

Where does polycystic ovary syndrome come from?

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Polycystic ovary syndrome (PCOS) is the commonest cause of infertility due to irregular ovulation and it is the commonest female endocrinopathy (1). Despite its high prevalence, intense research has failed to reveal its origins. Although PCOS has a very obvious heritable component, years of genetic research have failed to come up with a gene or group of genes to which a finger can be pointed. Candidate polymorphic or otherwise abnormal genes have drifted in and then quickly out of favour. Current hypotheses lean strongly towards an epigenetic phenomenon based on the Barker hypothesis which nominates the intra-uterine environment as key to what may present in adult life (2).

The most frequently investigated hypothesis for the developmental theory for the origins of PCOS has been hyper-exposure of the female fetus to high androgen levels.

Abbott *et al.* (3) first proposed this idea following their experiments on pregnant monkeys injected with testosterone or vehicle as controls, early or later in the pregnancy. The adolescent offspring, when compared with controls, demonstrated in the main, a PCOS phenotype of typical polycystic ovaries, high luteinising hormone (LH) serum concentrations, irregular or absent ovulation and even insulin resistance. Similar experiments, with similar results, have been performed in rats and sheep (4,5).

Although women with PCOS have higher serum concentrations of testosterone than normal controls, testosterone does not cross the placental barrier due mainly to the extraordinarily high aromatase activity in the placenta which 'protects' the fetus by rapidly converting androgens to estrogens. So if the hyper-exposure of the fetus to

androgens is to be key to the origin of PCOS, then some explanation of the source of the excess androgens is needed. The fetus itself is an unlikely producer of androgens but the placenta of PCOS mothers seems a very feasible source as it demonstrates both histological and enzymatic differences to the placenta of normal controls, both of which favour over-production of androgens (6,7).

In the article in *Nature Medicine*, Tata *et al.* (8) have added further fuel to the developmental hypothesis for the origin of PCOS by producing additional evidence implicating anti-mullerian hormone (AMH). This extraordinary hormone helps determine sexual differentiation having the power to convert the 'basic female' fetus into the male gender. When it was discovered that AMH is also produced by the pre-antral and small antral follicles in the human ovary, the obvious question was what on earth is it doing there? It became apparent that AMH has a part to play in controlling the development of primordial to primary and secondary follicles and as it counteracts the action of FSH in promoting follicular development and aromatase action it apparently aids in the selection of the dominant follicle (9). The high levels of AMH produced by the increased number of small and pre-antral follicles in the polycystic ovary have been implicated in the pathophysiology of the oligo/anovulation of PCOS (10).

In addition to the high levels of testosterone in women during the pregnancy of PCOS mothers that have been demonstrated previously, Tata *et al.*, have shown a significantly higher maternal serum concentration of AMH during pregnancy in normal weight PCOS women compared to pregnant controls (8). They then asked the

question whether this finding implicated high AMH during pregnancy in the pathophysiology of PCOS. They necessarily turned to pregnant mice and injected them with AMH, producing an excess of maternal testosterone, diminished placental metabolism of testosterone to estradiol and a PCOS phenotype in adulthood. This was elegantly demonstrated to be due to increased LH pulsatility induced by AMH stimulating GnRH neurons.

While this splendid research implicating AMH in the pathophysiology of PCOS progresses our knowledge, it is not the whole story by any means and poses several new questions. Like testosterone, AMH does not cross the placental barrier. However, as well as elevating maternal LH and testosterone levels, AMH inhibits CYP 19 α and 3 β -HSD-1 expression in the placenta increasing testosterone bioavailability and this is the probable mechanism of the AMH programming effect (8).

High maternal concentrations of AMH during pregnancy were predominately found in normal weight rather than obese PCOS women. It is the lean, rather than the obese PCOS women who have raised LH serum concentrations and only about 40% of all women with PCOS have raised LH concentrations.

This suggests several corridors by which a pre-natal exposure to androgens may be induced and the paper by Tata *et al.* suggests that high AMH levels may be one of them. The finding that AMH has an effect on GnRH neurones increasing GnRH pulsatility and consequently LH levels is really interesting as well as surprising.

Finally, Tata *et al.* suggest that, as pregnant animals treated with AMH and GnRH antagonist prevented the appearance of PCOS traits in the offspring compared with AMH alone, GnRH antagonist could be used as a therapeutic strategy to restore ovulation and fertility in normal weight PCOS women. This is a highly speculative observation as the use of a GnRH antagonist to induce ovulation is very counter-intuitive. There are proven successful ways to induce ovulation without use of an antagonist!

In summary, it would seem from this elegant paper, that AMH is implicated in the pre-natal programming of at least some of the PCOS that we see in adult life. It is another important link in this fascinating detective story.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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