

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 but also 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 transmutation 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.

In other words, understanding the origins of any disorder requires a consideration of the fitness-enhancing characteristics of associated physiologies. For example, could a vulnerability to PCOS, while detrimental to the fertility of affected individuals, be associated with improved fertility or fetal outcomes in most women within a population? Is vulnerability to PCOS associated with other fitness-enhancing physiologic phenomenon in related individuals?

ADAPTIVE FORCES IN PCOS EVOLUTION

One possible explanation of the persistence and prevalence of PCOS is that the trait could have been positively selected for in the past as humans adapted to their environment. For example, perhaps the trait offered a fitness advantage in the prehistoric environment or lifestyle, even if it has the opposite effect today. We will review some of the postulated fitness advantages of this trait and briefly assess the relevant evidence.

Metabolic Advantages and the “Thrifty Gene Hypothesis”

Holt (13) and Escobar-Morreale et al. (14) have argued that [1] the genes contributing to PCOS enhanced fitness in ancestral populations by promoting a “thrifty” phenotype that conserved energy (through moderate abdominal fatness and decreased insulin sensitivity), increasing survival and competitiveness during periods of food shortage; and [b] it is only in the presence of evolutionarily novel present-day food superabundance that fitness-reducing phenotypic manifestations occur (i.e., the disease is a consequence of a mismatch between the environments in which humans evolved and those in which they currently live).

Gleicher and Barad (15) similarly argue that in ancestral environments, enhanced adiposity during periods of abundance combined with a putatively later age of menopause increased fitness by allowing women with this trait to better weather periods of scarcity. In turn, Shaw and Elton (16) proposed a model of multigenerational facultative adjustment to food scarcity, wherein under conditions of chronic shortages, transgenerational transmission of insulin resistance and similar attributes prepare offspring and grand-offspring for harsh environments through greater metabolic efficiency. These investigators (16) also propose that in ancestral environments, the trait would have allowed for more rapid resumption of ovulation with weight gain following refeeding after food shortages, thus giving its possessors a reproductive head start over competitors who were slower to begin ovulating.

However, like all “thrifty genotype” hypotheses, attempts to explain PCOS in terms of unalloyed putative benefits during periods of scarcity in ancestral environments are incompatible with the observation that the prevalence of PCOS, while certainly high for a disorder, is too low to reflect the past influence of widespread positive selection—had the alleles responsible provided an absolute benefit in ancestral populations, we should expect their contemporary prevalence to be much higher (17).

Pushing the postulated onset of the fitness-reducing consequences of PCOS back from the present day to the beginnings of agriculturally based food security some

200 years ago in Europe, Corbett and colleagues (18) argue that the genes responsible enhanced fertility under conditions of chronic food shortage in ancestral hunter-gatherer populations but subsequently produced disease and thus were subject to marked negative selection in populations with a long history of successful agriculture and attendant food supply stability. However, while such accounts may potentially shed light on contemporary differences in frequency across populations, so long as they postulate sustained positive selection in ancestral hunter-gatherers they cannot explain the absence of fixation, that is, why the trait appears to have never been ubiquitous (or even extremely common) in any population. Likewise, such explanations struggle to explain why the prevalence of the disorder appears to be relatively homogenous across the globe.

Recognizing the challenge posed to adaptive accounts by nonubiquity, Shaw and Elton (16), breaking from positions that postulate that the fitness-reducing consequences of the trait are a product of the recent past, suggest instead that the trait never became more widespread because of reproductive decrements suffered by its possessors during past periods of abundance. In other words, these investigators suggest that the trait has *always* been subject to reversals of selection as a function of ecological vicissitudes. While not impossible, prose accounts of this type must be tested using mathematical models to determine whether the postulated benefits and costs are in accord with plausible reconstructions of past environments and populations, such that the trait has been neither eliminated nor carried to fixation.

Immune Advantages and the “Hygiene Hypothesis”

Drawing attention to the proinflammatory state characteristic of PCOS, Escobar-Morreale et al. (14) propose that the disease protection offered by the increased inflammatory state favored the trait in pathogen-rich ancestral environments. However, with the evolutionarily novel reduction of pathogen loads characteristic of modern environments, the fitness costs of chronic inflammation now loom large and negative. However, studies of contemporary small-scale societies with high pathogen loads reveal abundant capacity for facultative adjustment of inflammation (19); hence it is unclear what advantage the PCOS trait would have provided. These observations do, however, draw attention to the mismatch between pathogen loads in ancestral and modern environments, suggesting another possibility.

Supported by an increasing corpus of evidence, the hygiene hypothesis (see reference [20] for review) holds that the long history of interaction between humans and pathogens is such that the risk of dysregulated inflammation is elevated when we mature and live in environments that lack the antagonists with which we coevolved. In particular, chronic helminth infection may substantially diminish the consequences of inflammation with regard to diabetes, cardiovascular disease, and a variety of similar disorders (21–23). If so, then the proinflammatory state characteristic of PCOS may have carried fewer costs in ancestral environments, thereby lowering the threshold necessary for

processes such as either kin selection via allomothering or sexually antagonistic selection (see below) to maintain the trait in ancestral populations.

Child-rearing and Mothering Advantages

Taking a different perspective, Eggers et al. (24) proposed that PCOS is explicable in terms of the benefits to relatives from having a family member who enhances the fitness of her kin through “allomothering” afforded by her own reduced fertility. “Alloparents” are those individuals other than the mother that help her provision or otherwise care for her young. However, on its own this explanation cannot account for other fitness-reducing aspects of PCOS (e.g., insulin resistance) since, assuming all else remains the same, an otherwise healthy allomother provides greater benefits than one who is at risk of metabolic disease. This account is therefore only compatible with reconstructions of evolutionary trajectories in which the non-fertility-related fitness costs of PCOS are primarily the product of modernity. That said, the allomothering hypothesis has the advantage that it does not require waxing-and-waning positive and negative selection forces to explain the combination of persistence and nonubiquity of the trait, as balancing selection could well maintain it at a relatively fixed frequency.

Focusing on a different avenue for the promotion of inclusive fitness through provisioning and allomothering, some investigators have proposed that the trait may have entailed fitness benefits via increased longevity through the associations between reduced fertility, late-age conceptions, and lifespan (25), which would have allowed women to assist their adult children in caring for their grandchildren. Independent of issues of PCOS or other pathologies, extensive research has addressed what is termed the “grandmother hypothesis” (see reference [26] for review). This hypothesis seeks to explain the pattern, ubiquitous in humans but extremely rare across mammals, wherein female lifespan is typically far longer than the period of reproduction. The grandmother hypothesis argues that the inclusive fitness benefits of assisting one’s adult offspring to survive and thrive selects for the extension of female lifespan beyond the age of menopause.

Debate continues regarding the grandmother hypothesis (27), and the hypothesis itself does not posit distinct variants such as the PCOS phenotypes. Nevertheless, because there is always a trade-off between reproduction and somatic maintenance (27), in principle this general perspective could indeed be enlarged to accommodate variants in which the costs of reduced fertility are counterbalanced by the benefits of increased longevity and corresponding investment in living descendants, such as PCOS. Importantly, however, substantial reductions in fertility such as those encountered in PCOS may fall beyond the range that such an explanation can accommodate. Because a woman shares twice as much genetic material with her children as she does with her grandchildren, sacrificing even a single potential birth in favor of the indirect fitness benefits afforded by increased longevity will only increase net fitness when the latter benefits are very large

indeed, a threshold that is arguably beyond any benefits documented to date in the literature on grandmaternal effects on survivorship. Moreover, it is unclear that PCOS is, or ever was, in fact, associated with increased longevity—certainly, in the contemporary environment, the metabolic dysfunction associated with the condition causes a reduction, not an extension, of lifespan.

Lastly, examining questions of investment with an eye toward mothers rather than allomothers, Escobar-Morreale et al. (14) and Azziz et al. (28) propose that PCOS could have enhanced fitness in ancestral hunter-gatherers by increasing birth intervals, thus allowing for greater maternal investment in each child. However, studies of contemporary hunter-gatherers (29) indicate that birth spacing in normal women approaches the fitness-maximizing optimum under conditions that approximate those of ancestral environments, making this an unlikely source of positive selection on PCOS.

Reproductive Longevity Advantages

Some investigators have suggested that PCOS may be associated not with an overall extension of lifespan but with enhanced reproductive longevity (30). For example, GWAS studies for age at menopause have highlighted a key role for DNA repair pathways. Their putative relevance to PCOS is supported by the novel PCOS locus near *RAD50*, a gene that is involved in DNA double-strand break repair (31). Further, in support of an association between PCOS and reproductive longevity, anovulation in women with PCOS is characterized by arrested follicle growth at the early antral stage, when antimüllerian hormone (AMH) secretion from follicular granulosa cells is highest. While higher AMH concentrations could indicate a larger ovarian primordial follicle pool size, higher AMH concentrations are also known to inhibit the recruitment of further primordial follicles (32). This effect of AMH could explain the consistent association we find between PCOS-susceptibility alleles and higher serum AMH concentrations and might be a mechanism underlying the slowing of ovarian aging in PCOS. However, longitudinal and retrospective studies to date have failed to document a later age at menopause (33, 34), suggesting that the effect of these mechanisms and genetic variants on ovarian longevity in PCOS may be modest at best.

In Utero or Childhood Survival Advantages

PCOS genes may have been positively selected for if they provided a benefit to prenatals or children (of either gender), although they are detrimental in postmenarchal girls. In other words, progeny carrying gene variants that increase the risk for PCOS may have a reduced risk of being lost to miscarriage as a fetus or of suffering early death as a child. Although allomothering and increased maternal longevity (see above) could certainly result in improved childhood survival, to date there are no data on whether PCOS offers direct childhood advantages. Regarding obstetrical outcome, as suggested by Azziz et al. (28), it is possible that increased pregnancy spacing and fewer pregnancies in a lifetime would not only favor improved child-rearing but may also reduce

the risk of maternal death due to the complications inherent to grandmultiparity, which in turn would adversely affect childhood survival. However, as noted above, mechanisms such as lactational amenorrhea combined with facultative adjustment of the timing of weaning apparently serve to optimize birth intervals in normal hunter-gatherer women (29); hence it is unclear what additional advantages the PCOS trait might have rendered in this regard.

In assessing the in utero effects of PCOS on survival, we can only survey pregnant women with PCOS, whose progeny are also more likely to carry PCOS genes. In fact, there is little evidence that PCOS is associated with increased in utero survival; on the contrary, there is accumulating evidence to the converse (35). Whether the increased intrauterine stress enhances the postnatal survival of these fetuses remains to be determined.

Musculoskeletal Advantages

Azziz et al. (28) suggested that the greater lean muscle mass and bone density associated with this trait would have been favored in the demanding environments of the past; Escobar-Morreale et al. (14) make a similar argument regarding aggressiveness. However, given that all such attributes are constantly subject to selection, we should expect the prevailing normal ancestral female phenotype to have been characterized by optimal levels of these traits given their inherent costs. It is therefore difficult to see how increased androgenization at the (added) cost of the reduced fertility and other problems associated with PCOS would have enhanced fitness.

NONADAPTIVE EVOLUTION IN PCOS

Notwithstanding the above hypotheses, recent reports do not find evidence for a recent, strong positive selection of PCOS-susceptibility alleles (36, 37). One possible explanation is the observation that genes associated with complex-disease susceptibility appear to be under less pervasive purifying selection than are other classes of essential or disease genes. This may be because alleles that contribute exclusively to complex diseases [1] tend to explain only a small proportion of disease risk and to have late-onset effects, so they might have few fitness consequences; and [2] include loci that are under widespread purifying selection but are also enriched for targets of positive selection, thus appearing to be less conserved when considered as a class (38).

Thus, it is possible that PCOS has evolved and persisted not due to adaptive evolution but as a result of nonadaptive (i.e., any change in allele frequency that does not by itself lead a population to become more adapted to its environment; the causes of nonadaptive evolution are generally mutation, genetic drift, and gene flow [migration]) evolutionary mechanisms. For example, Casarini and Brigante (39) recently analyzed the PCOS phenotype-genotype relationship in silico, using single nucleotide polymorphisms of representative genes for analysis of genetic clustering and distance to evaluate the degree of genetic similarity. They observed that the overall genetic distance increased with geographic distance among populations in a phenotype-unrelated manner, sug-

gesting that the PCOS genetic gradient may result from genetic drift due to a serial founder effect occurring during sequential ancient human migrations.

It is also possible that rather than being positively selected for adaption to the environment the PCOS trait may have simply persisted (i.e., was not selected out) because [1] it did not have any effect either way (i.e., was asymptomatic) in the ancestral environment or lifestyle; or [2] it is in balance in the population, such that in one group it has a fitness advantage and in another it has a fitness disadvantage, but the population fitness is overall balanced. For example, it may be balanced between heterozygotes and homozygotes (e.g., bad for homozygotes, good for heterozygotes) or males and females (e.g., good for men, bad for women).

While we do not know whether the PCOS trait was prehistorically asymptomatic and we have limited data on whether a survival advantage is evident in female carriers of PCOS genes, it is possible that the trait may be in balance in the population due to differences in gene effects on the two sexes. Sexually antagonistic selection occurs when the same alleles that cause a fitness decrement in one sex enhance fitness in the opposite sex. For example, brothers of women with PCOS demonstrate elevated androgen levels (40) without any evident impairment in their fertility. It is therefore possible that via enhanced competitive or foraging abilities, increased intersexual attractiveness, or all of the above, the alleles at issue increased fitness in men carrying PCOS genes under ancestral conditions. If, on average, the fitness benefits to men carrying these alleles were equivalent to the fitness costs to women possessing them, then the alleles would neither increase nor decrease in frequency in ancestral populations.

Casarini and Brigante's in silico analysis suggested that the prevalence of PCOS among different human populations may be the result of the balance between positive selection in males and negative selection in females (39). In a subsequent review, Casarini and colleagues demonstrate that several genetic loci associated with the disease differently modulate the reproductive parameters of men and women (25). This observation then suggests that such genetic variants could lead to opposite effects in the two sexes in regards to reproductive success, supporting the possibility that intralocus sexual conflict could be a cause of the persistence of the PCOS genotypes among humans.

SUMMARY

PCOS is an ancient, likely prehistoric, disorder whose persistence in humans and its relatively homogenous global prevalence remains an evolutionary puzzle. While adaptive evolution due to positive selection driven by a number of putative advantages may have played a role in the evolution and persistence of PCOS, at present it appears more likely that PCOS has been the product of nonadaptive mechanisms, such as genetic drift and sexually antagonistic selection, which have permitted the trait to persist in humans over millennia without any benefits accruing to women who possess it.

Ultimately, insights into the evolutionary origins of PCOS will emerge through the study not only of unique

characteristics of affected individuals and their environments but also through a broad consideration of the multiple factors responsible for vulnerability to the disorder. In this regard, it will be critical to examine populations characterized by natural fertility, high levels of exposure to pathogens, and low consumption of processed carbohydrates to best understand the evolutionarily-relevant phenotypic consequences of the underlying genotypes.

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