Response: Commentary: Efficacy of Follicle-Stimulating Hormone (FSH) Alone, FSH + Luteinizing Hormone, Human Menopausal Gonadotropin or FSH + Human Chorionic Gonadotropin on Assisted Reproductive Technology Outcomes in the “Personalized” Medicine Era: A Meta-analysis

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A commentary on

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We appreciated the constructive comments by Professor Younis (1) to our article (2). He gave us the opportunity to further discuss issues raising by the lack of clear evidence in the setting of assisted reproduction techniques (ART).

Although 65 meta-analyses were published so far, our study represents the first attempt to consider all gonadotropin combinations currently used in clinical practice, mainly focusing on specific effects linked to luteinizing hormone (LH) or human chorionic gonadotropin (hCG) supplementation. The evaluation of how different therapeutic approaches impact on peculiar clinical settings, such as polycystic ovarian syndrome or hypo-responder women, was beyond the aims of the study. It would have determined a complicated stratification process, where many grouping variables would have been evaluated in too many undersized subgroups. Moreover, we agree with Professor Younis about the relevance of genetic characteristics. The polygenic nature of ovarian response implies that the ideal approach to controlled ovarian stimulation (COS) should be patient-specific and determined by genetic screening.

Recently, the Cochrane Collaboration evaluated the effect of LH addition during COS on live birth rate, placing no limit of age or clinical setting (3). In spite of the strict selection of randomized trials, the risk of selection biases remained relatively high. This was due to potential errors introduced...
It is common opinion that the type of GnRH analog used provides different residual LH activity, relying on the concept that <1% of LH receptors (LHCGR) occupied by the ligand are enough to elicit steroid synthesis (14). This is the concept known as “spare receptors” emerging from previous studies (15), often improperly handled by gynecologists to interpret and transpose the messages provided by in vitro studies to the clinics. The concept originates from the historical investigations of Dufau and Catt (15), who evaluated hCG-mediated cAMP increase and testosterone synthesis in rat Leydig cells, rather than human ovarian and endometrial cells treated by LH. The findings of such studies explained pharmacological mechanisms assessed exclusively in a specific context in vitro which cannot be used to explain clinical observations. In light of recent studies demonstrating fivefold lower LH- than hCG-mediated cAMP increase (16–18), as well as the inability of Leydig cells expressing rodent receptors to discriminate qualitatively intracellular signals mediated by the two human ligands (18), we should seriously reconsider if residual LH (putative) activity is mediated by LHCGR in granulosa cells. LH is not as potent as hCG in inducing steroidogenic signals. On the other hand, LH displays preferential proliferative signals in human granulosa cells (19), not appraisable in rodents’ Leydig cells, unable to discriminate qualitatively between LH- and hCG-specific signals. Rather, residual LH activity should be due to FSH receptor-LHCGR heterodimers activated by FSH and mediating LH-like stimuli. This is also suggested by animal models: while FSH alone triggers follicle maturation and ovulation in hypophysectomized mice, it fails to do the same in LH receptor-knockout mice (20). Anyway, since the residual LH activity is not routinely evaluated in clinical trials, this could not be considered in our meta-analysis.

Prof. Younis’ comments shift the interpretation of our findings toward a clinical point of view, focusing on the detection of parameters useful to choose the best COS protocol, as a crucial issue for personalized medicine. However, meta-analyses fail short to provide guidelines or recommendations for clinical practice, since relying on data already published, which could not be directly exported to the general population. Starting from different activities demonstrated in vitro (16), our study aimed at evaluating the different action of gonadotropins in vivo, considering the COS phase as an experimental model in which to test these molecules. Therefore, our meta-analysis is a starting point to design clinical trials aimed at evaluating the best gonadotropins combination for ART.

**AUTHOR CONTRIBUTIONS**

DS, LC, CA, and MS contributed to the manuscript draft.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.