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Review article

Polycystic ovary syndrome (PCOS): progress towards a better understanding and treatment of the syndrome

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Abstract. Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder in women of reproductive age. It has a strong hereditary component estimated at 60 to 70% in daughters. It has been suggested that environmental factors during the fetal period may be involved in the development of the syndrome in adulthood. However, the underlying mechanisms of its transmission remain unknown, thus limiting the development of effective therapeutic strategies.

This article highlights how an altered fetal environment (prenatal exposure to high levels of anti-Müllerian hormone) can contribute to the onset of PCOS in adulthood and lead to the transgenerational transmission of neuroendocrine and metabolic traits through alterations in the DNA methylation process.

The originality of the translational findings summarized here involves the identification of potential biomarkers for early diagnosis of the syndrome, in addition to the validation of a promising therapeutic avenue in a preclinical model of PCOS, which can improve the management of patients suffering from the syndrome.

Keywords. PCOS, AMH, Fetal programming, Heritability, Biomarkers, Epigenetics, Neuroendocrinology.

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1. Introduction

Polycystic ovary syndrome (PCOS) is a complex, heritable, reproductive-metabolic disorder affecting 10–20% of reproductive age women and is a leading cause of female infertility [1–3]. Previously published International Guidelines for the Assessment and Management of PCOS [3] recommend a clinical diagnosis requiring at least two out of the following three Rotterdam criteria: (i) the evidence of either

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biological or clinical hyperandrogenism; (ii) irregular ovulatory function (oligomenorrhea or amenorrhea); and (iii) polycystic ovarian morphology on ultrasound.

In addition to reproductive issues and neuroendocrine alteration of the hypothalamic-pituitary-ovarian axis [4], women with PCOS commonly experience long-term metabolic health consequences such as diabetes mellitus (both type 2 and gestational), hyperinsulinemia, glucose intolerance, systemic inflammation and obesity [3, 5–8]. Despite its high prevalence and detrimental impact on women's health, the exact etiology and underlying mechanisms associating the neuroendocrine and metabolic traits of PCOS remain unclear, hampering the development of effective therapeutics.

Recently, the diagnostic criteria for PCOS have incorporated the measurement of Anti-Müllerian hormone (AMH) levels in adult women as an alternative to ultrasound [9]. Elevated AMH levels, typically two to three times higher in women with PCOS [10–12], are associated with the severity of the condition and various clinical features. AMH is a glycoprotein secreted by the granulosa cells of the ovaries [13]. Its primary role is to negatively regulate the transition from primordial follicles to primary follicles [14], protecting growing follicles from premature maturation by counteracting the effects of FSH [15]. This may contribute to other PCOS symptoms such as hyperandrogenism and insulin resistance.

Interestingly, AMH receptor is expressed in hypothalamic gonadotropin-releasing hormone (GnRH) neurons [16, 17], pituitary [18, 19] and the placenta [20] suggesting that AMH could exert extragonadal actions [21] on the placenta and the brain (especially on the hypothalamus [16–20] and pituitary [18]), which could be implicated in the central dysregulations observed in patients with the syndrome. In addition, AMH receptor is expressed by endothelial cells, tanycytes and the majority of arcuate nucleus neurons. This suggests that peripheral AMH could act either directly or indirectly to activate GnRH neurons in the brain [17, 22].

Familial clustering and twin studies have shown that PCOS has a strong heritable component [23–25]. However, the mutations that have been identified [26] so far do not account for its high prevalence in the population, implying that fetal environmental factors such as androgens [27, 28] and AMH [20, 29–31] excess might play important roles in the onset of PCOS.

Clinical and animal model studies implicate hyperandrogenic gestational origins [32, 33] ith an altered maternal endocrine-metabolic environment that could promote epigenomic developmental programming of PCOS inheritance, consolidating the "developmental origins of health and disease" (DOHaD) theory [34]. Furthermore, increasing evidence indicates that fetal environment influences gene expression through transgenerational epigenetic modifications, leading to altered gene expression which could ultimately increase disease susceptibility [35]. Our team has developed a preclinical mouse model called "PAMH" (prenatal exposure to elevated anti-Müllerian hormone) [20, 36]. This model successfully reproduces key features of PCOS, including hyperandrogenism, ovarian dysfunction, neuroendocrine abnormalities, and metabolic disturbances. This article summarizes and puts into perspective the previously published study [37], which challenges the developmental origins of PCOS and investigates the implication of AMH in the onset and transgenerational epigenetic transmission of the condition across subsequent generations.

2. Results

2.1. *Preclinical transgenerational model of PCOS*

How does prenatal AMH exposure drive the transmission of reproductive and metabolic PCOS-like alterations across multiple generations in adulthood?

Throughout the history of modern medicine, from the rabies vaccine to gene therapy, preclinical models have played a crucial role in helping researchers to understand diseases and to develop effective preventive and therapeutic strategies. In the case of PCOS, significant efforts have been invested in generating animal models that accurately mirror the human condition and facilitate the optimization of potential treatments [33].

We have previously shown that women with PCOS exhibit higher levels of AMH during pregnancy [20, 29, 31]. To replicate these findings in a preclinical setting, we have established a promising preclinical PCOS model in rodents called "prenatal AMH treated", also named "PAMH" [36] which effectively mimics the human PCOS condition. This model

involves exposing pregnant mice to high AMH levels towards the end of the gestational period (Embryonic day E16.5–E18.5) (Figure 1A). Such treatment drives maternal hyperandrogenism with subsequent changes in the hypothalamic pituitary gonadal (HPG) axis and in hormone levels of both the dams and the progeny [20]. The temporal window of AMH treatment was selected because it falls beyond the developmental stages during which gonadal and genital tract differentiation occurs in mice (E12.5–E14.5), thus excluding any potential morphogenetic effects of exogenous AMH [38].

Considering the strong heritability of PCOS and the documented inheritance of the key neuroendocrine and metabolic characteristics observed in close relatives of women with PCOS [28, 39, 40], we sought to examine whether female offspring with PCOS-like traits (F1) from pregnant dams exposed to elevated levels of AMH during pregnancy (F0) are prone to transmitting PCOS-like traits to subsequent generations, specifically F2 (intergenerational) and F3 (transgenerational) offspring (Figure 1A).

Using a large panel of reproductive, endocrine, and metabolic phenotyping techniques, our study demonstrated that prenatal exposure to high levels of AMH during gestation in mice results in the intergenerational and transgenerational transmission of PCOS-like traits in female offspring of the F2 and F3 generations. Remarkably, these offspring exhibited all the major diagnostic manifestations of PCOS, including hyperandrogenism, oligo-anovulation, central alterations, and fertility impairments. Additionally, the study found significant metabolic alterations in the PAMH lineage, spanning from the F1 to F3 generations, compared to the control groups. These metabolic changes included an alteration in body composition (increase in body weight and fat mass), as revealed by nuclear magnetic resonance (NMR) analyses in the PAMH offspring. Notably, higher fasting glucose levels support a hyperglycemic phenotype, and its association with high insulin levels is indicative of insulin resistance. higher fasting glucose and insulin levels indicative of a hyperglycemic phenotype. Moreover, the study employed tissue-clearing techniques and whole-organ 3D imaging to analyze the distribution of insulin-producing β cells and glucagon-producing α cells in the pancreas, revealing hypertrophic pancreatic islets in PAMH F1 female mice compared to the controls.

The results of our study present convincing evidence supporting the inheritance of neuroendocrine, reproductive, and metabolic dysfunctions associated with PCOS across several generations in PAMH mice. To our knowledge, PAMH is currently the sole rodent model that completely satisfies the mouse equivalents of the Rotterdam criteria for PCOS—encompassing metabolic abnormalities like hyperglycemia, glucose intolerance, hyperinsulinemia, and type-2 diabetes—without the need for additional environmental factors such as a high-fat diet. These findings solidify the involvement of AMH in the pathogenesis of PCOS.

2.2. *Molecular pathways underlying PCOS transgenerational transmission*

Next, we investigated how these neuroendocrine, reproductive, and metabolic dysfunctions of PCOS are passed down through generations (Figure 1A).

To unravel the molecular mechanisms and gene pathways involved in the "fetal reprogramming" of PCOS and its inheritance, we conducted RNA sequencing (RNA-seq) analysis to identify differentially expressed genes (DEGs) in ovaries obtained from control offspring (CNTR) and third-generation females (PAMH F3). This analysis revealed 102 DEGs (54 downregulated and 48 upregulated) in PAMH F3 ovaries compared to control ovaries.

Given that environmental factors have the potential to affect epigenetic mechanisms, including DNA methylation, we sought to examine the influence of ancestral prenatal AMH exposure during gestation on the epigenome of PAMH F3 offspring, using a genome-wide methylated DNA immunoprecipitation (MeDIP) approach.

The profiling of transcriptomic and methylomic landscapes in ovaries of both control and PCOS-like females from the third generation—which represented the first generation of offspring not exposed to AMH—revealed an overall decrease in methylation in PAMH F3 females. Moreover, many affected genes in the ovarian tissue of PCOS-like females are associated with inflammatory and metabolic pathways typical of the human PCOS condition [32, 40, 41].

Importantly, these alterations in gene expression were detected in animals as early as 2 months of age, preceding the appearance of metabolic manifestations observed at 6 months, which suggests that

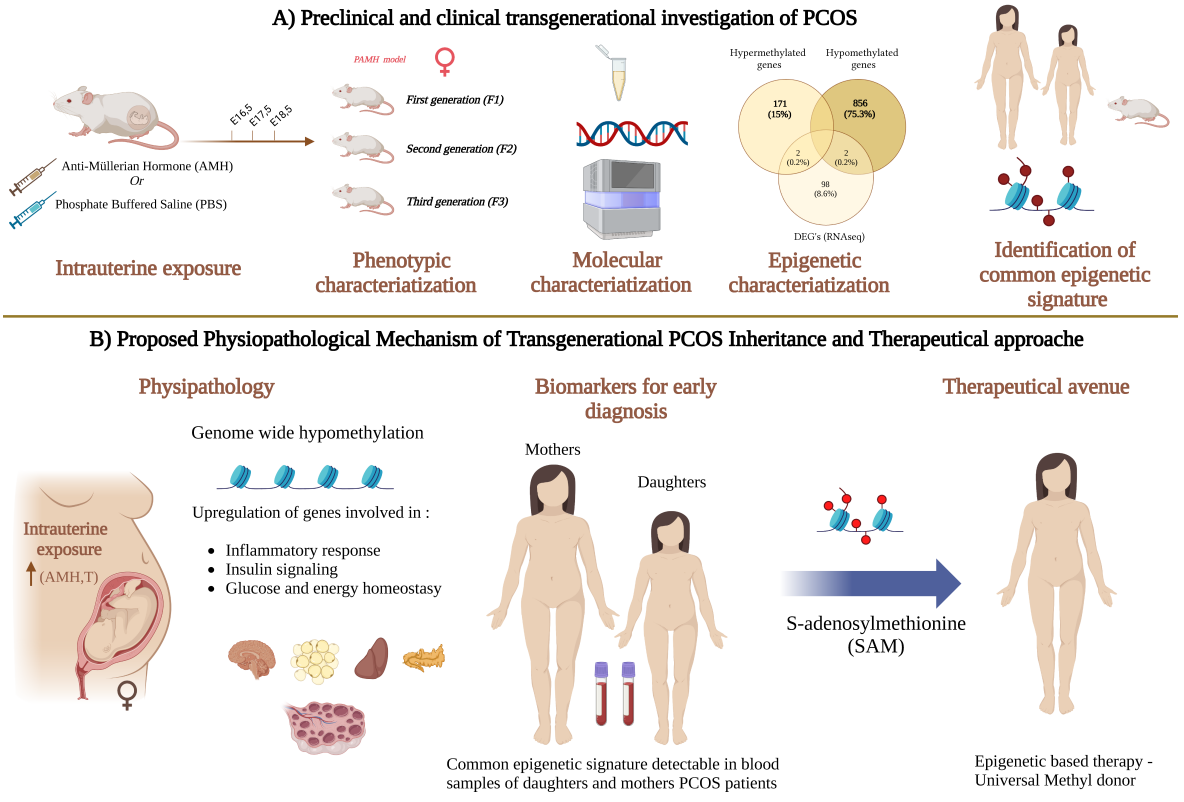

Figure 1. Polycystic ovary syndrome (PCOS): progress towards a better understanding and treatment of the syndrome. (A) Schematic representation of preclinical and clinical transgenerational investigations of Polycystic Ovary Syndrome (PCOS). (B) Proposed physiopathological mechanism of transgenerational PCOS inheritance and epigenetic-based therapeutic approach. Created with BioRender.com.

molecular changes could serve as potential predictors of physiological changes well before they occur. Our preclinical findings conclude that the DNA methylation profile reveals several key molecules associated with the PCOS phenotype that are epigenetically regulated through DNA hypomethylation. This is consistent with clinical studies that have reported DNA methylation changes associated with steroidogenesis, inflammation, hormone-related processes, and glucose and lipid metabolism in different tissues of women with PCOS [41, 42].

2.3. *Hope for early diagnosis for PCOS patients?*

Identification of common epigenetic biomarkers in a cohort of women with PCOS and their daughters, as well as in the preclinical model of PCOS.

To investigate how our preclinical findings might relate to the human PCOS condition, we searched by MeDIP-PCR for common epigenetic signatures in blood samples collected from both mothers and daughters diagnosed with PCOS in the Reproductive Medicine Department of Jeanne de Flandre in Lille University Hospital, France.

The study reports that several of the differentially methylated genes identified in ovarian tissues of PCOS-like mice of the third generation were also altered in blood samples from women with PCOS and from daughters of women with PCOS compared with healthy women.

These findings highlighted reveal common epigenetic signatures between females in the preclinical model and patients with PCOS compared to control groups (Figure 1A). This signature is characterized by hypomethylation of genes associated with: DNA demethylation (*TET1*), axon guidance (*ROBO-1*), inhibition of cell proliferation (*CDKN1A*), inflammation (*HDC*), and insulin signaling (*IGFBPL1*, *IRS4*).

Among these potential biomarkers, three genes are also hypomethylated in daughters diagnosed with PCOS (*ROBO-1*, *HDC*, and *IGFBPL1*).

Furthermore, epigenetic changes such as DNA methylation, known for their stability and ability to precede phenotypic manifestations [43], hold promise as diagnostic indicators for PCOS risk and prognostic indicators for disease progression. The identification of common epigenetic alterations in both human and mouse samples provide valuable insights into the shared biological pathways involved in PCOS development and supports the translational potential of the mouse models, which could pave the way for future explorations of targeted therapeutic interventions for this complex disorder.

2.4. *Therapeutical avenue for PCOS management: preclinical efficiency of an epigenetic-based therapy*

Since our methylation studies pointed to a preponderance of hypomethylation in PCOS condition, we challenged the reversible nature of epigenetic modifications and examined the therapeutic potential of using the universal methyl group donor S-adenosylmethionine (SAM) in an epigenetic preclinical investigation in our rodent model.

To further explore an epigenomic basis for this transgenerational transmission of PCOS-like phenotypic expression and in an attempt to re-methylate, PAMH F3 females were exposed to SAM treatment and their endocrine and metabolic parameters were monitored. Our findings demonstrated that SAM treatment restored normal ovulation and testosterone concentrations, body weight, and body mass composition to control conditions in PCOS-like animals. However, circulating AMH levels after treatment were not measured. SAM treatment also normalized pancreatic islet hypertrophy but did not significantly lower total glucose levels of PAMH F3 animals. Our study further explored the effect of SAM treatment on gene expression levels in mice with PCOS-like symptoms and found that SAM treatment may have a positive effect on reducing inflammation associated with PCOS-like symptoms in mice.

3. Conclusion

These findings strengthen the DOHaD concept that an adverse foeto-maternal environment in PCOS has lasting effects on the health of future generations. These findings, together with those of Risal and colleagues [28] indicate communication between ovaries, germ cells, and serum, and support the translational relevance of findings in mice. Collectively, our study highlighted the role of elevated levels of AMH during pregnancy and established a new PCOS model through AMH treatment, demonstrating the inheritance of key characteristics. Our findings revealed novel insights into the transgenerational transmission of PCOS-related reproductive and metabolic dysfunctions, providing compelling evidence of its association with altered DNA methylation patterns (Figure 1B). This study identified potential promising biomarkers shared between mothers and daughters that could enhance early diagnosis of the disease and its progression. Finally, the experimental effectiveness of a novel epigenetic therapy opens new perspectives for the treatment of PCOS.

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

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