RESPONSE TO THE LETTER-TO-THE-EDITOR TITLED "ADENOMYOSIS AND ENDOMETRIOSIS IN INFERTILITY- HOW DO WE OPTIMIZE THE HOUSE AND THE GARDEN?"

Edgardo Somigliana, M.D.[1,2] ORCID 0000-0002-0223-0032 edgardo.somigliana@unimi.it

Paola Viganò, Ph.D.[2] ORCID 0000-0003-3674-5912 paola.vigano@policlinico.mi.it

Veronica Bandini, M.D.[1] ORCID 0000-0003-1788-9670 veronica.bandini@unimi.it

Laura Buggio, M.D.[2] ORCID 0000-0002-1199-1888 buggiolaura@policlinico.mi.it

Nicola Berlanda, M.D.[2] ORCID 0000-0002-1797-1984 nicola.berlanda@policlinico.mi.it

Paolo Vercellini, M.D.[*1,2] ORCID 0000-0003-4195-0996 paolo.vercellini@unimi.it

From [1]Department of Clinical Sciences and Community Health, Università degli Studi, Via Commenda 19, 20122 Milano, Italy and [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 12, 20122 Milano, Italy

*Correspondence: Paolo Vercellini, M.D.

Department of Clinical Sciences and Community Health, Università degli Studi and

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Via Commenda 12, 20122 Milano, Italy

Electronic address: paolo.vercellini@unimi.it

We thank Kalaitzopoulos and Quaas for their interest in our review (1). In their letter, they expressed concern that the potential impact of the different ovarian stimulation protocols on assisted reproductive technology (ART) outcomes in patients with endometriosis- and adenomyosis-associated infertility has not been adequately addressed. In this regard, they cited the meta-analysis by Nirgianakis *et al*. (2), which showed a low clinical pregnancy rate in patients with adenomyosis who underwent short pituitary down-regulation protocols, but not in those who used an ultra-long or modified ultra-long down-regulation protocol.

We acknowledge the potentially different impacts of various ovarian stimulation protocols, but the limitations associated with the quantitative synthesis of the available data on this aspect are so numerous that the '*impact of adenomyosis and endometriosis on reproduction and pregnancy can only be roughly assessed'* (1). Such limitations include suboptimal study design (lack of randomization), small sample sizes, the inclusion of patients with both endometriosis and adenomyosis, making it difficult to accurately assess the impact of each condition separately, and inadequate adjustment for confounding factors. Therefore, it seems premature to draw conclusions based solely on the findings of the two retrospective studies on the short down-regulation protocol included in the overview by Nirgianakis *et al*. (2).

Interestingly, based on the observation of a critical role of ovarian stimulation in ART outcomes in the presence of adenomyosis, Kalaitzopoulos and Quaas propose the use of a segmental approach as a possible strategy for women with an enlarged adenomyotic uterus, i.e., a short stimulation protocol to maximize oocyte yield and the vitrification of the resulting embryos, followed by a prolonged GnRH analog administration before frozen-thawed embryo transfer (FET). This approach is already currently used in the most severe cases. However, the results of the available retrospective studies regarding the potential benefit of a GnRH analog treatment before FET are controversial, and since the basis for the decision to pretreat was not always defined, allocation bias seems likely.

A single, very recently published, randomized trial comparing endometrial preparation regimens with and without GnRH analog pretreatment in patients with adenomyosis undergoing FET cycles failed to show significant between-group differences in clinical pregnancy rates, miscarriage rates, and live birth rates (3). However, due to the small sample size, a type II error cannot be excluded. Therefore, well-designed studies are still needed to support the biologically plausible clinical scheme proposed by Kalaitzopoulos and Quaas.

Finally, before implementing strategies aimed at improving ART outcomes in patients with adenomyosis, it should be clarified which forms of the disease may have a negative impact. A recent well-conducted prospective study failed to identify specific detrimental features (4), but further evidence is required.

REFERENCES

1. Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. Fertil Steril. 2023;119:727-40.
2. Nirgianakis K, Kalaitzopoulos DR, Schwartz ASK, Spaanderman M, Kramer BW, Mueller MD, et al. Fertility, pregnancy and neonatal outcomes of patients with adenomyosis: a systematic review and meta-analysis. Reprod Biomed Online. 2021;42:185-206.
3. Eslami Moayed M, Moini A, Kashani L, Farid Mojtahedi M, Rezaee T, Tabasizadeh H, Maajani K, Yamini N. Pregnancy outcomes in women with adenomyosis, undergoing artificial endometrial preparation with and without gonadotropin-releasing hormone agonist pretreatment in frozen embryo transfer cycles: An RCT. Int J Reprod Biomed. 2023 24;21:481-490.
4. Neal S, Morin S, Werner M, Gueye NA, Pirtea P, Patounakis G, Scott R Jr, Goodman L. Three-dimensional ultrasound diagnosis of adenomyosis is not associated with adverse

pregnancy outcome following single thawed euploid blastocyst transfer: prospective cohort study. Ultrasound Obstet Gynecol. 2020;56:611-617.

DISCLOSURE STATEMENT:

E.S. discloses payments from Ferring Pharmaceuticals for research grants and honoraria from Merck-Serono for lectures. All other authors declare they have no conflicts of interest.