Evolutionary determinants of polycystic ovary syndrome: part 2

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Polycystic ovary syndrome (PCOS) is a prehistoric complex genetic trait, perhaps dating back at least 50,000 years. The disorder also represents an evolutionary paradox, demonstrating clear reproductive disadvantages (i.e., lack of evolutionary fitness), albeit persisting tens of thousands of years. Here we examine possible explanations for this paradox. We evaluate a variety of possible benefits accruing to women in ancestral populations who possessed this trait, including considerations of whether dramatic changes in environment and lifestyle from the ancestral past to the contemporary present have altered the selection dynamics operating on the trait. Putative benefits include metabolic functioning, immune system dynamics, patterns of child-rearing and mothering, reproductive longevity, in utero or childhood survival, and musculoskeletal advantages. However, there is limited evidence that the persistence and relative homogeneity in the prevalence of PCOS can be accounted for by direct positive selection. Rather, PCOS evolution has likely been driven by nonadaptive evolutionary mechanisms, including genetic drift due to a serial founder effect and population balance due to sexually antagonistic selection. Ultimately, insights into the evolutionary origins of PCOS will emerge through the study not only of unique characteristics of affected individuals and their environments butalso through a broad consideration of the
potential adaptive and beneficial aspects of vulnerability to the disorder, importantly including examination of populations whose fertility, disease load, and diet resemble those of ancestral humans. (Fertil Steril® 2016;106:42–7. ©2016 by American Society for Reproductive Medicine.)

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine-reproductive-metabolic disorders of humans, affecting between 5% and 15% of women worldwide (1). The disorder is considered a complex genetic trait, with a high degree of heritability (2). PCOS appears to be an ancient, likely prehistoric, disorder. An evolutionary puzzle is posed by the conjunction of PCOS's clear detrimental effects on reproductive fitness, its high degree of heritability, its substantial prevalence, and its apparent antiquity, which begs the question, "Why has natural selection not eliminated this trait given that, under conditions of natural fertility, those who have it leave fewer descendants than those who do not?"

Below we review some of the principal existing attempts to address this evolutionary puzzle (see also reference [3]) and suggest that perhaps PCOS persisted not because it offered positive advantages, as some have proposed, but because it did not offer any disadvantages. Overall, a better understanding of the evolutionary origins of PCOS will potentially allow us to better identify the fundamental and intrinsic aspects of the disorder.

PCOS IS AN ANCIENT PREHISTORIC DISORDER

PCOS is an ancient disorder. In the modern era, the first concrete medical report of PCOS in contemporary medical literature is the seminal account of Stein and Leventhal (4). These investigators were the first to describe a series of patients, rather than isolated cases, with the triad of polycystic ovaries, hirsutism, and oligo-/amenorrhea, clinically linking what had previously been seemingly unrelated features (5). The importance of the report was furthered by the fact that a possible therapy for the syndrome (i.e., bilateral ovarian wedge resection) was also conveniently included. These aspects of the account, along with the facts that Stein and his collaborators were relatively prolific writers, consistent and clear in their message and descriptions, and that the disorder was and is highly prevalent, have resulted in what would eventually be called PCOS, gaining clear recognition and importance in contemporary medical practice (5).

While Stein and Leventhal's report was the first in modern times to refer to

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the association of menstrual dysfunction and hyperandrogenism, this clinical intersection had been recognized long before the advent of modern medicine. The earliest known recording of androgenization in women occurs in the Hippocratic *Epidemics* (6), where the eminent physician or one of his many students records two cases, one in the ancient Greek polis of Abdera and the other on the island of Thasos opposite the city.

The first notes that "Phaethusa in Abdera, the wife of Pytheus, who had had a child formerly when she was very young, upon her husband's being banish'd, miss'd her Menses a long time; and her joints grew afterwards painful and red. Upon this her body became manly, and hairy all over; a beard thrust out, and her voice became rough. Every thing was try'd by us that was likely to bring down her Menses, but all to no purpose; and not long after she dy'd." The second report states, "The same thing happen'd in Thasus to Namusias the wife of Gorgippus. All the physicians that I talk'd with were of opinion, that the only hope left was in her Menses coming down again as they ought: But this cou'd never be brought about, tho' we try' d every thing; and she dy' d not long after." The translator, Francis Clifton, M.D., Physician to His Royal Highness the Prince of Wales and Fellow of the College of Physicians and of the Royal Society, notes of the first report, "A very odd case." And indeed it was. A dramatic transmogrification with a tragic end.

But as extreme as those cases were, patients with milder and more chronic androgenization appeared to be not uncommon. The preeminent gynecologist of his millennium, Soranus of Ephesus (c. 98–138 A.D.), noted that "[s]ometimes it is also natural not to menstruate at all… It is natural too in persons whose bodies are of a masculine type … we observe that the majority of those not menstruating are rather robust, like mannish and sterile women" (7). Maimonides (1135–1204 A.D.), the celebrated Middle Ages physician, reported that "…there are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman's nature tends to be transformed to the nature of a man, this does not arise from medications, but is caused by heavy menstrual activity" (8). And Ambroise Pare (1510–1590) the barber surgeon to the French kings Henry II, Francis II, Charles IX, and Henry III, observed in his 24th book *On the Generation of Man* that "Many women, when their flowers or tearmes be stopped, degenerate after a manner into a certaine manly nature, whence they are called Viragines, that is to say stout, or manly women; therefore their voice is loud and bigge, like unto a mans, and they become bearded" (9).

These reports indicate that menstrual dysfunction in combination with hyperandrogenic symptoms appears to have not been uncommon, even over the past 2,000 years of human history. Soranus notes that it is "natural" not to menstruate at all, and that "It is natural too in persons whose bodies are of a masculine type," while Pare uses the term "many" to denote the number of women whose menses cease in association with the appearance of androgenic ("bearded") signs. Hence, even long before humanity had begun to consume the massive quantities of processed foods and simple sugars that we do currently, suffer the sedentary lifestyle we now have, or face the obesity epidemic of today, PCOS-like features were apparently not that unusual.

Inferences based on contemporary epidemiologic and genetic data complement historical accounts and in fact support the conclusion that PCOS is not only an ancient disorder but a prehistoric one. For example, although substantive epidemiologic data are still missing from large parts of the world, including Russia, Latin America, and Africa, the relatively similar prevalences of the disorder across a wide span of the globe and among ethnically and racially diverse groups of people (1), particularly when using the "classic" (National Institutes of Health 1990) definition of PCOS, suggest that the disorder dates back to an era before *Homo sapiens* began to differentiate into regional populations following migration across the globe from their home in east Africa (~50,000–80,000 years ago).

Similar conclusions can be obtained from the results of recent genome-wide association studies (GWAS) in large populations of women with PCOS. These studies identified a number of similar genetic variants in both Han Chinese and European-descent populations of women with PCOS (10), again suggesting that the disorder is quite old.

PCOS: AN EVOLUTIONARY PUZZLE

In many ways, PCOS represents an evolutionary paradox, whereby a disorder that currently demonstrates clear reproductive disadvantages (i.e., lack of evolutionary fitness, which in the evolutionary sense describes an individual's reproductive success or the probability that the line of descent from an individual with a specific trait will not die out, i.e., will survive) seems to have persisted—possibly hundreds—of thousands of years with a relatively high degree of prevalence. As we ask why PCOS surfaces in a diverse range of human populations given its association with infertility and shouldn't "it" and "its"' genes have been selected against, it is helpful to keep in mind the contribution of Niko Tinbergen. Tinbergen—winner of the Nobel Prize in Medicine and Physiology in 1973, along with two others for founding the field of ethology—observed that understanding why a behavior or disorder develops requires consideration of not just proximate but more evolutionarily informed (phylogenetic and functional) explanations (11).

Tinbergen's four "whys?" which refer to the four fundamentally different types of problems raised in biology (What is it for? How did it develop? How did it evolve? and How does it work?) (12) serve as the framing foundation of evolutionary medicine and are especially valuable when trying to understand the evolutionary roots of a disorder such as PCOS in which the clinical phenotypes are associated with reduced fertility and fecundity. A Tinbergenian approach to PCOS reframes the question "Why has PCOS persisted?" to "Why has the *vulnerability* to PCOS persisted?" "Vulnerability" in this context refers to the inherent potential for pathology to be embedded within biological characteristics associated with normal physiologic development and function. An example of this form of vulnerability might be the potential for a septic patient to become dangerously hypotensive due to fever-induced and heat dissipating vasodilation or the potential for obstructing or disfiguring scar formation due to robust wound healing physiology.