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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First available online on September 3, 2019 in Advances in Therapy, Zubiaur et al. [1] suggested that the CYP2C19 phenotype may help explain some of the variability in serum progesterone concentrations when taken orally or vaginally and stated that there are “no other pharmacogenetic studies of progesterone” with which to compare their results. In fact, our published pharmacogenomics study of etonogestrel metabolism is an important comparator [2]. Etonogestrel, a progestin found in some forms of contraception including the continuous-release subdermal implant, is metabolized in very similar processes to progesterone [3]. Clinical data also support that the etonogestrel contraceptive implant and other progestins (e.g., dienogest) have similar pharmacological properties as progesterone, further supporting common metabolic and pharmacodynamic pathways between these steroid hormones [4, 5]. Like Zubiaur and colleagues, we utilized a candidate gene approach for our investigation, including genetic variants in CYP2C19, CYP2C9, and three other metabolizing enzyme genes (CYP3A4, CYP3A5, CYP3A7). However, unlike Zubiaur et al. [1], we did not find that variants in CYP2C19 were associated with differences in serum etonogestrel concentrations among our 350 contraceptive implant users [2]. Alternatively, we found that a variant in CYP3A7 (the *1C variant) was significantly associated with 23% lower etonogestrel concentrations than the respective wild-type genotype [2]. We also found that body mass index was significantly associated with serum etonogestrel concentrations and should be accounted for in pharmacokinetic investigations with similar steroid hormones [2].

We agree with Zubiaur and colleagues that genome wide association studies are needed to further explore the pharmacogenomics of steroid hormones, particularly in light of the findings by Zhang et al. [6] regarding the limited role that CYP3A4 appears to have in the metabolism of steroid hormones. However, given the disparate findings regarding CYP2C19 variants between our studies, additional research is...
warranted to determine how much this specific CYP isoenzyme and variants within its gene truly influence progesterone and progestin metabolism.

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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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