REPRODUCTIVE HEALTH

Transgenerational PCOS transmission

There is a transgenerational increase in the susceptibility of female offspring to developing PCOS that occurs via the female germline and is linked to fetal exposure to excess androgen.

H. M. Picton and A. H. Balen

Polycystic ovary syndrome (PCOS) affects approximately 10–20% of women worldwide, resulting in a huge economic health burden and significant morbidity and reduced quality of life for those who have it. The syndrome encompasses a constellation of symptoms that includes disrupted secretion of reproductive hormones such as luteinizing hormone from the brain and steroid hormones such as androgens from the ovaries, together with alterations in metabolism associated with insulin resistance. In this issue of *Nature Medicine*, building on suspected transgenerational effects of PCOS, Risal and colleagues[1] report a significant increase in the susceptibility of the daughters of women with PCOS to develop PCOS themselves, which contributes transgenerationally and is linked to exposure to maternal androgen excess, but not maternal obesity, in a mouse model of PCOS.

PCOS presents as a diverse syndrome. The criteria used to diagnose PCOS include identification of two out of three symptoms: menstrual cycle disturbance, androgen excess and the presence of polycystic ovaries as visualized by ultrasound[2,3]. The problems experienced by women with PCOS vary greatly, may change over time and are frequently worsened by being overweight. Young women are, for example, particularly affected by the oversecretion of ovarian androgens that cause acne and hirsutism and contribute to irregular and/or heavy periods, reduced fertility and pregnancy complications[4]. In contrast, for older women there are significant associations with metabolic diseases such as diabetes and cardiovascular disease.

The etiology of PCOS has proven difficult to elucidate, as there are up to ten phenotypes that constitute the syndrome, and indications such as the levels of androgen excess, ovarian dysfunction and insulin resistance vary between populations[5]. Although our understanding of the inheritance of PCOS is limited, recent transgenerational studies suggest that PCOS runs in families and that male as well as female relatives of individuals with PCOS have increased risk of insulin resistance. It has also been proposed that the combination of the maternal endocrine milieu and placental function in utero may influence fetal hypothalamic function, gonadal development and fat deposition and hence contribute to the transmission of PCOS across generations.

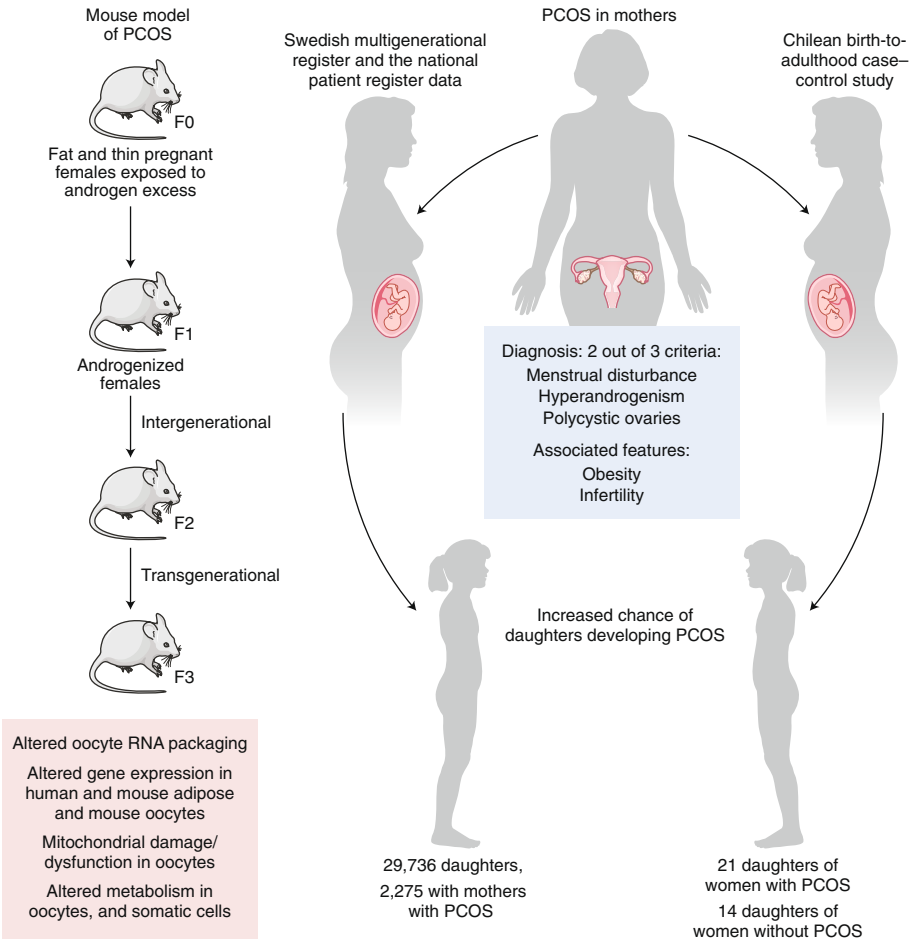

Fig. 1 | Strategy used to investigate multifaceted dynamics involved in the development and transmission of PCOS.

As reported in this issue, Risal et al. carried out studies on two independent populations of women and their daughters with and without PCOS. They used the 'Rotterdam' consensus definition of PCOS[2] (Fig. 1) to diagnose the syndrome in both a Swedish nationwide register study and a longitudinal, Chilean case–control study. They found in the register-based study a fivefold increased risk of developing PCOS in the daughters of women with PCOS compared to daughters from mothers without PCOS. In the longitudinal study, 71% of the Chilean daughters of women with PCOS were themselves found to have

PCOS. While this evidence suggests that the daughters of women with PCOS are more likely to be diagnosed with PCOS when they reach adulthood than if they were born to mothers without PCOS, it remains unclear whether this relationship is causal or is due to confounding genetic factors. Longitudinal studies of cohorts of mothers, daughters and granddaughters are difficult to carry out in humans.

Risal et al. used a mouse model of PCOS to disentangle the transgenerational inheritance of PCOS. Elevated ovarian androgen production is a common marker of the PCOS phenotype that is associated with the severity of reproductive and metabolic dysfunction, and hence the authors chose to study its effects[6,7]. Furthermore, elevated exposure to androgen in utero is known to compromise fetal development and adult health. The authors exposed pregnant female mice (the F0 generation) in late gestation (embryonic day 16.5–18.5), with or without diet-induced obesity and altered glucose homeostasis but similar insulin levels, to the androgen dihydrotestosterone (DHT). The susceptibility of female offspring to developing PCOS-like phenotypes was then analyzed across three generations, since the first (F1)-generation fetuses and the germ cells that produced the second (F2) generation were directly exposed to the androgenized maternal intrauterine milieu from F0 mothers.

In the mouse experiments, the authors found that circulating steroid levels, lean mass and glucose metabolism were unchanged in F2 and F3 female offspring from F0 DHT-exposed mothers, and circulating testosterone in F1 was lower than in F0. However, adipocyte size, gene expression, adipogenesis, lipid biosynthesis and energy metabolism were all altered, suggesting that adipose tissue dysfunction in PCOS is due to prenatal androgen exposure. The authors found that the maternal combination of prenatal androgen exposure and obesity significantly compromised F2 fetal viability, which may reflect observations that obese women with PCOS are at higher risk of preeclampsia, gestational diabetes, miscarriage, preterm birth and perinatal mortality. With respect to addressing a mechanism by which transgenerational effects occur, the authors carried out ultrastructural and molecular analysis of mature MII mouse oocytes. They found that the mitochondrial morphology, number and DNA content were affected by DHT exposure and obesity in the F1–F3 generations. Maternal exposure to DHT, but not obesity, also affected the differential expression of key genes involved in RNA binding, DNA repair, germ cell and reproductive processes, glucose homeostasis and steroid hormone signaling pathways in MII oocytes from the F1–F3 generations. Alterations in the transcriptome of MII oocytes from the androgenized mouse model mirrored changes in gene expression profiles shown in subcutaneous adipose tissue and serum from women and their daughters with PCOS in the authors' case–control study. Finally, the researchers identified four candidate genes—*TIAL1*, *FABP5*, *RNF141* and *INIP*—that were altered in expression in the serum of women with PCOS in a manner similar to that of the mouse MII oocytes from the androgenized lineage.

While mouse models of PCOS such as that used by Risal et al. are informative, and it is possible to provoke the development of a PCOS-like phenotype using androgen as they did, it must be remembered that this model only approximates the complexity of PCOS in humans. Indeed, other mouse models have been used to demonstrate that prenatal administration of anti-Müllerian hormone may lead to hyperactivated gonadotropin-releasing hormone neurons in the hypothalamus and consequent hyperandrogenism[8], suggesting that there is more at play in the transmission of PCOS than simply the delivery of exogenous androgens as used in the current work. Despite this, the data presented by Risal et al. provide an intriguing glimpse of a potential bimodal mechanism for PCOS transmission via a direct impact on fetal programming, adipose function and development of the reproductive axis and via the female germline.

PCOS transmission through the female germline can be explained by the biology of oogenesis and embryogenesis. Importantly, the maternal and paternal genomes do not contribute equally to embryo fate, and the cytoplasmic components of an early embryo are inherited entirely from its parent oocyte[9]. Similarly, the fertilization and developmental competence of each embryo are dependent on efficient metabolism driven by mitochondria that are also derived exclusively from each parent oocyte[10]. Thus, disruption of oocyte gene expression and mitochondrial morphology, copy number and activity as observed in F1 animals by Risal et al. not only will adversely affect oocyte energy metabolism and reduce the fertile capacity of oocytes per se but will also be transmitted to all somatic cell lineages of the subsequent embryos, and in so doing may significantly influence embryo viability and implantation potential and disrupt the metabolic machinery, and hence health, of somatic cells of the F2 and F3 generations.

As the global epidemic of obesity and metabolic disease risk spreads, the likelihood of transgenerational inheritance of PCOS will increase. The clinical utility of biomarkers for the early detection of PCOS transmission from mothers to daughters and granddaughters requires further validation. ❐

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Competing interests

The authors declare no competing interests.