receiving any other medication/intervention affecting the

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pregnancy rate or being at any clinical trial with intervention(s) with unknown effect on fertility" leads to exclusion. Therefore, concurrent treatments were not a confounder. Regarding the "partner fertility parameters", table II reports spouse age, sperm count, morphology, and motility among the participants who achieved spontaneous pregnancy. Finally, since lifestyle includes different objective and subjective variables, one of the most important of them, body mass index (BMI), was chosen as a subjective variable. However, other variables, such as drinking and smoking, are missing. In contrast, including more variables could increase the risk of type I error.

Furthermore, the letter emphasizes the heterogeneity in PRP preparation methods, which is correct. However, this issue is not unique to our study and applies broadly to PRP interventions across various medical fields. Our study did not use commercial kits for PRP preparation and followed an already established method routinely performed in our center by the same trained operators and devices. This reduces performance bias related to procedural heterogeneity at the study level.

Finally, the letter recommends further randomized controlled trials (RCTs). While further standardized RCTs are needed to assess IO-PRP efficacy for ART, as suggested by a recent meta-analysis (5), mostly on observational studies, any RCT to investigate the rate of spontaneous pregnancy following IO-PRP is unethical, as this requires withholding eligible participants from a potentially effective intervention. For this reason, we only suggested conducting further observational studies at the end of our conclusion.

Conflict of Interest

The authors declare that there is no conflict of interest.

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