Polycystic ovary syndrome: a transgenerational evolutionary adaptation

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Polycystic ovary syndrome has a common association with anovulatory infertility, while the physical symptoms are often associated with the increased androgens that are part of the endocrine profile. There is a well-recognised association with lipid and glucose metabolism anomalies and, when undergoing ovulation induction, ovarian hyperstimulation syndrome. This common condition is familial, but a contributory gene has yet to be found. The question of why a gene that predisposes to anovulation, diabetes and heart disease might have perpetuated so frequently is addressed. Three hypotheses for evolutionary advantage are discussed. The food deprivation hypothesis considers the role of the observed increase in ovulation when women with the condition lose weight in relation to seasonality. The refeeding hypothesis considers the androgenic and slightly enhanced anabolic metabolism in relation to periods of privation and the advantage of preferential early ovulation when refeeding after a period of privation. The transgenerational privation hypothesis considers the effect of persistent, severe, yet subfatal privation on individuals both in utero and throughout life. While an androgenic, anabolic state would improve efficiency in the use of food for protein synthesis and fat storage, benefiting the fetus both in relation to its in utero development and neonatal survival, survival and reproductive capacity as an adult benefits by a genotype expressing itself in women of successive generations.

Keywords Adaptation, evolution, PCOS, refeeding, transgenerational.

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Introduction

When Stein and Leventhal 1 first reported the clinical entity that is now known as polycystic ovary syndrome (PCOS), the condition was clearly circumscribed as comprising amenorrhoea, polycystic ovaries and obesity. We now know this syndrome to be a more nebulous combination of clinical, biochemical and ultrasound parameters. Not one of these is consistent or diagnostic. 2 Its 21st century presentation is often the result of the somatic effect of androgens but is most commonly associated with infertility and oligoamenorrhea. Obesity, a common but not uniform finding, tends to be centrally distributed (large waist-to-hip ratio). The condition is strongly associated with development, later in life, of type II diabetes, 3 abnormal lipid profiles and cardiovascular disease. 4 Hyperinsulinaemia in the presence of normal glucose, insulin resistance, is very common. Within women seeking fertility treatment, there is a high tendency to over stimulation and ovarian hyperstimulation syndrome. This reflects the origins of the ‘cysts’: they are recruited nonmatured follicles. PCOS is therefore a condition featuring over recruitment of follicles with limited maturation and ovulation, combined with abnormalities associated with nutrition (glucose and fat metabolism).

The combination of features that comprise PCOS have fuelled debate as to its origins and development. It has been argued 5,6 that the condition has an evolutionary basis, but to date there has been no systematic approach to the construction of hypotheses relating to evolution, and the implications of an evolutionary perspective for clinical practice have not been considered. In this paper, research into genetic and environmental influences on PCOS is briefly reviewed to give a conceptual overview of the condition. Using an evolutionary framework, three hypotheses are presented as to why PCOS might have increased fitness (defined as differential survival or reproduction) in the past. Finally, the broad implications of an evolutionary perspective for clinical practice in this area are briefly discussed.
Genetics

While all disease ultimately comes down to genetic tendencies and the influence of environmental factors, a very strong genetic basis is widely accepted as being likely for PCOS. There is clear interpopulation variation in the frequency of the phenotypic expression of PCOS (reviewed by Shaw and Elton8), and the disease is familial.8,9 Further, the condition is more common in monozygotic twins than in dizygotic twins,10 although this concordance is not especially robust, so there is no unequivocal support from twin studies for an entirely genetic origin.11

There is some evidence12 for PCOS susceptibility close to the D19S884 dinucleotide repeat marker, linked to the insulin receptor gene on chromosome 19p13.2. The interest in chromosome 19 stems from research in diabetes and the assumption that genes, which code for PCOS might be in the same locus. There is a suggestion that the Pro12-Ala polymorphism in the PPARγ gene might have a role in modifying insulin resistance in women of European origin with PCOS. Those in possession of the gene appear to have increased insulin sensitivity compared with those with the Pro/Pro genotype.13 However, there is no similar finding in African-American women with PCOS.13 Attempts to link PCOS with the calpain-10 gene, which is associated with insulin resistance and type II diabetes, have been inconclusive to date.14,15

Environmental factors

Low birthweight has repeatedly been observed to have associations with a number of sequelae in later life. Many of these are secondarily associated with PCOS. Low-birthweight females have a greater chance of precocious pubarche, hyperinsulinaemia and hyperandrogenism.16 Moreover, there has been a similar observation by Hales and Barker17 of dislipidaemia and insulin resistance. One hypothesis is that poor fetal and infant growth can promote the development of PCOS in individuals with genetic susceptibility when exposed to a nutritional environment of excess later in life.

While there is no natural animal model of PCOS, models have been created by prenatally androgenising sheep and rhesus macaques.18,19 In humans, therefore, exposure to androgens during pregnancy might well result in similar induction of the disease when the infant reaches puberty. In humans, exposure to excess androgens, possibly as a result of the action of genes that regulate the relevant pathways, might occur during the short-lived activation of the hypothalamic-pituitary-gonadal axis in infancy as well as at puberty.9 This in turn might lead to endocrine disturbance, including insulin resistance and elevated luteinising hormone (LH), and abdominal adiposity, the effects of which can be mediated or magnified by diet.9

Evolutionary perspectives on PCOS

The strong role that genetic factors apparently play in PCOS plus its high general prevalence worldwide could indicate an evolutionary basis to the syndrome. At some point in our evolutionary history, PCOS might have been selectively advantageous, resulting in the high levels observed today. It has been suggested that women with PCOS who have a high chance of being obese and anovulatory during times of normal or excess food availability, and who begin to ovulate on weight loss, have a selective advantage by being able to reproduce during periods of food shortage when other women become anovulatory.20,21 When faced with a modern westernised lifestyle characterised by abundant food and limited physical activity, however, the ‘thrifty genes’ that might have been advantageous under certain environmental conditions contribute to PCOS and become disadvantageous.4

An evolutionary basis has also been suggested for another condition of insulin resistance, type II diabetes. Neel22 observed that modern populations, specifically the Pima, have high levels of insulin resistance and postulated that they were at some point in the past subjected to environments with extremely poor food availability, possibly with feast famine cycles. The suggestion is that a ‘thrifty gene’ would code for famine-resistant glucose metabolism. It is noted that there is a tendency to high waist-to-hip ratio and carbohydrate intolerance in many hunter-gatherer populations throughout the world, including North and Central America, Asia, Middle East, Australia and Oceania (reviewed by Wood23). The evolutionary advantage is for a genotype that tends towards an anabolic metabolism and fat deposition in populations of hunter-gatherers who are mainly not obese when living in their traditional lifestyle, in which food supplies are at or just above subsistence level and are in some cases seasonal. Wood23 explores the concept that genetic predisposition to central obesity as coded by genes that influence leptin, cholecystokinin and ghrelin might in its own right provide an evolutionary advantage in types that were less well fed.

Discussions of the evolutionary basis of PCOS have, on the whole, been peripheral to a larger picture of obesity and type II diabetes. Since PCOS affects around 1 in 12 women in western populations,2 it is important to approach it in its own right. Hence, three hypotheses relating to the circumstances under which PCOS might have evolved are presented below. It is hoped that these will form the basis for future research that specifically tests the possible evolutionary dimensions of the condition.

The food deprivation hypothesis

There is no doubt that obese, amenorrhoeic women with PCOS who lose weight have a high chance of spontaneously restarting their menstruation and ovulation. Clark et al.24

demonstrated that a mean weight loss of 10.2 kg in a group of obese, infertile women (of whom 80% had PCOS) resulted in spontaneous medically unassisted pregnancies in one-third of the study group within 6 months. Saris\textsuperscript{23} in a study of obese native Hawaiians who replaced a westernised diet with a traditional low calorie, low fat diet, observed a weight loss of 7.8 kg over 3 weeks. It is therefore likely that in times of seasonal deprivation a rapid weight loss would result in ovulation in a subgroup of obese women who are genotypically PCOS. Conception during time of severe food deprivation might appear at first glance to be disadvantageous. Ulijaszek\textsuperscript{26} observed that in the Gambia, where the wet season is the ‘hungry season’, those pregnancies in the third trimester at that time resulted in a lower birthweight infant. However, conception in the wet season, when fertility was at its lowest for the general population, resulted in lower neonatal mortality. Thus, it is possible that the onset of severe food deprivation, whether incidental or seasonal, might present reproductive advantages to women with the PCOS genotype. Essentially, the food deprivation hypothesis suggests that the genes influencing it are likely to be those that affect nutrition (i.e. coinciding with the aforementioned theories of an evolutionary advantage to type II diabetes and obesity).

**Refeeding hypothesis**

The food deprivation hypothesis stresses rapid weight loss as the trigger for ovulation. However, individuals in traditional subsistence economies are less likely than those in developed regions to experience the type of ‘overnutrition’ that leads to obesity. Thus, PCOS genotype females with obesity would be less prevalent. Indeed, those genotypes might be subject to the same sort of nutritional deprivation that leads to amenorrhoea in the general population. So, inspite of the possession of anabolic metabolism, chronic food deprivation may, as with anyone else, lead to famine-related amenorrhoea. Under these circumstances, conception would obviously not take place. However, as they come out of severe food deprivation and refeed, the part-recruited follicles that line the edge of the ovary in women with PCOS might be more easily recruited. Such follicles demonstrate ready recruitment in the face of superovulation in assisted reproduction cycles, as evidenced by the association between PCOS and ovarian hyperstimulation syndrome.\textsuperscript{27}

The onset of ovulation in anorexic women being refed seems to be closely linked to the ‘adipocyte’ hormone leptin, which in this context has been described as ‘the metabolic gate to gonadotrophin secretion’.\textsuperscript{28} It is known\textsuperscript{29} that in women with PCOS the amount of circulating leptin is related to body mass index (BMI) and is not independently affected by sex hormones, gonadotrophins or insulin. So, leptin, the ‘metabolic gate’, remains under the direct influence of available nutrition in the environment. Those with PCOS, therefore, have the same metabolic triggers to refeeding as non-PCOS individuals. However, the PCOS syndrome favours a more androgenic endocrine state. Women exhibiting PCOS, being more anabolic than those without the syndrome, will reach the critical BMI first when refeeding. This will open the leptin ‘gate’ and favour earlier ovulation. If the period of plenty is of limited duration, the first to ovulate would have a reproductive advantage in as much as the resultant pregnancy would be more likely to complete before another period of privation arrived.

**The transgenerational privation hypothesis**

The food deprivation hypothesis seems to be an investment in conception during food shortage in anticipation of a predictable period of plenty. This is most compatible with seasonality. However, the refeeding hypothesis would probably optimise completion of pregnancy and lactation in a situation where times of relative plenty were not guaranteed in duration, favouring its evolution in an environment characterised by intermittent but unpredictable periods of extreme food shortage, such as famine caused by climatic events. Both hypotheses centre on the advantages to an individual during their own lifetime. However, the transgenerational nature of some conditions, including insulin resistance, is increasingly being recognised\textsuperscript{30} and demonstrates that the nutrition of mothers and even grandmothers can have a profound influence on the health of offspring in adulthood. If a population suffers persistent, severe, yet subfatal privation, an anabolic, anabolic state would improve efficiency in the use of food for protein synthesis and fat storage. Men with naturally high androgens and no need to provide support for a pregnancy might be less vulnerable than most women in this environment. Women with PCOS have high levels of circulating androgens,\textsuperscript{31} and the role of prenatal androgens in the development of PCOS-like states has been documented in macaques.\textsuperscript{18} Thus, women with a PCOS genotype might well benefit from the additional endogenous androgens in suboptimal nutritional environments. The advantages are direct not only in terms of nutrition and in the use of protein and carbohydrate in a single generation but also indirect in as much as pregnancies arising at this time, while inducing intrauterine growth restriction, would result in offspring who have an ability preferentially to store fats.\textsuperscript{32} Those offspring who were female would be more likely to develop a PCOS-like state because of exposure to higher levels of androgens during gestation, as demonstrated by the macaque model. This in turn would promote follicular readiness and the preferred early ovulation in adulthood if they themselves experience fluctuations in resource availability. The possession of a gene, which is androgenic and influences lipid and sugar metabolism might well have an amplifying effect on the next generation under the appropriate environmental circumstances. It is possible that such a genetic component is
very ancient indeed and, in conditions such as lactose intolerance, is the original state, which has become less compatible with life in modern developed countries where resources are stable and plentiful.

**Discussion**

Each of the three hypotheses outlined here seeks to establish the evolutionary advantages of PCOS. Although they all revolve around food deprivation, the proposed mechanisms behind each theory would operate under slightly different conditions. The food deprivation hypothesis stresses the origin of the condition in seasonal environments, in as much as the investment in the pregnancy at a period of severe food shortage relies on the expectation of food as the pregnancy matures. The reliability of the expected seasons is entirely compatible with this aspect of hypothesis. Under this hypothesis, the genes responsible would be related to the individual’s survival against nutritional odds. In this respect, it is similar to the ‘thrifty’ gene hypothesis and renders PCOS as just another form of diabetes (type III diabetes) that happens to have reproductive additional benefit, the androgenisation and follicular recruitment against the nutritional odds. In contrast to the food deprivation hypothesis, the refeeding hypothesis is based on the concept of intermittent famine/plenty, which is not necessarily seasonal or even annual. In this case, the advantage would be in rapid ovulation with the onset of refeeding, with the goal to complete the pregnancy (and preferably wean the offspring) before the next incidence of severe deprivation. The refeeding hypothesis places the primary genetic origins of this as a follicular recruitment gene; the disease becomes one of excess follicular recruitment but has, in addition, some nutritional benefits. In other words, the emphasis of this hypothesis, which has not previously been suggested in the literature, is the reverse of that suggested in the food deprivation hypothesis. Finally, the transgenerational privation hypothesis implies a chronic underfed state in which those with the appropriate gene have a more anabolic state and hence enhanced basal metabolic efficiency than do the rest of the female population, leading to reproductive advantages across the generations, both through the effective use of food and through the impact on ovulation outlined in the refeeding hypothesis. The transgenerational privation hypothesis contrasts with the first two hypotheses in that it also yields a longer term strategy in relation to the next generation and to its basal metabolic rate and reproductive sensitivity.

It is quite possible that the PCOS genotype may have been in existence before modern humans evolved approximately 150 000 years ago. It has been argued that due to the demands of ‘growing’ large-brained fetuses, female primates require a suite of reproductive adaptations that predispose to ovulatory dysfunction similar to that seen in PCOS. Thus, the origins of the condition (whether or not it has subsequently been advantageous in resource-poor environments) might be relatively ancient. The exact timing of such a development may be related to the demands of the hominin brain, which began to increase appreciably in size during the Pleistocene. However, it could also have emerged much earlier, with the great apes or even the Old World primates, all of which have brains that are larger than would be expected for their body masses. Nonetheless, the environmental pressures faced by hominins throughout most of their evolutionary history were considerable and very probably had reproductive consequences some of which have previously been reviewed.

One issue that needs to be addressed, regardless of the preferred hypothesis, is why PCOS is not at even higher levels in the population, given its potential importance as a reproductive strategy in situations where there is significant resource deficiency. A number of explanations are plausible. One controversial explanation is that since direct evidence of fertility and potential fecundity in human females is concealed, morphological features associated with reproduction, such as fat patterning, might be very important in mate choice and perceived attractiveness. Many women with PCOS, even when they are nonobese, exhibit androgenic fat patterning and thus might be less attractive to potential mates. We see the gynaecoid form represented by ‘Venuses’ from the late Palaeolithic as well as being part of fertility rituals across different cultures. This explains the relatively consistent transcultural gynaecoid features of female attractiveness. However, there is likely to be a strong genetic element to PCOS and women with the condition do reproduce, weakening this argument considerably. Kin selection and PCOS are discussed at length elsewhere. More probable is that although PCOS confers an advantage at certain times, it is disadvantageous at others when food is more readily available. The total reproductive window is therefore reduced for women with PCOS. Alternatively, it is possible that as food supplies become increasingly buffered against seasonal or climatic fluctuations, the polymorphism has moved from being balanced to transient, with the deleterious effects of PCOS outweighing the advantages, leading to selection against individuals with a genetic predisposition to PCOS.

An attempt has been made in this paper to build on previous work, suggesting an evolutionary basis to the condition by constructing testable, detailed hypotheses. Nonetheless, the three hypotheses presented here require a greater depth of data than is currently available to support or refute them. Clearly, it is impossible to test whether PCOS existed in early hominins. Moreover, there is no good evidence that PCOS occurs spontaneously in nonhuman primates, although it has been induced under laboratory conditions. However, given sufficient resources, it should be possible to examine links between seasonality and PCOS, as populations which live under extreme seasonal pressures still exist, as do those that have few seasonal pressures. One further challenge within this framework would be assessing whether it is the ‘refeeding’ element that is crucial for restoration of
fertility. It may also be possible to examine PCOS incidence in populations with suboptimal nutrition and undertake longitudinal surveys to test the transgenerational privation hypothesis.

In conclusion, consideration of the evolution and origins of this condition might well influence future research into the site of candidate PCOS genes. Currently, most of this work is directed towards chromosome 19 and its relationship to diabetes, but it is possible that the emphasis needs to be elsewhere, perhaps the X chromosome, as the primary genes may be reproductive. Having an evolutionary perspective on PCOS might also be beneficial in clinical practice, which has not yet been explored fully. Although clinicians should guard against determinism, outlining the condition in terms of reproductive advantages in past populations might clarify the need for weight loss, including exercise as well as caloric restriction, as the front-line treatment for PCOS.

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