

Case Study: Observations of Testosterone/Estradiol Levels and HPTA Response in a MTF Transgender Patient Undergoing Hormonal Feminization Therapy

Dr Justin Saya, MD
Defy Medical
May 11, 2016

Case Presentation

Patient consent was obtained to use laboratory data and case details from patient, however care is taken to maintain patient privacy and limit any potentially identifying information.

Patient is a biological male presenting at an age of 20 – 25 years old having been referred by his counselor for hormonal treatment to assist MTF transgender transformation. A thorough examination and consult was performed on patient including counseling, lab review, and all appropriate consents were reviewed and signed. Once appropriateness of treatment was determined, MTF transformative hormonal treatment was initiated in the form of estradiol cypionate twice weekly injections. For the purpose of simplicity and a focused discussion, dosages of estradiol cypionate will not be included, but rather the resulting serum estradiol levels (via LC-MS/MS) from gradual estradiol cypionate dosage escalation.

Results/Data

Estradiol (pg/mL) and total/free testosterone (ng/dL – pg/mL) levels were monitored for this patient with the results throughout the first year of treatment documented below in Table 1. Note, as estradiol cypionate dosages were gradually increased over the course of the year (left to right), estradiol lab values via LC-MS/MS increased as expected. There was also an interesting pattern that emerged in the concurrent serum testosterone levels which will be discussed below.

Table 1: Estradiol and corresponding Testosterone Levels during MTF Transgender Estradiol Cypionate Treatment

Estradiol pg/mL (via LC-MS/MS)	12	22	29	43	62	81
Testosterone Free/Total (ng/dL)/(pg/mL)	476/9.8	676/23.4	537/15.8	412/7.4	16/1.4	8/0.9

Discussion/Conclusions

It is a well-documented physiologic phenomenon that the endocrine system operates under the principle of “negative feedback”, whereby end-product hormones (i.e. testosterone, estradiol, etc) exert suppression via a negative feedback loop to the hypothalamus – pituitary. This negative feedback loop operates primarily as an evolutionary safety/preventative mechanism to maintain physiologic hormone levels and prevent artificially high or “supra-physiologic” hormone levels (and the resulting health/survival risks attributed to same). Of course, this negative feedback loop can be “over-ridden” through the administration of **exogenous** hormones (estradiol cypionate, testosterone cypionate, etc), thereby allowing one to achieve supra-physiologic hormone levels without the limitations imposed by negative feedback. In other words, being able to increase hormone levels (T, E, etc) **above** the biological “set point” or “limit point” where negative feedback kicks in to prevent further escalation. I would also argue, as a scientist/physician, that determining where this “set point” or “limit point” **is** would offer insight into determining where various hormone levels are **intended** to be by biological design. After all, who could argue against the wisdom of our biological design/blueprint?

Evaluating this data reveals an interesting pattern. It was observed that as estradiol cypionate treatment was initiated and resultant estradiol serum levels increased, there was initially an **increase** in testosterone levels above **baseline** values. This pattern was observed as estradiol levels increased from 12 pg/mL -> 22pg/mL -> 29pg/mL (with corresponding T levels 476/9.8 -> 676/23.4 -> 537/15.8). Clearly there was NO HPTA suppression as estradiol levels increased from 12pg/mL to 29pg/mL, arguably indicating that **these** estradiol levels are **within** the design of biological physiologic levels. In fact, as testosterone levels actually INCREASED as estradiol levels increased from 12pg/mL -> 22pg/mL it may be argued that there was HPTA STIMULATION achieved from this increase in estradiol from 12->22 and, consequently, estradiol levels of 22pg/mL are biologically preferred (or “encouraged/supported” by the HPT axis). This would actually fit nicely with most prevailing current data that estradiol levels **below** 20pg/mL may impart certain health risks (interesting isn’t it).

Equally as interesting was the pattern that emerged as estradiol levels continued to climb. From the data it appears HPTA suppression began to exert its impact as estradiol levels climbed to 43pg/mL. Note, although LH/FSH levels were not measured in this case as a measurement of HPTA suppression, the decline in T levels as E levels increase (only attributable to HPTA suppression from exogenous E treatment) is used as an indicator for PRESUMPTIVE HPTA suppression. As estradiol levels reached 43pg/mL it appears the HPTA suppression was **beginning** as this was the first time that testosterone levels were suppressed to below initial baseline levels (476/9.8 baseline vs 412/7.4). Upon further analysis of the data, it is also clear that as estradiol levels continued to climb from 43->62 ->81, there was a **profound** and powerful HPTA suppression (via negative feedback from increasing estradiol levels) that kicked in to drastically suppress testosterone levels 412/7.4 -> 16/1.4 -> 8/0.9. Thus, in summary, it appears that for this particular **biologically male** patient, mild HPTA suppression was beginning to exert negative feedback effects as estradiol levels rose to 43pg/mL and this HPTA suppression via negative feedback accelerated rapidly to almost **complete** suppression by the time estradiol levels had increased to 62pg/mL.

So what does this mean? Perhaps nothing, or perhaps this may point to a "biological set point" or "biological upper limit/ceiling" for estradiol levels in genetic males, after which profound HPTA suppression kicks in as a **preventative/protective** measure to prevent further increase. If this is the case, it would appear this "ceiling" or biological upper set-point for estradiol (when exposed to normal physiologic endocrine feedback mechanisms) would lie somewhere in the range of 43pg/mL – 62 pg/mL. However, with the HPTA suppression appearing to **begin** with estradiol levels in the 40's and the **drastic/profound** suppression evident with estradiol levels of 62 pg/mL, I would argue that the "set-point" or "biological ceiling" would seem to be somewhere between these two extremes, with an educated assumption based on these data and my own clinical experience of 50-55pg/mL. Further, it would be a sound argument to state that any estradiol levels that fall outside (above) the biological set point (wherever that may be) for HPTA suppression (which once again is ingrained into our endocrine system as a self-limiting protective mechanism) would classify as supra-physiologic (i.e. above the levels for which normal HPTA suppression in a male would PREVENT levels from rising).

There are limitations to this study including small sample size, not monitoring LH/FSH but instead relying on observed testosterone suppression as a surrogate measure of HPTA suppression, and lack of more precise measurement of estradiol levels, particularly during the interval of apparent HPTA suppression of 43pg/mL – 62pg/mL. Nonetheless, I feel that this data represents a unique and novel insight into what one might consider 'physiologic' estradiol levels as measured by the endocrine system's own measuring stick – HPTA suppression via the evolutionary negative feedback mechanism.