Reviewer’s report

Title: The human fetal adrenal produces cortisol but no detectable aldosterone throughout the second trimester.

Version: 0 Date: 31 Oct 2017

Reviewer: Sam Mesiano

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This study by Johnston at al., examines steroid hormone synthesis by the human fetal adrenal glands during the second trimester. Although the study is descriptive it is important in the field as it provides important information regarding the steroidogenic activity of the fetal adrenal cortex during second trimester.. It maps adrenal steroidogenesis by examining steroids and steroidogenic enzyme expression and localization in 109 adrenal specimens from fetuses between 11 and 21 weeks of gestation. The number of adrenals examined is a major strength. Steroids were assayed by LC/MS and mRNA was assayed by qRT-PCR. IHC and western blotting were used to localize and quantify protein levels. As a secondary analysis the study also examined the effect of smoking on adrenal steroidogenesis. The study design and execution is excellent. Assays were well-described and appeared to be specific. Data were appropriately analyzed and interpreted. Overall this is an outstanding study that is important in understanding the human feto-placental unit and specifically the capacity of the fetal adrenal cortex to produce steroids during the second trimester.

Specific questions/comments:

1) What was the frequency of ultrasound.

2) How were the terminations performed? D&E or PG-induced delivery?

3) How was blood obtained from the fetus?

4) Authors should acknowledge the pioneering work of Jaffe and colleagues in establishing the functional zonation of the 2nd trimester human fetal adrenal cortex. Also, the conclusions of the study are as predicted by Mesiano and Jaffe (Endocrine Rev 18(3) 1997) and in Mesiano S, Coulter CL, Jaffe RB 1992 Localization of cytochrome P450 cholesterol side chain cleavage, cytchrome P450 17 -hydrox-ylase/17,20-lyase, and 3 -hydroxysteroid dehydrogenase isomerase steroidogenic enzymes in the human and rhesus fetal adrenal gland: reappraisal of functional zonation. J Clin Endocrinol Metab 77:1184 -1189. This body of research should be acknowledged and discussed.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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