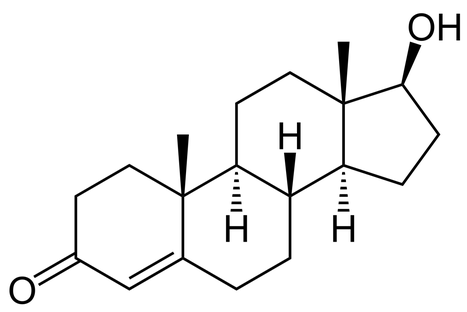
High testosterone? Think again!

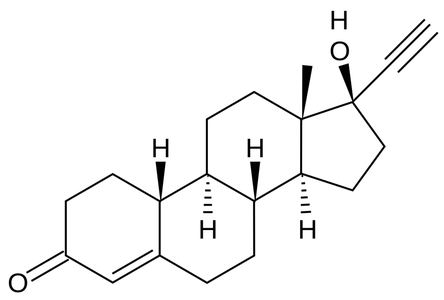
Babiker T[1], Perry M[2], McDonald T[2], Brooke A[1], O' Connor J[2]

Affiliations:
1: Department of Diabetes and Endocrinology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
2: Department of Clinical Chemistry, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

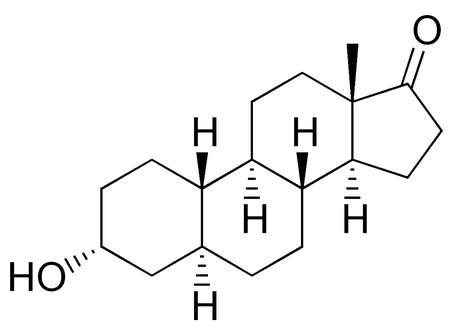
Background: 3 female premenopausal patients presented with high isolated testosterone without symptoms of androgen excess or illicit drug use.



Testosterone



Norethisterone



19-norandrosterone

Case 1
A 22 year old female presented with daily vaginal bleeds having been on depot injections of progesterone with supplementary norethisterone. Testosterone was 14.5 nmol/L with suppressed gonadotrophins (LH < 0.1 iu/L, FSH 0.2 iu/L, oestradiol <19 pmol/L). Her norethisterone was stopped. A repeat biochemical profile after 3 weeks was normal (testosterone 0.8 nmol/L, FSH 4.1 iu/L, LH 3.4 iu/L, oestradiol 230 pmol/L).

Case 2
A 43 year old female presented with a 3 week history of prolonged menstrual bleeding. She commenced norethisterone; 2 days later testosterone was 7.6 nmol/L, SHBG 66.9 nmol/L, free androgen index 11.36, LH 0.4 iu/L, FSH 1.2 iu/L, oestradiol 198 pmol/L. Repeat testing 12 days after stopping norethisterone was normal: testosterone 0.8 nmol/L, 85.4 nmol/L, free androgen index 0.94, FSH 6.3 iu/L, LH 5.5 iu/L, oestradiol 839 pmol/L, cortisol 302 nmol/L).

Case 3
A 20 year old female with dysmenorrhoea on the oral contraceptive pill commenced norethisterone with resolution of her symptoms and amenorrhoea. She took lamotrigine for epilepsy but denied other medications. Initial testosterone was elevated: 7.7 nmol/L, SHBG 9.4 nmol/L, free androgen index 81.91, FSH 1.3 iu/L, LH <0.1 iu/L. After 3 weeks, her biochemistry had improved: 17OHP <1 nmol/L, cortisol 169 pmol/L, FSH 0.6 iu/L, LH <0.1 iu/L, testosterone 4.2 nmol/L, SHBG 10.1 nmol/L, free androgen index 41.58. After a further 2 weeks her testosterone was normal (0.9 nmol/L).

Norethisterone, a synthetic progestin, is metabolised to 19-norandrosterone (as is nandrolone) via 5-alpha-reductase but has only weak androgenic activity[1]. It is a component of several combined and progestogen only pills.

Other departments have found similar assay interference and have found that other assays such as the Siemens AVIA Centaur assay may also be affected, but not in testosterone measurements obtained by liquid chromatography-tandem mass spectrometry[2].

All patients had elevated testosterone associated with norethisterone use, which normalised 19 to 41 days after norethisterone was stopped.

We hypothesise that 19-norandrosterone interferes the Roche Modular E170 Testosterone II assay used, giving a falsely elevated testosterone.

References
1. Lemus, Ana E., et al. "5 α-Reduction of norethisterone enhances its binding affinity for androgen receptors but diminishes its androgenic potency." *The Journal of steroid biochemistry and molecular biology* 60.1 (1997): 121-129.
2. Jeffery, Jinny, et al. "Norethisterone interference in testosterone assays." *Annals of Clinical Biochemistry: An international journal of biochemistry and laboratory medicine* (2013): 0004563213512800.

Royal Devon and Exeter NHS
NHS Foundation Trust