# Polycystic ovary syndrome: an ancient disorder?

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Polycystic ovary syndrome (PCOS) appears to be an ancient disorder, which has persisted in human evolution despite reduced fecundity because of the benefits to affected women such as greater sturdiness and improved energy utilization, a rearing advantage for their children and kin, and a reduction in the risk of perinatal mortality. This raises the possibility that gene variants that are eventually found to be associated with PCOS will be similar across ethnic groups and races. (Fertil Steril® 2011;95:1544–8. ©2011 by American Society for Reproductive Medicine.)

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And all the days of Methuselah were nine hundred sixty and nine years: and he died.—Genesis 5:27.

Is polycystic ovary syndrome (PCOS) an ancient disorder? Or is it a disorder of recent development, the consequence of rising metabolic stress in an increasingly obese society? And if it is ancient, why has it persisted despite its reproductive disadvantage? And can the antiquity and evolutionary history of PCOS inform our efforts to unravel its genetic makeup?

## ANCIENT MEDICAL RECORDS

While there is little in the Egyptian papyri (Kahun, Edwin Smith, and Ebers) regarding the antiquity of PCOS, an examination of later ancient medical records provides clues. Hippocrates (460–377 B.C.) notes, "But those women whose menstruation is less than three days or is meagre, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant" (*Diseases of Women 1.6*) (1). 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" (*Gynecology*, Book I. Art. 23 and Book I. Art. 29) (2).

The medieval physician Moises Maimonides (1135–1204 A.D) noted 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" (Fin Liber Comm. Epidemirum VI, 8) (3). Most directly, the celebrated renaissance surgeon and obstetrician Ambroise Pare (1510–1590 A.D.) observed, "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" (*The 24th Book of the Generation of Man*) (4).

These statements made over a period of more than two millennia describe a combination of signs, including menstrual irregularity, masculine habitus, subinfertility, and possible obesity, which are suggestive of PCOS. They also describe the disorder in terms that translate today as "sometimes" or "many," indicating that the condition was sufficiently common to merit description.

## THE RACIAL PREVALENCE OF PCOS

An examination of the global prevalence of PCOS today may be instructive in elucidating differences between the races. Reports from the United States, the United Kingdom, Spain, Greece, Australia, and Mexico demonstrate a strikingly similar prevalence of PCOS, as defined by the National Institutes of Health 1990 criteria, ranging from 6% to 9% (5–10). While many populations remain to be studied and most of the subjects in these reports were whites of European descent, the African-American (6) and Mexican (10) women included also demonstrated similar prevalences. Consequently, considering that humans had migrated from Africa by 50,000 years ago (11), the PCOS genotype(s) appears to have emerged earlier than the onset of racial diversity.

## IS THE PREVALENCE OF PCOS AFFECTED BY THE INCREASING RATES OF OBESITY?

The prevalence of PCOS appears to be only minimally affected by the increasing rates of obesity and the excessive consumption of Western-type food. For example, the prevalence of PCOS is relatively similar across countries with different rates of obesity (e.g., United States vs. Spain or Mexico) (5, 6, 10). Likewise, we have been unable to detect significant differences in the dietary intake or composition of

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women with PCOS compared with matched controls (12). In a study of over 600 unselected women from the general population, the prevalence of PCOS increased minimally and nonsignificantly with increasing body mass (13). In contrast, the average body mass of over 700 women with PCOS diagnosed over a 15-year interval increased linearly and in concert with the increasing obesity of the surrounding population (13). Taken together, these data suggest that the epidemics of excess caloric intake and being overweight play a limited role in the development of PCOS.

## BUT WHY SHOULD A DISORDER THAT REDUCES REPRODUCTIVE POTENTIAL THRIVE AND PERSIST ACROSS MILLENNIA?

It is likely that, as for other susceptibility alleles for modern metabolic diseases (14, 15), the origins of PCOS began in Paleolithic hunter-gatherer communities, in which environmental stressors favored the survival of those males, females, and offspring with the greatest capacity for energy storage necessary to endure prolonged episodes of privation, the so-called thrifty genotype (16–18). If so, such a thrifty genotype may have enhanced survival during times of food deprivation, with reduced postprandial thermogenesis from insulin resistance, diminishing energy expenditure as an additional evolutionary advantage (19).

Furthermore, we should note that few women with PCOS are actually sterile and the PCOS family size can be normal in today's society of medical therapy and family planning (20), proof that conditions restricting reproduction, whether social or environmental, ameliorate the reproductive disadvantage to PCOS families. Moreover, in a study of over 300 women with PCOS, those women treated with placebo ovulated approximately one-third the expected (monthly) frequency (21); thus, women with PCOS are able to conceive, albeit at a rate lower than normal. Considering the reproductive benefits of coitus initiation at an early age, a higher coital frequency, the absence of effective contraceptives, and the absence of widespread obesity, it is quite possible that the pregnancy rates of ancient PCOS women would have been significantly higher than at present, particularly if relative insulin resistance was able to divert circulating glucose as dietary energy for ovulatory function during low-energy conditions (22).

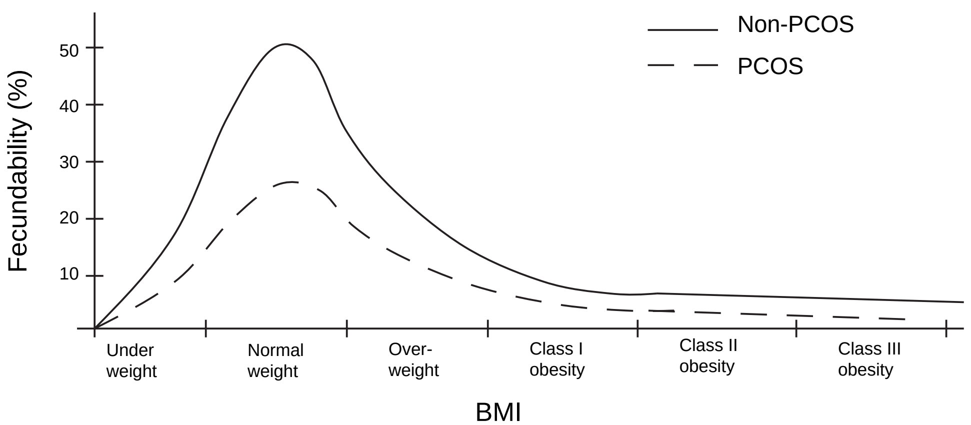
In addition, among nomadic hunters it would have been advantageous and even necessary for women to space childbirth, as they could generally carry and care for only one young child at a time (23). Childbirth-related complications were an important cause of mortality in reproductive-aged women in antiquity (and in present-day Africa), and a lower parity may have reduced the death rate of these women and the risk of progeny abandonment. The lower fecundity of women with PCOS could also have created a rearing advantage for their progeny, with their fewer children receiving a greater amount of the available food and protection. And these progeny, both as a result of their inherited genotype and possibly the effect of their intrauterine environment, would have also been more able to survive periodic deprivation.

It could also be argued that PCOS favored the survival of those family units containing these women, as females with PCOS and few, if any, children of their own could have served as allo-mothers to their kin (24). With aging, women with PCOS may have attained significant nurturing skills, given their wisdom and strength to survive a physically demanding environment, creating a source of capable child-rearing labor not focused on or threatened by pregnancy. Finally, in such a physically demanding environment, the greater lean muscle mass and bone mineral density of women with PCOS (25–28) would have also been advantageous to their own survival and that of their progeny. Thus, the disease susceptibility alleles for PCOS may have been ideally adapted to the need for high physical strength and activity, the erratic and often low nutrient availability, and the lower fecundity advantageous to the hunter-gatherer.

In a recent interesting analysis, Corbett et al. (29) propose that the body mass index (BMI)-fecundity relationship of PCOS is simply shifted leftward, such that patients with PCOS would have normal fertility at the very low BMIs experienced by hunter-gatherers (and including populations through the 1800s) during periods of food scarcity, while their non-PCOS counterparts would experience subnormal fertility during that period of time. In contrast, and based on our observations of BMI and fertility in PCOS (6, 13), we suggest that the BMI-fecundity relationship in PCOS is simply decreased at all BMIs (see Fig. 1). Thus, patients with PCOS should be considered subfertile, not infertile. In our model, the persistent reproductive capacity of PCOS women in antiquity does not rely on a shifting of the BMI-fecundity curve but on (1) the BMIs in general being lower in the pre-1800s and thus the lessening of the rate of subfertility in PCOS, although not fully approaching the fertility

**FIGURE 1**

Hypothetical BMI-fecundity relationship in PCOS.

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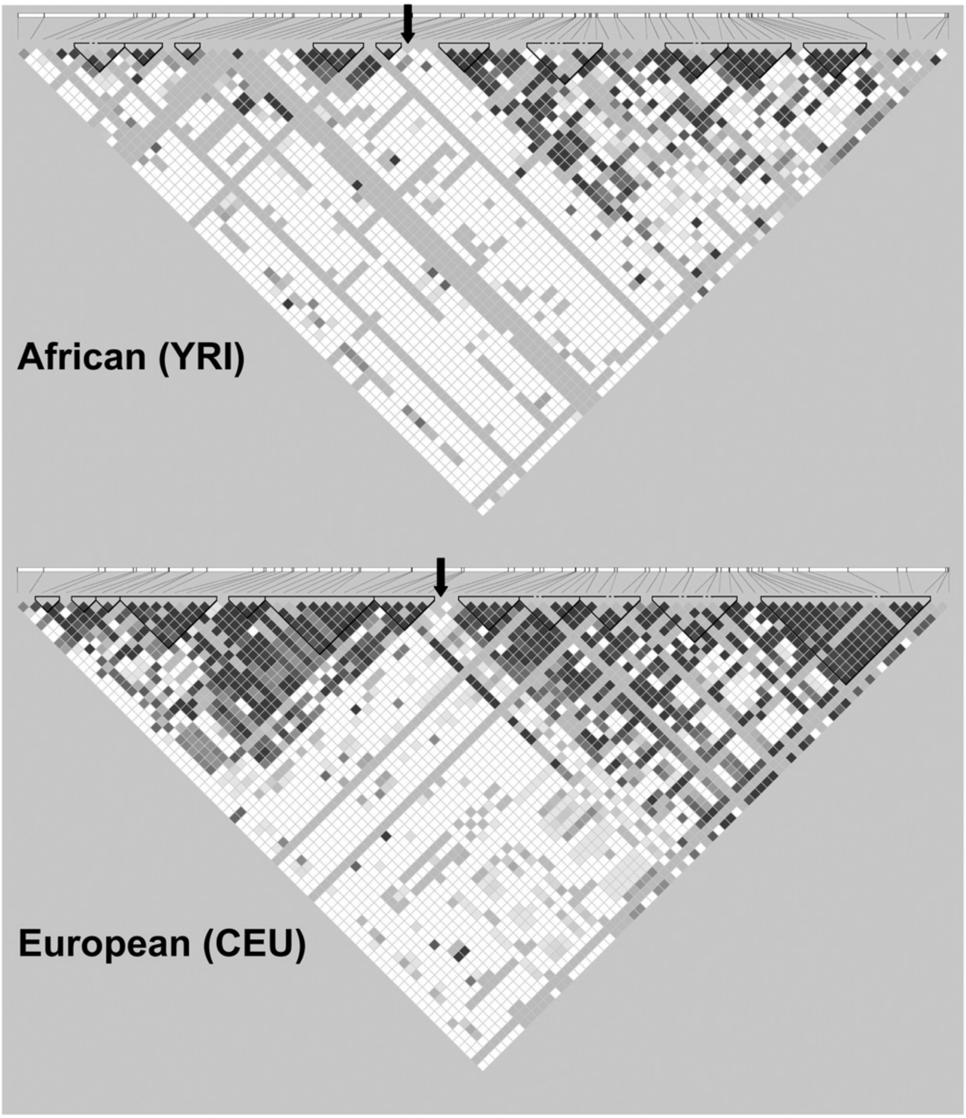
of non-PCOS (i.e., normal) women; and (2) the reduced obstetrical morbidity/mortality associated with the subfertility.

## WHY DID THE PCOS GENOTYPES SURVIVE THE NEOLITHIC REVOLUTION?

If the PCOS alleles developed, as other metabolic complex traits appear to have done, in the hunter-gatherer Paleolithic period of the Stone Age, why did these genotypes survive the Neolithic revolution of some 10,000 years ago, with its adoption of farming, animal domestication, and sedentary settlements? In fact, ancestral genetic traits determining modern metabolic diseases, such as cardiovascular disease and diabetes, did persist in sedentary societies and were evident even in ancient Egypt (c. 1500 B.C.) (30, 31). But these disorders generally would have affected individuals who were older (30) and would have had little impact on the reproductive potential of the affected individuals, perhaps being of limited selective importance in a society whose average lifespan was approximately 35 years.

**FIGURE 2**

Effect of time on linkage disequilibrium. Both LD plots represent a 100-kB area centered around the microsatellite D19S884 (location approximately indicated by black arrows), a marker for which one allele has been associated with PCOS in multiple studies (37). The data were downloaded from the International HapMap Project (Phase II+III, Release 27, http://hapmap.ncbi.nlm.nih.gov); plots were generated using Haploview (ver. 4.2, http://www.broadinstitute.org/mpg/haploview). The top LD plot is from Yoruba subjects from Ibadan, Nigeria (YRI), and the bottom panel is that of the Utah residents with ancestry from northern and western Europe (CEU). The LD plots display D' values for each pair of single nucleotide polymorphisms (SNPs) in the box at the intersection of the diagonals from each SNP. The darker boxes indicate greater degrees of LD for the corresponding pair of variants. Triangles around boxes indicate haplotype blocks determined by the confidence intervals algorithm in Haploview. The older Yoruba population exhibits less extensive LD and smaller haplotype blocks.

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In contrast with the hunter-gatherer society, having larger numbers of children was a necessity for the survival of agricultural communities to provide the necessary labor while overcoming the high neonatal mortality evident at the time (32). In an agricultural environment, in which sufficient food eventually became available, PCOS should have been an adaptive disadvantage to any affected female and might have been eliminated over the past 10,000 years, consistent with the rapid evolution observed for other traits (33). This hypothesis, however, assumes that the reproductive disadvantage of PCOS is absolute.

However, as for hunter-gatherers, the reproductive disadvantages of women with PCOS in the Neolithic and subsequent periods would have been less severe than currently presumed. Like hunter-gatherer females, women with PCOS in sedentary agricultural societies may have been able to conceive, albeit at a rate lower than normal, may have had lower maternal mortality, would have been able to serve as allo-mothers to their kin, and would have been sturdier than average; their progeny may have had the advantage of their genotype, their intrauterine environment, and the increased maternal attention and protection. Furthermore, significant periodic privations remained a fact of life through the late 1700s and early 1800s, for which women with PCOS are better suited to survive (29).

Finally, affected male relatives, while demonstrating evidence of androgen excess (34) and insulin resistance (35), do not demonstrate obvious impairment in fertility or ability to attract a suitable partner and in ancient times would even have had the metabolic advantages of females with PCOS and thus were readily able to transmit susceptibility alleles. Consequently, the metabolic and physical advantages of affected women and their progeny, the rearing advantages of their family units, the heterogeneity of the phenotype and genotype, and the ready transmissibility of the genotype by affected males could have potentially equalized any disadvantages arising from the overall lower number of children begotten by PCOS women.

## CAN THE ANTIQUITY OF PCOS INFORM OUR EFFORTS TO IDENTIFY SUSCEPTIBILITY GENES?

PCOS is likely the result of a myriad of genetic variations resulting in a complex genetic trait. In fact, mathematical modeling has suggested that Mendelian disease genes appear to be under widespread purifying selection, especially when the disease mutations are dominant (rather than recessive); in contrast, the class of genes that influence complex disease risk show little signs of negative selection, possibly because this category includes targets of both purifying and positive selection (14). If PCOS were indeed ancient, we would expect that the susceptibility genes would in great measure be shared between different ethnic groups.

A potential challenge in identifying genes for an ancient disorder is that the linkage disequilibrium (LD) surrounding susceptibility loci may be relatively restricted, as predisposing loci arising in ancient times would be more separated from neighboring markers by recombination. This is suggested by the fact that older population groups (e.g., Africans) have less extensive LD blocks than more recent populations (e.g., Europeans) (36) (Fig. 2). Limited LD would necessitate very dense (e.g., 1 million or greater) sets of markers to identify these loci. It remains to be seen whether such considerations hinder gene discovery in genome-wide association studies (GWAS) of PCOS currently underway and highlights the potential utility of candidate gene studies in PCOS, wherein targeted genetic regions are readily covered at much greater density than by GWAS.

It is difficult to predict what effect the ancientness of PCOS would have on the effect sizes of susceptibility alleles. Purifying selection against alleles with severe consequences may have resulted in a set of remaining susceptibility loci with mild effects on PCOS risk. Alternatively, balanced selection due to the selective advantages described above could have preserved susceptibility alleles with more substantial effect sizes. If GWAS do identify PCOS susceptibility loci, an examination of whether such loci manifest evidence of positive selection would provide genetic support to our hypothesis that PCOS persisted through the ages by conferring a survival advantage.

## CONCLUSIONS

Taken together, these observations suggest that PCOS is an ancient disorder, arising from ancestral gene variants selected during the Paleolithic period and maintained over the past 10,000 years after the onset of Neolithic culture. Such ancient genes were likely transmitted transgenerationally through offspring conceived between fertile carrier males and subfertile affected females; the reduced fecundity of affected women potentially would have been offset, at least in part, by their greater sturdiness and improved energy utilization, a rearing advantage for their children and kin, and a reduction in the risk of maternal mortality. While this analysis cannot allow us to determine whether the gene variants eventually found to be associated with PCOS will be similar across ethnic groups and races, it does raises the possibility that a dense set of markers will be required to elucidate them in genome-wide approaches.

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