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LETTER

Author's Response to: 'Letter to the Editor in Response to: "Effect of Polymorphisms in CYP2C9 and CYP2C19 on the Disposition, Safety and Metabolism of Progesterone Administrated Orally or Vaginally"'

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We are pleased to reply to Lazorwitz et al. [1] letter response in regard to our manuscript published in Advances in Therapy on September 2019 [2]. First, we commend the efforts of Lazorwitz A. and colleagues in searching genetic factors that may influence etonogestrel plasma concentrations, especially for exploring Cytochrome P450 (CYP) enzymes as they have traditionally been considered of little relevance for the metabolism of progestogens.

The reasons why we decided not to compare our results with theirs were: (a) structural differences between progesterone and etonogestrel (i.e., on position 17, Fig. 1) may alter CYP specificity, (b) the endogenous nature of progesterone vs. the exogenous nature of etonogestrel and (c) the differences in the study population, i.e., postmenopausal women vs. contraceptive implant users. To be able to compare our results with those of Lazorwitz et al. [1], it must be assumed that both compounds are metabolized in the exact same way. More difficult to assume are the limitations stated in "(b)" and "(c)". Postmenopausal women and contraceptive implant users are not comparable in terms of endogenous progesterone plasma levels. In addition, endogenous progesterone may have different effects on exogenous progesterone or etonogestrel metabolism. These differences in the study design and drug characteristics may explain why we found an association between CYP2C19 phenotype and progesterone levels that was not found in their study.

Nevertheless, their findings on *CYP3A7**1C are surprising. This CYP enzyme has been reported to contribute in a minor extent to progesterone metabolism [3]. However, their findings are coherent, as the presence of this variant leads to the expression of the silenced fetal gene in adults [4]. The latter would increase etonogestrel metabolism, explaining the 23% lower plasma levels reported for *CYP3A7**1C carriers compared to wild type patients. It would be of great interest to genotype our study population for this variant. However, due to the low prevalence of this variant and our relatively small sample size, it is highly unlikely that we would observe significant effects. In addition, we did not observe

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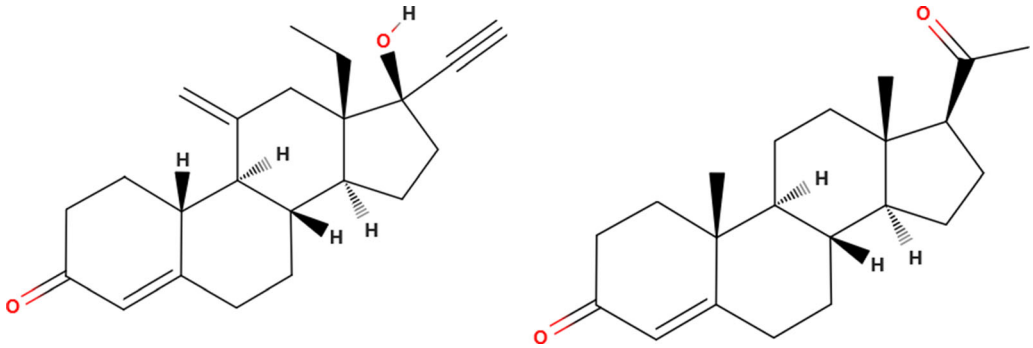

Fig. 1 Chemical structures of (**a**) left, progesterone and (**b**) right, etonogestrel. Images created with an image processing software (created at http://molview.org/)

effects of weight on progesterone plasma levels. This may be due to the low variability in weight among our volunteers, probably caused by the application of trial's inclusion criteria.

In summary, both studies claim the relevance of CYP enzymes in progestin (etonogestrel) and progesterone metabolism. The extent to which this occurs must be demonstrated in additional studies, i.e., the associations with *CYP3A7**1C and CYP2C19 phenotype must be replicated.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Peer Review. Please note, contrary to the journal's standard single-blind peer review process, as a commentary this article underwent review by a member of the journal's Editorial Board.

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