Author’s response to reviews

Title: Twenty-four hours secretion pattern of serum estradiol in healthy prepubertal and pubertal boys as determined by a validated ultra-sensitive extraction RIA

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Referee 1:

Major compulsory revisions:

We have now revised the manuscript according to the reviewer’s comments. The changes are made in “Abstract” and “Discussion”. The language has been scrutinized by a UK colleague at the department.

- We agree that it is not optimal to write “the first approach” and have therefore exchanged the last sentence in the abstract with the following sentence:
  Conclusion: With the use of an ultra-sensitive extraction RIA, we have provided clinically useful normative data for estradiol secretion in boys.

- In the first comment, the reviewer mention 1 peer-reviewed abstract, 1 article, and 2 book chapters. These do not add anything to our manuscript. The abstract is 10 year old and therefore of minor interest and the article is incorrect and does not present any E2 levels in boys (title: Simultaneous RIA of plasma FSH, LH…and E2 during the menstrual cycle)!

- We agree that a limitation of our study is the sample size of 44 boys and from these we have 62 estradiol profiles. However, despite this, it is a unique material where the limited number of subjects is well compensated by the 24h estradiol profile on each occasion and this establishes the quality and beauty of the present study. The sample size is commented and added to the discussion, page 10, first paragraph. According to the reviewer the lowest number of subjects in a group is 3, this is incorrect, the lowest sample size is in pubertal stage late-2, where n= 9, not 3!

- We do not know what ailment the reviewer alluded to. Our extraction RIA is sensitive, specific and gives clinical reliable results (in contrast to direct immunoassays), all this is already discussed thoroughly in the present manuscript. We have previously shown that by the extraction procedure we eliminated the interfering substances from the child sera (Ankarberg-Lindgren Norjavaara 2008:158;117-124, page 120, second paragraph.
• It is well established that direct immunoassays do not perform well at low estradiol concentrations, not even those with low analytical detection limit. We do not agree with the reviewer that the last sentence in the second paragraph in the discussion is incorrect. We insist that <18-34 pmol/L (Andersson et al), 17-24 pmol/L (Gässler et al), <20-81 pmol/L (Elmlinger et al), 7-25 (Ikegami), <29 pmol/L (Kushnir) etc. is HIGHER than our result of <4-6 pmol/L for prepubertal boys. We insist that 5.3 pmol/L (Paris), 1.5±4.1 pmol/L (Janfaza) is comparable to our results.