Evolutionary determinants of polycystic ovary syndrome: part 1

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Polycystic ovary syndrome (PCOS) is a common and complex genetic disorder that develops under varying degrees of hyperandrogenemic and hyperinsulinemic conditions that cause phenotypic variability ranging from mild hirsutism to anovulation and infertility. In addition to increased risk of reproductive disability, PCOS is associated with metabolic diseases including type 2 diabetes, dyslipidemia, and cardiovascular disease. Similar prevalence rates and shared genetic susceptibility of PCOS among different populations suggest that genetic risk factors were already present in the ancestors of humans. Contemporary human genetic studies inform us that the origin of human ancestors is from Africa. Sharing common susceptibility loci between Chinese and European ancestry suggests that PCOS may have persisted for more than 50,000 years, before the migration of humans out of Africa. Although PCOS is the most common cause of anovulatory infertility, its high prevalence is still a paradox. From an evolutionary perspective, the pathogenic mechanisms underlying PCOS might be candidate factors for survival advantage of the human being. Former compensatory advantageous factors may become pathogenic mechanisms underlying complex metabolic disease with prolonged life expectancy and transition to sedentary lifestyle. (Fertil Steril® 2016;106:33–41. ©2016 by American Society for Reproductive Medicine.)

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PCOS is a complex genetic disorder of women in reproductive age (1). The prevalence of PCOS according to proposed diagnostic criteria has been reported to be 6%–19% in different studies (2, 3). The syndrome is characterized by hyperandrogenism, chronic oligo-/anovulation, and insulin resistance, and it is associated with increased risk of reproductive disability and metabolic diseases such as type 2 diabetes, dyslipidemia, cardiovascular disease (4, 5). The interactions of multiple inherited genetic factors related to hyperandrogenism and environmental or acquired factors, such as sedentary lifestyle and westernized dietary habits, can together trigger the dysregulation of androgen synthesis, which is the main factor causing ovarian follicles not to grow as much as a dominant follicle, resulting in oligo-/anovulation. The secretion dynamics of GnRH pulses are changed due to lack of progesterone peaks through the luteal phase of the menstrual cycle, which in turn leads to the increase of LH secretion. An increased LH secretion causes stimulation of androgen synthesis and secretion by the ovaries. The adrenals also contribute to androgen excess in PCOS (6). The inherited genetic factors and westernized lifestyle can also induce insulin resistance and/or obesity that both cause a hyperinsulinemic milieu and low-grade chronic inflammation, which are other stimulators of androgen synthesis (1). Consequently, PCOS develops under varying degrees of hyperandrogenemic and hyperinsulinemic conditions that cause phenotypic variability ranging from mild hirsutism to anovulation and infertility.

In simple terms, an evolutionary approach aims to understand the life history of an organism or a phenotypic trait. To be classified as a subject of an evolutionary study, first the phenotypic trait of interest should demonstrate variation in the population under study. Second, some proportion of the variation should be genetic; therefore, the trait should be heritable. Finally, the phenotypic trait should have an effect on fitness. PCOS, as a phenotypic trait, clearly fulfills all of these three requirements, and as a clinically important phenotype transcending human evolution it is a good case for evolutionary medicine (7).

When traditional proximate (immediate) cause–oriented medicine is not sufficient to fully understand a disease and offer innovative therapies, a novel approach focusing on the ultimate (evolutionary) causes underlying a chronic condition such as PCOS has a lot to offer to medicine (8). Ultimate causes affect human populations for much longer spans of time, on the order

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of thousands of generations, compared with the short life span of an individual. An evolutionary approach to the life history of PCOS can give us an important perspective for understanding the adaptive value of traits underlying the disease, with certain traits, such as hyperandrogenism and insulin resistance, being advantageous at one stage of human development (prehistoric times) and detrimental at another stage (modern times). In this succinct review on the evolutionary determinants of PCOS, we start with a synopsis of human development, followed by a determination of how long PCOS has been with the human lineage based on evidence from genetic data. Finally, we discuss possible selective advantages that the major PCOS clinical traits might have conveyed in our ancestors.

A SYNOPSIS OF HUMAN DEVELOPMENT

Similar prevalence rates of PCOS among different contemporary human populations (2, 9, 10) and shared genetic susceptibility among these different groups (11) suggest that the genetic risk factors were already present in our human ancestors before they migrated out of Africa. This suggestion necessitates a closer look at the history of human development.

Anthropologic and molecular studies show that humans diverged from their most common recent ancestors with chimpanzees around 6 million years ago and evolved in Africa adapting to the ever-changing needs in their environment (12, 13). Comparative morphology and paleontologic studies reveal that physiology, body shape, brain size and associated tool-making and communication skills, diet, and social structure were changing, in what appears to be in burst intervals, since the early hominids to anatomically modern humans (14–18). Up until 50,000 years ago, Africans with more modern skeletons were lean-bodied simple hunters directed at easy-to-kill land animals. These are the conditions that most probably selected the metabolic thrift, increased fat storage, and muscle and bone strength in our early ancestors.

By the Late Stone Age, around 50,000 years ago, coinciding with the major dispersal of humans out of Africa, sometimes called the Great Leap Forward, more sophisticated stone tools and cultural artifacts began to appear and hunter-gatherer societies started to exhibit accelerating cultural evolution and larger and denser populations (19). Late Paleolithic (40,000–10,000 years ago) people were rather inventive and made technologic innovations that enabled them to inhabit new niches, including rather cold and harsh geographic areas (20). The vital statistics of Late Paleolithic people are rather hard to decipher owing to scarcity of remains. It is argued that child mortality was high, women died before the age of 40 years (possibly owing to risks associated with childbearing) and men before the age of 60 years. Their community groups contained more older people, possibly enhancing group survival, and enabling young women to have additional children much sooner, explaining the larger and denser populations (21). In this new social structure, "grandmothering" might have been an advantage selected for that allowed for the longer post-reproductive life span unique to humans.

Hunter-gatherer groups became increasingly more adapted to sedentary lifestyles, better managing their proximate natural resources, which led to an agricultural revolution in the Near East (Fertile Crescent), China, and Mesoamerica around 10,000 years ago, initiating the cultural period of the Neolithic (22–24). The sudden population increase could, in part, be due to better nutrition, which fostered the development of earlier menarche in women, resulting in a longer period of fertility, and a stable food supply might mean fewer miscarriages and childhood deaths. Also, decreased mobility allowed for shorter intervals between births.

However, the development of agriculture and animal domestication also imposed a heavy disease burden on practicing societies, in some cases reducing the average life expectancy to lower levels than those of hunter-gatherers (23, 25). Dependence on fewer crops might have led to selective nutrient deficiencies. And animal-derived and -transmitted infectious diseases (zoonosis) and the development of epidemics owing to the high population density exerted a significant selection on these populations, signatures of which are still evident in our genetic makeup today. Therefore, early reproduction age success should still have been rather important in these communities.

HOW LONG HAS PCOS AFFECTED HUMANS? EVIDENCE FROM GENETIC DATA

In line with the fossil record hypothesis that modern humans arose in Africa around 200,000 years ago, human genetic studies demonstrate that all modern human mitochondria and Y chromosomes are descendants of their respective common ancestors in Africa (26–28). Today, most human genetic diversity is found in Africa, and the vast majority of genetic diversity is found within populations rather than between human populations (29–31). Humans are genetically a very homogeneous species, where the average difference between two human genomes is less than 0.1% (32, 33) indicating a very small effective population size (the number of individuals in a population who contribute to the offspring to the next generation) (34, 35).

One of the methods to understand human evolution is to estimate the history of human population size (36). Individual genome-sequencing studies are also potentially informative regarding human evolution (37). The Khoisan-speaking hunter-gatherer populations of southern Africa, also called collectively the San, and other native groups from central and southern Africa, exhibit the highest known levels of genetic divergence from other populations. Therefore this important genetic feature was used in a study aimed at investigating ancient human demography, and the San's divergence time was estimated to be around 130,000 years ago (38). The study also predicted that ancestors to Chinese and Europeans diverged from Africans about 50,000 years ago.

Taken together, contemporary human genetic studies inform us that since their origin from an African common ancestor, humans have been through multiple evolutionary bottlenecks, particularly affecting those populations moving out of Africa, resulting in only a small number of individuals contributing to today's genetic pool diversity (37, 38).

With the advance of very-high-throughput genotyping technologies, we began to understand the influence on PCOS of this small, but significant, genome-wide variation observed between and among human populations. The first