Reviewer's report

Title: Streak ovaries in association with Aromatase deficiency due to a novel CYP19A1 mutation

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Reviewer: Anna Lauber-Biason

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Gagliardi et al describe a patients with features of in utero hyperandrogenism and mutation in the aromatase CYP19A1 gene. The novelty of this report is the presence of ovarian dysgenesis, previously unreported in aromatase mutated patients.

Although potentially intriguing, the paper has some flaws that need to be addressed:

Major:
1. Some of the clinical characteristics of the patient do not agree with an isolated aromatase deficiency. For instance, this patient did not have adrenarche, suggesting a combined problem in adrenals and gonads. The association of in utero virilization that does not proceed later is a feature of P450 oxidoreductase (POR) deficiency. This entity is also associated with aromatase deficiency in some cases, due to the fact that POR is necessary for proper function of all microsomal P450 enzymes, including P450c21, P450c17 and P450Aro (see Flück et al, Nature 2004, Flück and Miller, Current Opinion in Pediatrics 2006). In this view, I feel it is necessary to check the progesterone levels, elevated in CYP17A1 deficiency (also in gonadectomized patients) and the sequence of POR. Oligogenic endocrinological diseases are not as rare as previously thought (see the example of hypogonadotropic hypogonadism).

2. Sex hormones and gonadotropins levels are close to impossible to judge in gonadectomized individuals, even under estrogen replacement. I am not sure what conclusions can be drawn from these measurements.

3. The “homozygous” duplication can also be a “hemizygous” mutation and since the parents are not available no definitive conclusion can be made. Please discuss this point.

4. Although I realize that nowadays three-dimensional models of mutated proteins are sometimes accepted as a surrogate of functional studies, I would like to see real enzymatic functional studies or at least hard data, i.e. a Western blot, to prove that the protein is really longer.

Minor

1. In the “Background” section the authors claim (page 3, lines 76-79) that the aromatization of 16OHDHEA into E1 is the major source of estrogens in pregnancy: this is not correct, since estradiol is still the major estrogen in
pregnancy. This statement should be modified.

2. The major reason why aromatase deficiency was only recently described is that the dogma was that without placental estrogens there is no pregnancy. The discovery of CYP19A1 human mutants changed this dogma (together with those mentioned on page 4, lines 115-117). The statement on page 4, line 94 should be modified.

3. In the evaluation of ambiguous genitalia, different scales/standards are available, the most used being the Prader I-V scale. It would be good to have the Prader grading in the case presentation.

4. Is there anything known about the bone age of the patient?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interest