EBioMedicine 39 (2019) 25–26

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Do estrogen receptor variants explain the enigma of human birth?

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During pregnancy progesterone maintains uterine quiescence. In most mammals the onset of labor is precipitated by a fall in circulating levels of progesterone and a rise in plasma concentrations of estrogen which promotes uterine contractile behaviour. In humans, however, progesterone and estrogen concentrations in maternal blood increase progressively across gestation and only fall after the delivery of the placenta. A major enigma has therefore been how is the onset of human labor physiologically regulated with no change in circulating sex steroid concentrations? In the last few years substantial progress has been made in resolving this paradox firstly in relation to progesterone and in this issue of *EBioMedicine* for estrogen by Anamthathmakula et al. [1]. It seems it all revolves around the receptors for these steroids.

For progesterone, Csapo suggested in 1965 that a "functional" withdrawal of progesterone occurred [2]. The concept is that in some way progesterone is unable to exert its biological action on the myometrial cells to prevent contractions. In the intervening years several potential mechanisms for this functional withdrawal have been suggested. These have included alterations in the expression of co-factors required for progesterone action, inhibition of progesterone action by inflammatory factor NFκB and changes in progesterone metabolising enzymes [3–5]. The strongest data implicate a role for alterations in expression of the A and B isoforms of the progesterone receptor. Progesterone receptor B mediates the relaxant effects of progesterone in the myometrium while in the breast the shortened progesterone receptor A, which lacks an activating domain, antagonises the action of progesterone receptor B. Work by Mesiano et al. [6], demonstrated *in vitro* that this antagonism of progesterone receptor B by the A isoform also occurs in the myometrium. Bisits et al. demonstrated using directed graphs and subtractive hybridization data comparing laboring and non-laboring human myometrium that progesterone receptor and estrogen receptor changes occur in the causal pathway leading to labor [7]. Most recently elegant studies by Nadeem and colleagues have shown that at term increased activity of the progesterone metabolising enzyme 20 alpha hydroxysteroid dehydrogenase within myometrial cells leads to a fall in the intracellular concentration of progesterone [8]. The fall in intracellular progesterone deactivates progesterone receptor B but, unexpectedly, unliganded progesterone receptor A is capable of stimulating the contraction associated protein connexin 43. Thus progesterone "functional withdrawal" appears to be due to a combination of changes in progesterone receptor isoforms and metabolising enzymes. The authors of this work suggest that the changes in progesterone pathways are initiated by estrogen. This leads us back to the paper by Anamthathmakula et al.

Estrogen physiology in the pregnant human is complex. Human plasma during pregnancy contains four different estrogens: estradiol, estriol, estrone and estetrol although the first two predominate. All four increase in concentration across pregnancy. Further complicating the picture, estriol is derived from Dehydroepiandrosterone sulphate (DHEAS), which is produced from the fetal adrenal under the stimulation of placental Corticotrophin Releasing Hormone. DHEAS is 16 hydroxylated in the fetal liver before acting as the precursor to estriol production in the placenta. Estradiol in contrast is produced from DHEAS synthesised in both the maternal and fetal adrenals. So, if estriol and estradiol are both increasing across gestation how can the onset of labor be signalled? One possibility is that changing concentrations of the two estrogens could alter the response of the estrogen receptors. Melamed et al. [9] have shown that homodimers of estrogen receptors occupied by either estradiol or estriol are effective in activating the estrogen receptor but heterodimers of estadiol and estriol are not. Estriol increases more rapidly than estradiol in late pregnancy and the consequent increase in estriol homodimers may initiate estrogen receptor signalling [10]. However, could alterations in estrogen receptor isoforms play a part, which seems to be the case for progesterone signalling? In their paper, Anamthathmakula and colleagues provide strong support for this concept. They demonstrate that uterine specific splicing events mediated by hnRNPG generates the alternative estrogen receptor alpha (ERα) isoform ERdelta7, which acts as a dominant negative repressor of the uterotonic action of the transcriptionally active forms of the estrogen receptor alpha (ERα66 and ERα46). ER delta7 disappears in myometrium at term, allowing estrogen action to occur. hnRNPG, which mediates this alternative splicing, is inhibited by estrogen leaving the question as to why the estrogen at term is able to suppress at that stage of pregnancy but not before? Perhaps the changing ratios of estradiol and estriol driven by placental corticotrophin releasing hormone have a role to play? We are getting closer to understanding how we are born and changing steroid receptors appear to be central to the process.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.11.038.
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https://doi.org/10.1016/j.ebiom.2018.12.012

Conflict of interest

The authors have no conflicts of interest to declare.

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