Genetic Differences May Reflect Differences in Susceptibility to Vulvodynia in General or in Spontaneous Remission Propensity

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Dr. Goldstein et al. have published their data on cytosine–adenine–guanine (CAG) trinucleotide repeats on an androgen receptor (AR) gene among a select group of vulvodynia cases and noneffected controls and have argued that their data suggest these women with vulvodynia who had started combined oral contraceptives (COCs) prior to pain onset, and whose pain resolved after COCs were discontinued, were more likely than controls to have a greater number of CAG repeats in the AR gene and were also likely to have a lower free testosterone level [1]. They suggest this finding identifies a subgroup of genetically predisposed women in whom oral contraceptives are more likely to instigate their vulvar pain that may be relieved on discontinuation of this medication.

Unfortunately, the study as conducted compared two groups who differed in a number of ways, making interpretation of the results problematic. In a case control study, the goal is to have the groups as similar as possible, with the variable in question (a genetic difference predisposing to vulvodynia that is instigated by COCs and resolving when COCs are discontinued) being the main difference between the two groups, thereby allowing one to conclude that a difference noted may be associated with that variable. The authors proposed to demonstrate a gene–environment interaction but have looked at only one part of such a model. In the reported study, all women were taking COCs, but one group had developed vulvodynia and the other had not; hence, the differences noted in CAG repeats on the AR gene might be related to the susceptibility to vulvodynia in general, rather than to the use of COCs. In addition, remission in vulvodynia is increasingly understood to occur [2,3], and hence the genetic profile of those with remission after COCs were discontinued needs to be compared with that of those whose vulvar pain did not remit when COCs are removed. A number of other interpretations of the data would be consistent with the findings. The genetic difference noted could have also been related to differences previously reported among those with and without vulvodynia, such as having comorbid pain conditions (fibromyalgia, interstitial cystitis, irritable bowel disorder, temporomandibular dysfunction, etc.) [4], depression, or having increased sensitivity itself [5]. All of these are possible interpretations of the data presented, but they, like the interpretation proposed in the article, are not provable with the data provided.

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Genetic Differences May Reflect Differences in Susceptibility to Vulvodynia in General or in Spontaneous Remission Propensity: A Response

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Dear Editor,

We are pleased to have this opportunity to further discuss our study and agree that there are important caveats and limitations to our findings, as we have already delineated in our publication. While there may be alternative interpretations to the data, we believe that our conclusions are the most biologically plausible and consistent with the data. In our study, the cases were women who developed vestibulodynia after starting combined hormonal contraceptives (CHCs). The vestibulodynia resolved after cessation of CHCs and treatment with topical estradiol and testosterone. By their mechanisms of action, CHCs cause an endocrinopathy due to a decrease in serum-free testosterone. We postulate that it is the *combination* of low free testosterone and the longer CAG repeat polymorphism in the androgen receptor gene that increases the risk of vestibulodynia.

This perspective was further supported by the fact that the control group had a lower free testosterone than the subject group but had longer CAG repeat lengths overall and did not develop vestibulodynia. Further, the members of the control group were