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Review

Which origin for polycystic ovaries syndrome: Genetic, environmental or both?

Le syndrome des ovaires polykystiques, est-il d'origine génétique, environnementale ou les deux ?

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Abstract

Polycystic ovaries syndrome (PCOS), the most common female endocrine disorder, affects 7–10% of women of childbearing age. It includes ovarian hyperandrogenism, impaired follicular maturation, anovulation and subfertility. Insulin resistance, although present in most cases, is not necessary for diagnosis. It increases hyperandrogenism and long-term metabolic, cardiovascular and oncological risks. The origin of hyperandrogenism and hyperinsulinemia has a genetic component, as demonstrated by familial aggregation studies and recent identification of associated genomic variants, conferring a particular susceptibility to the syndrome. However, experimental and epidemiological evidences also support a developmental origin via a deleterious foetal environment, concerning the endocrine status (foetal hyperandrogenism), the nutritional level (intrauterine growth retardation), or the toxicological exposure (endocrine disruptors). Epigenetic changes recently reported in the literature as associated with PCOS, enhance this hypothesis of foetal reprogramming of the future adult ovarian function by environmental factors. Better characterisation of these genetic, epigenetic, or environmental factors, could lead to earlier prevention and more efficient treatments.

Keywords: Polycystic ovaries syndrome; Hyperandrogenism; Insulin resistance; Genomic variant; Epigenetics; Environmental endocrine disruptors; Foetal programming

Résumé

Le syndrome des ovaires polykystiques (SOPK), la plus fréquente des endocrinopathies féminines, touche 7 à 10 % des femmes en âge de procréer, associant une hyperandrogénie ovarienne à des troubles de la maturation folliculaire avec anovulation et hypofertilité. Une insulino-résistance non indispensable au diagnostic est le plus souvent présente majorant l'hyperandrogénie thécale et entraînant à long terme des risques métaboliques, cardiovasculaires et carcinologiques. L'origine de l'hyperandrogénie et de l'hyperinsulinisme comprend une composante génétique, démontrée par les études d'agrégation familiale et la mise en évidence d'association à des variants génomiques conférant une susceptibilité particulière à développer ce syndrome. Mais des arguments expérimentaux et épidémiologiques soutiennent également une origine développementale via un environnement fœtal délétère sur le plan hormonal (hyperandrogénie fœtale), nutritionnel (retard de croissance intra-utérin), ou toxique (perturbateurs endocriniens). Les modifications épigénétiques associées au SOPK, rapportées dans la littérature, soutiennent cette hypothèse de programmation fœtale à distance et de modulation chronique par des facteurs environnementaux. Une identification de ces facteurs génétiques, épigénétiques, et environnementaux pourrait conduire à une prévention plus précoce et à des traitements plus efficaces.

Mots clés : SOPK ; Hyperandrogénie ovarienne ; Insulino-résistance ; Maturation folliculaire ; Variant génétique ; Épigénétique ; Perturbateurs endocriniens environnementaux ; Programmation fœtale

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1. Abbreviations

AhR aryl hydrocarbon receptor
AMH anti-mullerian hormone
BMI body mass index
BPA bisphenol A
CYP17A1 cytochrome P450 17 hydroxylase gene
DENND1A differentially expressed in normal and neoplastic cells domain containing 1a gene
DOHaD developmental origin of health and diseases
EEP environmental endocrine disruptors
EGFR epidermal growth factor receptor
EPHX1 epoxide hydroxylase 1
ERα, ERβ estrogen receptor α, β
GPR30 G-protein related receptor 30
GWAS genome wide association study
HAIR-AN hyperandrogenemia-insulin resistance-acanthosis nigricans
IGF 1 insulin growth factor 1
IGF-BP insulin growth factor binding proteins
IR insulin receptor
IRS 1 insulin receptor substrate 1
LH luteinizing hormone
LH/HCG R luteinizing hormone/human chorionic gonadotropin receptor
miRNA micro-RNA
NCOR 1 nuclear corepressor factor 1
PCOS polycystic ovaries syndrome
PCOM polycystic ovaries morphology
PFOA perfluoro-octanoic acid
PFOS perfluoro-octane sulfonate
P450 scc P450 side chain
SHBG sex hormone binding globulin
StAR steroidogenic acute regulatory protein
PPARγ peroxysome proliferator-activated receptor γ

2. Introduction

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder in women, affecting between 7 and 10% of women of childbearing age [1,2]. This prevalence depends on the criteria used, which have been the subject of numerous consensus meetings. NIH consensus was the first one, dating back to 1990, and retained a clinical and/or biological hyperandrogenism associated with cycle disorders, excluding all classic causes of hyperandrogenism [3]. The Rotterdam consensus in 2004 defined PCOS by the presence of two of the following three criteria: dys- or anovulatory cycles, hyperandrogenism (clinical and/or biological) and/or morphological polycystic ovaries (PCOM) on ultrasound [4]. More recently in 2009, following a compilation of the literature, the Androgen Excess and PCOS Society favoured hyperandrogenism (clinical and/or biological) as a mandatory factor, associated either with ovulation disorders or with the morphological appearance of polycystic ovaries (PCOM) [5]. However, PCOS actually has multiple [6] phenotypic forms, often partial, which may be accompanied by both reproductive problems (cyclic disorders, failing ovulation leading to hypofertility, risk of ovarian hyperstimulation, unsuccessful in vitro fertilization, high incidence of spontaneous miscarriages, increased risk of pregnancy-induced hypertension and/or gestational diabetes), and long-term complications (metabolic, cardiovascular or cancer) linked to the associated hyperinsulinemia, present in a majority of cases.

Since the first description of PCOS in 1935 by Stein and Leventhal [5,7], many hypotheses have been stated and several mechanisms have been identified as participating in its overall pathophysiology: such as the thick and follicular rupture-resistant shell, ovarian hyperandrogenism, LH hypertonia, hyperinsulinism, intra-ovarian follicular maturation impairment with an excess of anti-mullerian hormone (AMH), a paracrine factor blocking physiologically the follicular maturation. But the real origin and the precise physiopathology of this so frequent syndrome, remain to be elucidated. The main question is to assess what part belongs to genetics, the involvement of which is suggested by familial cases, including homozygous twins and association with certain variants identified by modern whole genome screening techniques, and, on the other hand, what part belongs to environment which participation is supported by epidemiological and experimental evidence, linking a deleterious (metabolic, nutritional, vascular, hormonal or toxic) environment of the early female gonad at critical periods of exposure such as foetal, perinatal or peri-pubertal period, with a PCOS-related picture at adult. Anyway, this conflictual duality can be overcome by environmentally induced epigenetic changes, which have been recently reported as associated to this syndrome.

We will successively describe the different mechanisms that have been deciphered over time and have been proposed to explain the chain of events leading to this syndrome and summarize the evidence supporting a genetic, an environmental and/or an epigenetic origin.

3. Cellular and molecular mechanisms

The polycystic ovaries, as described by Stein and Leventhal [7] were surrounded by a thick, white, smooth and pearly shell, prompting in the past ovarian decortication [8] and more recently ovarian "drilling" nowadays realized by laser puncture [9], both supposed to reduce the number of atretic follicles thereby reducing thecal cell mass and local androgen excess. LH hypertonia continuously stimulating steroidogenesis, was at the centre of the vicious circle proposed by Yen et al. in the eighties [10]. It was believed that ovarian hyperandrogenism, by leading after peripheral aromatisation, to non-cyclic peripheral hyperestrogenism, was able to maintain permanent hypersecretion of LH. However, the hypothalamic primum movens of this circle was not clearly elucidated. The hyperandrogenic climate, whether ovarian or extra-ovarian, has since long been considered to be able to contribute to follicular maturation impairment, but it was in the 2000s that the concept of a foetal hyperandrogenic environment, was proposed as a "climate" able to determine the future female gonad to a PCOS phenotype [11]. Hyperinsulinemia associated with PCOS has also been reported for a long