CHAPTER 5

SEASONALITY, CLIMATIC UNPREDICTABILITY, FOOD DEPRIVATION AND POLYCYSTIC OVARY SYNDROME

Laurence Shaw

Reproductive Medicine and Endoscopic Surgery - Obstetrics and Gynaecology

Deputy Medical Director

The London Bridge Fertility Gynaecology and Genetics Centre

One St Thomas' Street

London Bridge

London

SE1 9RY

Email: LMAShaw@aol.com

Sarah Elton

Functional Morphology and Evolution Unit

Hull York Medical School

University of Hull

Cottingham Road

Hull

HU6 7RX

UK

Email: sarah.elton@hyms.ac.uk

TABLE OF CONTENTS

5.1 Introduction

Stein and Leventhal's finding of polycystic ovaries, which they eponymously described as part of a circumscribed clinical syndrome [1], has evolved to become a nebulous entity with polycystic ovaries as a prominent component. Biochemical aspects, both endocrine and non-endocrine, have become part of a wider "polycystic ovary syndrome" (PCOS), recognised as a very common cause of anovulatory infertility [2 – 4]. Whilst the original Stein-Leventhal Syndrome described multiple ovarian cysts, obesity, hirsutism, menstrual abnormalities and amenorrhoea, symptoms of PCOS also include acne and androgenic alopecia. Obesity, when it occurs, tends to include centrally-distributed adipose tissue. These features, singly or together, are not evident in all affected women [5]. Despite this, most show a degree of insulin resistance [6]. PCOS is thus a complex endocrine disorder, for which the diagnosis is not always straightforward [6, 7]. However, many practitioners now agree that it can be defined on the basis of at least two of the following features in combination: presence of polycystic ovaries on ultrasound examination; oligo-/anovulation; clinical or biochemical evidence of androgen excess [5].

In PCOS, interference with the pituitary ovarian axis results in over-recruitment of follicles to a size of about 5mm, with no subsequent selection and maturation of a single 'leading' follicle. The resultant cohort of many 5mm follicles align themselves under the surface of the ovary but the oocytes never mature and erupt. Ovulation does not occur; luteinizing hormone (LH) remains elevated but never surges. Polycystic ovaries overproduce androgens, although some of the excess androgens observed in women with polycystic ovaries could be adrenal in origin [6]. Elevated androgen

levels in women may lead to hirsutism and menstrual irregularities [8]. High levels of androgens also appear to be related to increased risk of cardiovascular disease, high insulin levels, and Type 2 diabetes [9, 10]. In addition, hyperinsulinaemia can act to further stimulate ovarian androgen production, resulting in an interaction effect between hyperandrogenism and hyperinsulinaemia [8], although there is no evidence of a similar effect on adrenal androgens [11]. Obesity, observed in a large proportion of women with polycystic ovaries, exacerbates these endocrine disturbances. Weight loss can lead to a reduction in insulin resistance and an improvement in endocrine status that often results in resumption of ovulation [6]. In clinical practice, women with PCOS seeking fertility treatment are frequently advised that weight loss is the first avenue that should be explored [12, 13].

5.2 Prevalence Of Polycystic Ovaries And PCOS And Phenotypic Differences In The Expression Of Associated Traits

The presence of polycystic ovaries does not automatically imply the presence of the associated syndrome. Based on studies conducted in the UK and Australasia, polycystic ovaries themselves (but not necessaily PCOS) are found in over a fifth of females (see review by [5]), and do not necessarily result in diminished fertility [14]. In some populations the prevalence of polycystic ovaries has been observed to be much higher than one in five, with the highest recorded to date, over half, being in randomly-selected South Asians living in the UK [15]. Some non-randomly selected samples also show inter-population differences. Polycystic ovaries were observed in 45% of Yoruba women from western Nigeria attending a UK fertility clinic, in contrast to 11% in the infertile European women studied [16]. However, other studies

examining the prevalence of polycystic ovaries in women seeking fertility treatment recorded no differences between ethnic groups [17].

Based on UK and Australasian studies, around 1 in 12 females have polycystic ovary syndrome [5]. Although differential diagnosis of PCOS hampers rigorous inter-population comparisons, a body of evidence is accumulating that suggests variations in the prevalence of the syndrome exist across different cultural or geographic populations [4, 18 - 20; see also Table 1]. In the U.K., there appears to be a higher prevalence of PCOS in British South Asian women than in their European counterparts [4]. This is also the case in New Zealand, where Indian women with PCOS are over-represented compared to the general population [19]. An increased prevalence in Caribbean Hispanic and Mexican American women [21, 22], as well as in Aboriginal Australians [20], has also been suggested. In contrast, one study has found that Chinese women with PCOS living in New Zealand were under-represented compared to the population as a whole [19].

TABLE 1 HERE

Population-based phenotypic differences in the expression of traits associated with PCOS have also been observed. One study of women with PCOS from different populations (Japanese, Italian and U.S.) indicated that although adrenal androgen excess and insulin resistance appeared to be at similar levels in all three populations, levels of obesity and hirsutism showed considerable interpopulation variation [23]. This is probably related to proximate environmental influences as well as the biological variation observed in the general populations from which these women

came [23], with people from Japan, for example, being on the whole less hirsute than those from the Mediterranean. In some cross-population studies, however, significant endocrine differences have been observed. Mexican American women with PCOS are more insulin resistant and show higher incidences of insulin resistance than their European counterparts [24], as well as having lower circulating levels of dehydroepiandrosterone sulphate (DHEAS), an indicator of adrenal androgen production [11]. European women from Iceland have higher androstenedione, lower testosterone, less acne and are less hirsute than European women with PCOS from Boston, U.S. [25]. British South Asian women have higher fasting insulin concentrations, lower insulin sensitivity and exhibit more severe symptoms of PCOS than do UK European women [4]. Middle Eastern women with PCOS also have higher insulin levels than Western European women, independent of age and BMI [26]. In New Zealand, Maori and Pacific Island women with PCOS are most likely to be overweight and have the highest rates of insulin resistance [19].

5.3 Genetic And Developmental Predispositions To PCOS

PCOS is very likely to have a genetic basis, as it appears to run in families [27, 28] and there is greater concordance of PCOS-related traits in monozygotic than in dizygotic twins [29], although some of the evidence from twin studies is equivocal [30]. However, interpopulation differences in prevalence and phenotypic expression of PCOS also lend support to the notion that PCOS has a genetic component. Nonetheless, identifying specific genes is proving to be far from straightforward [28]. The association between the calpain-10 gene, insulin resistance and Type 2 diabetes led to research into whether it also has a link to PCOS [31, 32], but the results to date

have been inconclusive. One relatively small study identified an association between the calpain-10 112/121-haplotype combination and an increased risk (based on odds ratios) of PCOS in African Americans and Europeans [31]. A second, slightly larger, study found no robust association between the calpain-10 gene and PCOS [32]. Much larger studies might be required to detect clear links, if they exist, between the two [32]. However, the $Pro^{12}Ala$ polymorphism in the PPARγ gene might have a role in modifying the insulin resistance of European women with PCOS, as those with the Pro/Ala genotype appear to have increased insulin sensitivity compared to those with the Pro/Pro genotype [33]. However, this finding does not extend to African American women [33]. Polymorphisms of the insulin receptor substrate-1 (IRS-1) gene appear to be associated with the phenotypic expression of PCOS in some populations [34] including Europeans [35], but not Taiwanese women [36]. However, there is strong evidence for a PCOS susceptibility locus that maps close to the D19S884 dinucleotide repeat marker, linked to the insulin receptor gene on chromosome 19p13.2 [37]. On current evidence, therefore, it is likely that a small number of genes involved in regulating steroid biosynthesis and glucose homeostasis contribute to PCOS [27], although a great deal of work still remains to be done in identifying candidate genes [28].

There is also likely to be a strong developmental component to PCOS. Females with low birthweight apparently have greater chance of precocious pubarche, a risk factor for PCOS, and also the development of hyperinsulinaemia and hyperandrogenism [38], although a subsequent study on a larger cohort did not support this finding [39]. Comparison of South Asian and European women born and resident in the UK with South Asian women who live in the UK but were born in Pakistan suggests that the

relatively poor early environment experienced by first generation Pakistani immigrants to the UK is an important contributory factor in the relatively high levels of free androgens observed in these women [10]. Low birthweight has also been highlighted as an important precursor of dyslipidaemia and insulin resistance later in life [e.g. 40 – 42]. One hypothesis is that poor fetal and infant growth can promote the development of PCOS in individuals with a genetic susceptibility, especially when exposed to a nutritional environment of 'excess' later in life. It is also possible that exposure to excess androgens during development plays a central role in the development of PCOS [28]. Prenatally androgenized animal models (sheep and rhesus macaques) display many of the traits associated with PCOS in humans [43, 44]. 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 [28]. This in turn might lead to endocrine disturbance, including insulin resistance and elevated LH, and abdominal adiposity, the effects of which can be mediated or magnified by diet [28].

5.4 Evolutionary Perspective On PCOS: Seasonality And Unpredictable Environments

The strong role that genetic factors apparently play in PCOS plus its high general prevalence worldwide could indicate an evolutionary basis to the syndrome. In other words, at some point in our evolutionary history, PCOS might have been selectively advantageous, resulting in the high levels observed today. A number of authors have argued along these lines, particularly in terms of the 'thrifty genotype' [7, 45 – 47]. It is hypothesized 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 [7, 46]. 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 [45].

A similar argument has been played out for another condition of insulin resistance, type 2 diabetes. It has been suggested that modern populations, specifically the Pima and some Pacific island groups, with high levels of insulin resistance were at some point in the past subjected to environments with extremely poor food availability, possibly with feast/famine cycles [48, 49]. As with PCOS, genes that today predispose individuals to insulin resistance could have therefore conferred a selective advantage for survival, but in times of relative abundance, they cease to do this and instead result in serious health problems [48]. Long periods of food shortage during the colonizations of the Americas and Pacific have been suggested as the primary selective agent for such a 'thrifty genotype' in some populations [48, 49]. However, this explanation cannot be easily extended to another population with very high levels of insulin resistance, South Asians, who are unlikely to have experienced colonization-induced famine on the scale hypothesized for Native Americans and Pacific Islanders. Instead, it is possible that general undernutrition could have resulted in selection for individuals with 'thrifty genes' across many human populations. Comprehensive data for interpopulation differences are not available, but on current evidence it seems probable that Western Europeans, who are frequently used as a

reference in cross-population studies of insulin resistance and associated disorders, have unusually low levels of insulin resistance compared to most other human groups [50, 51]. This implies that they are better adapted than many human groups to the 'Westernized' diets and lifestyles now being adopted worldwide, although it is not clear whether this adaptation occurred recently and relatively rapidly [51] or much earlier [50].

If an evolutionary basis to conditions of insulin resistance is assumed, it is possible that adaptation to seasonality, rather than to more extended, migration-induced feast/famine periods, accounts for the high levels of PCOS evident in many populations. Much of human evolution occurred in seasonal environments, and seasonal fluctuations have the potential to be important selective pressures [52]. Seasonality has a profound effect on human biology and health, and has been correlated with changes in the incidences of a range of conditions including infectious disease, peptic ulcer, asthma, stroke and congenital anomalies [53]. Seasonal variations in fertility, birth and reproductive performance have also been observed [54, 55]. The term 'seasonality' covers a range of phenomena, including photoperiod, climate and resource availability, and it is possible that some or all of these factors contribute to differential fertility and reproduction [54, 55]. However, there appears to be a particularly close link between negative energy balance and lowered birth rates [55]. In these circumstances, birth rates might be suppressed through physiological responses to undernutrition that result in anovulation [55, 56]. In women with PCOS, however, the weight loss that accompanies a reduced energy intake, even if it is relatively modest, may well facilitate rather than impair ovulation, allowing them to

conceive at times when other women are less likely to. This could constitute a ‘food deprivation hypothesis’.

The transition between anovulation and ovulation might occur quite quickly in times of seasonal food shortage, as caloric reduction can lead to relatively rapid weight loss. In obese native Hawaiians, replacement of a Westernised diet by a traditional, relatively low calorie (1600 kCal), low fat diet led to an average weight loss of 7.8 kg over three weeks, equating to a BMI reduction of 2.6 kg/m^2 [57]. In obese subjects under severely restricted caloric regimens (between 400 – 800 kCal/day), weight losses of between 1.4 and 2.5 kg per week have been observed in both males and females, leading in some cases to a weight loss of nearly 15kg over six weeks [58]. Clinical studies of the impacts of weight loss on fertility have also demonstrated that pregnancy can occur reasonably soon after starting controlled diet and exercise programmes. In a study of obese infertile women on such a programme (around 80% of whom had PCOS), the mean weight loss was 10.2 kg, the vast majority resumed spontaneous ovulation within six months, and nearly 30% of the total sample also achieved a medically unassisted pregnancy in that time [59]. Although this study was undertaken over a six month period, other research has shown that the metabolic profile of women with PCOS can improve within four to eight weeks of starting a diet and exercise programme [60], and ovulation can occur on the loss of approximately 5.5 to 6.5 kg or 2 – 5% of previous body mass (as reviewed by [61]). In some populations, weight loss in women during the ‘hungry’ season can be as much as 5 kg, although modal values appear to be closer to 2 – 3 kg (reviewed in [55, 62]). Interestingly, greater weight loss has been seen in women with higher BMIs than in those who are more lean [62]. Women with PCOS living in traditional subsistence

societies are unlikely to reach the levels of obesity observed in developed or rapidly developing populations, but they might well have raised BMIs compared to other women in the same community. Further work is required to assess the prevalence and presentation of PCOS in such populations, as well as the phenotype of women with the condition. However, extrapolation from observations on general responses to seasonality indicate that it would be very possible for anovulatory women with PCOS living in environments with seasonal fluctuation in resource availability to lose sufficient weight to ovulate then conceive.

Conception during the 'hungry' season could have advantages and disadvantages for mother and child. In rural Gambia, infants conceived in the wet season, at the time when fertility is lowest, appeared to have lower mortality rates than those conceived at other times [55]. If this holds for other populations, and if women with PCOS are most likely to conceive when the fertility of other women is reduced, there is potentially an immediate fitness benefit associated with PCOS. By conceiving at the time of greatest food shortage, it is probable that at the most energetically-expensive time in pregnancy, the third trimester [63], there will be a reasonable supply of food, even though the most abundant period occurred in early pregnancy. In the Gambia, infants of mothers whose third trimester coincided with the wet season had lower birthweights, a risk factor for infant mortality [55], again highlighting the potential advantages of conceiving during the wet season. However, this birth timing may be disadvantageous in terms of lactation and subsequent growth into adulthood, with evidence from the Gambia tentatively indicating that females born in the dry season (between April and August) grow into lighter and smaller adults [64].

The ‘food deprivation hypothesis’ presented here relies on seasonal food shortage and consequent weight loss. However, it is likely that in many societies, food reserves are carefully managed in order to prevent severe and dramatic food shortages. Such behaviour may significantly reduce the period of time in which energy intake is well below energy expenditure, and in turn decrease any selective advantage of conception during this time. Clearly, in-depth, systematic studies are required to adequately test whether there are links between seasonality and PCOS. One alternative that nonetheless draws on food deprivation is that PCOS is an adaptation to climatic ‘unpredictability’. In areas of the world with high reported levels of PCOS, including the Indian subcontinent, parts of the Americas and Australia, indigenous populations are faced with frequent climatic unpredictability, such as drought, failure of monsoons, hurricanes, cyclones and El Niño effects. All of these can lead to severe food shortages, which in turn might impact, through the mechanisms discussed briefly above, on fertility in women with and without PCOS. Indeed, famine can have a major impact upon the fertility of a population [65], and those caused in the past by climatic events are likely to have been frequent and severe enough to act as selective pressures on humans, with one possible result being the emergence of high levels of PCOS. In addition to maintaining the population during these periods of extreme food shortage, babies born to mothers with a tendency towards insulin resistance might have a greater ability to survive famine periods. Women with gestational diabetes tend to have babies who are of above average weight at birth [66]. In one population with high levels of insulin resistance, South Asians, infants have a tendency to have low body weights but have a high proportion of adipose tissue [67]. Infant mortality is a common and significant result of famine [68, 69], so if babies are able to ‘buffer’ themselves through either a larger body mass or greater adiposity laid down during

gestation, they may have a better chance of survival. Again, the role of unpredictable climate and resulting food deprivation as a selective pressure for PCOS requires further, systematic testing, but on current evidence, it cannot be discounted that PCOS is adaptive in environments with fluctuating or unpredictable resources.

This notwithstanding, conception during periods of hunger seems paradoxical. It may be important to distinguish here between famine and chronic malnutrition, as the physiological mechanisms that regulate fertility in each of these situations differ. Famine may result in starvation amenorrhoea, in which ovulation ceases entirely as a result of either extremely low energy intake or turnover [70]. Under conditions of chronic malnutrition, however, conception is usually still possible but fertility is managed in other ways, such as through an increase in the length of time before postpartum resumption of ovarian function [70], which influences birth spacing. Thus, one question is whether having a PCOS phenotype is advantageous not in environments characterised by chronic malnutrition but in conditions that precipitate starvation anovulation. In times of constant plenty, follicular recruitment in women with PCOS is excessive. The FSH drive cannot mature such a high number and they arrest at about 5cm diameter. The total surface area of granulosa provides oestrogen feedback to the pituitary which produces LH, resulting in the characteristic hormone profile of PCOS. Weight loss in women with obese polycystic anovulation often results in ovulation, so in famine situations these phenotypes may be the first to recruit follicles in response to improving nutrition. Thus it is not starvation that stimulates ovulation in this alternative ‘re-feeding hypothesis’, but the return of food.

A third possibility is a ‘trans-generational privation hypothesis’. If a population suffers persistent, severe, yet subfatal, privation (chronic malnutrition), it would be beneficial to have an enhanced androgenic and hence anabolic state that increases the efficient use of food for protein synthesis or fat storage. Clearly, females would have greater vulnerability than males, so those women with higher endogenous androgens might be better off. Such advantages would act directly, via nutrition (as described above) and also indirectly, as their female offspring would tend towards a preferred anabolic state. This is supported by the observation that prenatally androgenised laboratory macaques develop PCOS-like traits [44]. Moreover these offspring would possess the characteristic of preferred early ovulation, outlined in the ‘re-feeding hypothesis’. However, in environments with limited resources, it must also be considered that emotional stress might interact not only with reproduction but also with the creation of androgenic states in adult women and their female offspring. Food deprivation is inherently emotional stressful, and the effects of stress might reinforce in- or sub-fertility [71]. Stress has also been shown to influence metabolic abnormalities in adults with metabolic syndrome [72]. Importantly, stressful situations, including those caused by undernutrition, can lead to increased cortisol stimulation in neonates, encouraging rapid increases in body weight which may eventually result in pre- and post-pubertal hyperandrogenism and hyperinsulinemia and an increased probability of PCOS [72]. These observations draw attention to the proximate factors that could contribute, either on their own or in combination with genetic adaptations, to the prevalence of PCOS in certain populations.

A limitation of evolutionary medicine is often the lack of testable hypotheses. Thus, it would be particularly interesting to compare the incidence of PCOS in populations

who have experienced recurrent famine with those that have not, or groups that have marked seasonal privation with those that have very little variation. Seasonal energy stress appears to have the greatest impact in India and parts of sub Saharan Africa [62], so it might be expected that if PCOS is an adaptation to seasonality, the prevalence would be highest in populations from these areas. South Asians certainly show very high levels of polycystic ovaries [15] and PCOS [4], although as the subcontinent has considerable geographic differences in the intensity of seasonal stresses, more detailed examination of the prevalence of PCOS in different regions would be advantageous, especially if viewed in the context of past population movements. Data on indigenous African populations are scarce. One of the few, albeit non-random, studies of polycystic ovaries in African women found that the prevalence of polycystic ovaries was high in infertile Yoruba women [16], although no endocrine data were reported. The Yoruba traditionally inhabit east Benin and western Nigeria, a region that Ferro-Luzzi & Branca [62, p. 161] label as having low to moderate seasonality. If these women are also found to have the associated metabolic syndrome, this observation does not necessarily support the general hypothesis that polycystic ovaries are an adaptive response to extreme seasonal resource fluctuation. Outside Africa, high levels of PCOS are reported in aboriginal Australians [20] and Mexican Americans [22]. Neither of these groups is usually thought to be under extreme seasonal resource stress, although it has been pointed out that traditional views of Aboriginal Australian subsistence might overestimate the resources available at certain times of the year and underestimate the effort expended in procuring them [73].

It is possible that the emergence of PCOS predated current population distributions or even modern humans themselves. 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 [74]. Thus, the origins of the condition (whether or not it has subsequently been advantageous in seasonal environments) might be relatively ancient. Similarly, because of steadily decreasing global temperatures and increasing aridity, seasonality is likely to have been a significant selective pressure as far back as the late Miocene and early Pliocene [52]. It is impossible to test whether PCOS existed in early hominins and if it could have conferred a benefit in the changing environments of the late Miocene, Pliocene and Pleistocene. However, whichever hypothesis is considered, primate models might shed some light on the evolutionary basis of the condition. Although prenatally androgenised laboratory macaques develop PCOS-like traits [44], to date there is no evidence for a similar syndrome in wild-living monkeys. Establishing whether 'PCOS' occurs spontaneously in non-human primates, and whether it is found in species such as baboons and macaques, and indeed other mamals, that evolved and currently live in seasonal environments, would provide an important comparative perspective on the condition in modern humans and potentially their ancestors.

5.5 Why Is PCOS Not At Even Higher Levels In Modern Populations?

Regardless of the circumstances under which high levels of PCOS evolved, it is plausible that PCOS gives reproductive benefits in environments with fluctuating resources. Women with PCOS, who generally have high androgen levels, also appear

to have greater bone mineral density [75] and muscle mass [45] than non-PCOS women. This might provide additional advantages in terms of greater capacity for physical work and endurance [45], which may be especially desirable in regions where subsistence requires considerable energy expenditure. Given these possible benefits, an obvious question is why PCOS is not found at even higher levels. 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 [76], and therefore reproductive success. Many women with PCOS, even when they are non-obese, exhibit fat patterning that is most commonly seen in males, and it has been argued that as a result of this, they might be less attractive to potential mates [76]. However, this argument is weakened considerably by the simple observation that there is likely to be a strong genetic element to PCOS and that women with the condition do reproduce. More probable is that although PCOS confers an advantage at certain times, it is disadvantageous at other times, 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. Under this model, it is possible, for example, that the prevalence of PCOS in European countries was at higher levels in the past, as has been hypothesised for type 2 diabetes [51].

5.6 Critical Analysis Of The Evolutionary Perspective On PCOS

The notion that PCOS is a manifestation of the selective pressures in our evolutionary past is an attractive one. However, despite having over forty years to test Neel's original 'thrifty genotype' hypothesis [48], formulated to account for type 2 diabetes rather than PCOS, the search for candidate 'thrifty' genes has been problematic and no consensus has yet been reached about the validity of the concept [77; see also Chapter 4]. Particular criticism has come from proponents of the 'thrifty phenotype' hypothesis, who argue for a strong developmental, rather than genetic, basis to insulin resistance [42]. However, the 'thrifty phenotype' is not without major limitations, not least the lack of solid evidence found to date, the uncritical use of birthweight as an indicator of fetal growth restriction, and the need for more sophisticated studies to elucidate patterns and mechanisms [78]. Barker [79, p. 250] argued that, under the thrifty genotype hypothesis, high levels of type 2 diabetes would be evident in south Asian populations until a more 'primitive' way of life was adopted once more, reasoning that could presumably be extended to PCOS. However, recent 'consensus' work on insulin resistance and associated conditions, including PCOS, indicates that there is an underlying genetic component which is 'primed' by proximate influences, some of the most important of which may well occur during fetal or early life [28]. This suggests that elements of 'thrifty genotype' and 'thrifty phenotype' are not mutually exclusive. In addition, by removing the selective pressure of uncertain food supplies, under an evolutionary model the PCOS polymorphism may be expected to move over time into a transient state, as the genes that predispose to conditions of insulin resistance are selected against.

This notwithstanding, one major theoretical problem with the thrifty genotype hypothesis as it is often presented for PCOS is the need to invoke group selection to explain one of the major advantages of the condition. The idea that women with PCOS are able to 'rescue' the population in times of energy shortage through losing weight, ovulating and subsequently conceiving, stresses the benefits to the group but not to the individual. Although group selection might well be more important in human evolution than is currently acknowledged [80], it remains an unpopular concept in evolutionary biology, partly due to the popularity of 'selfish gene' models and also because it is rarely or never observed in 'real' populations [81]. However, the hypothesis does not stand or fall on the validity of group selection. There might be fitness benefits to the individual in conceiving at a time when other women do not, as infant mortality might be lower, at least in some populations [55]. Interestingly, and adding weight to this, Bangladeshi babies who survived the 1974-1975 famine had significantly lower mortality in the months following the famine than would normally be expected for those age cohorts, suggesting that selection had taken place [68]. Thus, although the advantages to the group might be tangible and important, advantages to the individual are also possible under the PCOS thrifty genotype hypothesis.

In the context of evolutionary medicine, there is still much work to be done to test the thrifty genotype hypothesis, especially for PCOS. The three hypotheses presented in this chapter require more data than are currently available in order to support or refute them. 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 potential region for future

study is the highly seasonal Gambia, where decades of research into maternal health have already been undertaken. One further challenge within this framework would be assessing whether it is the 're-feeding' element that is crucial for restoration of fertility. It may be harder to test whether climatic unpredictability has influenced PCOS prevalence, as it not only requires knowledge of current climatic activity and its interaction with food supply but also needs accurate reconstruction of past climates and subsistence practises. The same is true of the 'trans-generation privation hypothesis'. This issue goes to the heart of the limitation of evolutionary medicine: that much selection has occurred in periods for which there are little or no accurate data, and under population regimes that can, at best, only be approximated.

5.7 Do Evolutionary Hypotheses Relating To PCOS Aid Clinical Practice?

The wealth of research into PCOS that has been undertaken in the past decade has shed much light on the causes and treatment of PCOS, particularly in the context of infertility. The recognition that polycystic ovaries and the related syndrome are highly prevalent has led a number of authors to suggest an evolutionary basis for PCOS [7, 45 – 47], and although the hypotheses require much more rigorous testing, the underlying idea is plausible, especially in the context of fluctuations in resource availability caused by either seasonal stresses or climatic unpredictability. However, diseases and medical conditions can have proximate and ultimate causes, and focusing on the evolutionary background to a condition may not necessarily lead to the most effective treatment and management of it.

Given that PCOS is argued to be adaptive in environments in which there are periods of extreme and sometimes rapidly-occurring food shortage, and that weight loss appears to trigger ovulation in many women with the syndrome, 'crash' dieting could be seen by some as a useful and relatively easy way of restoring fertility. Removed from the context in which PCOS evolved, however, this strategy is likely to produce a harmful cycle of 'yo-yo' weight loss and gain, which may result in increased BMI and possibly harmful metabolic complications [82]. Instead, endocrinologists managing conditions of insulin resistance recommend long-term lifestyle modification that is sustainable and achievable [60]. Overemphasising the possible evolutionary basis of PCOS might conversely lead women with the syndrome and their healthcare providers to adopt a fatalistic attitude towards its management. Concern has been raised about 'genetic determinism' in clinical treatment for the related condition, type 2 diabetes, especially with respect to marginalised and deprived Native American groups [77, 83]. There is the potential for this to occur in the context of PCOS, for example in South Asian women living in Europe and North America. South Asian women exhibit a higher prevalence of PCOS than is found in the general Western population [4], but, like other immigrant populations, they may have difficulty in accessing necessary healthcare [84]. Such barriers, whether they be socioeconomic, linguistic or cultural, could be reinforced by stressing the possible evolutionary basis to the syndrome and creating the illusion that it is not worth seeking treatment because PCOS is inevitable in South Asian women.

Nonetheless, a recognition that individuals who have a genetic predisposition to the disease can have their risk reduced through prevention of maternal malnutrition might be a useful public health strategy. This type of approach recognises the

genetic/evolutionary backdrop to the condition whilst seeking to control the proximate environmental influences that influence the development and severity of the condition. However, even the adoption of this approach is far from straightforward. Maternal size acts as a constraint on fetal size, and nutritional intervention in pregnancy may in fact lead to an increased rather than decreased risk of insulin resistance in the offspring, due to the so-called 'thin-fat baby' phenomenon [78]. This might be especially marked in South Asian infants, who have a tendency to have less muscle mass and greater fat mass – the 'thin fat baby', a body composition that predisposes to insulin resistance [67, 85]. Thus, improvement in intergenerational nutrition might well be necessary to seriously address insulin resistance [78], a management option that might also be useful in tackling PCOS.

Such are the possibly negative impacts of evolutionary hypotheses in PCOS. On the positive side, comprehension of the origins of diseases can be highly beneficial to patients. Contrary to the 'crash diet' risk is the belief by PCOS sufferers that they are "fat because they have PCOS" and that if the disease is treated then they will be thin. It has already been mentioned that the first line treatment for PCOS is weight loss. If the patient attends with the feeling that they will get a cure and thereby become thin they will react poorly to the advice they are given. With a sympathetic explanation that in another time their efficient use of food, a scarce commodity, would have made them the first to conceive, there may be less stigma and a more constructive acceptance of their need to reach an optimal BMI. Crash dieting is not recommended; it is not suggested here, after all, only that famine improves fertility in women with PCOS. Another arm to the ideas presented in this chapter is that reintroduction of food following a famine-induced anovulation initiates follicular recruitment. So,

careful explanation of this to the patient could emphasise exercise as the more helpful part of lifestyle change over and above diet.

A positive and long term benefit to evolutionary understanding is as a guide to future research, both medical and anthropological. If there is a strong belief that this is a genetically driven disease, then continued search for the genes concerned might lead to a more fundamental treatment than exists at the moment. If not actual gene therapy, it may be that the source protein might hold the key to future treatment developments. However, what is, or what are, the gene(s)? Where are they located? Do the responsible genes code for insulin resistance, lipid metabolism, follicular recruitment sensitivity, or do they work at the level of the switch for rendering follicles atretic (i.e. as part of the maturation and degeneration process)? Understanding the evolution of the disease helps in the search for the answers to these questions. From the answers will come future treatments.

5.8 Conclusions

PCOS is a nebulous and complex endocrine condition. This is reflected by the fact that its definition has changed frequently during the second half of the 20th century. Currently, possession of two characteristics is required from a list of recognised features in order to make the diagnosis. Its familial nature, the level of twin concordance and variation in different populations lend weight to a genetic basis to this condition. However it is accepted that gene expression is subject to environmental influence, including during fetal or early life. The syndrome links reproductive performance with nutrition in the form of glucose and lipid metabolism, factors at the

heart of survival. If genetics are at the core of such a common condition, the question of whether there is an evolutionary advantage to the possession of the gene or genes is inevitably raised.

Three hypotheses have been proposed in this chapter. The first concerns the observation that PCOS sufferers tend to ovulate when weight is lost. Indeed, that forms the primary treatment of the condition. Perhaps there might be an advantage for members of a population to conceive during a food shortage. The observation in the Gambia of lower mortality amongst infants conceived in the wet season, a period of food deprivation, lends weight to this. This ‘food deprivation hypothesis’ sees a positive enhancement in ovulation when food is short and as such might suggest that the primary effect of the gene is related to glucose metabolism. The second hypothesis suggests that individuals with a PCOS-like condition living in a ‘traditional’ environment would not be as well fed, even in times of plenty, as they would in an industrialised environment. In this scenario, the advantage occurs at the end of a period of food deprivation as the food source increases. These women are the first to ovulate in response to this re-feeding. An anabolic propensity for food storage is an appropriate adjuvant preparation for early pregnancy. This ‘re-feeding hypothesis’ implies that the gene might be one that drives ovarian follicular recruitment sensitivity to FSH. The third hypothesis suggests that the origin of the gene may pre-date modern humans, possibly being related to the onset of seasonal environments in the late Miocene, or the climatic fluctuations that characterised Pleistocene environments. A beneficial strategy favouring insulin resistance might have improved survival at that time. This ‘trans-generational privation hypothesis’ again suggests a gene inducing insulin resistance.

Food deprivation lies at the heart of these hypotheses, as insulin resistance buffers the individual against food shortage. Although the advantages of insulin resistance are described elsewhere in relation to type 2 diabetes mellitus, it is likely to be at its most profound if associated with follicular recruitment. Significant pressure on food resources would have been needed to favour these genes. In the case of the 'trans-generational hypothesis', the strategy might have been part of a wider suite of adaptations necessary to deal with long-term environmental change. In the case of the 'food deprivation' and 're-feeding' hypotheses, fluctuations in resource availability leading to food deprivation probably would be severe but frequent. Climatic unpredictability is one source of this, but the most regular occurrence of food deprivation is, of course, seasonality. Variability in the frequency of PCOS from population to population suggests that inhabiting seasonal environments might have contributed to selection for the PCOS genotype. Studies comparing PCOS in indigenous peoples from highly seasonal and less seasonal areas might throw some light on this. As the diagnosis is so ill-defined, negative correlations might be less relevant than positive ones.

One further question is whether the adaptation is primarily for nutritional survival with a reproductive add-on, or whether the opposite is true. Discovering where the genes are located and for which proteins they code would help to elucidate the evolution of PCOS and also aid patient education. Even if alterations in intergenerational maternal nutrition help to reduce the overall prevalence of the syndrome or severity of the symptoms, greater knowledge of the genetic and evolutionary basis to PCOS would guide future treatment strategies. Only within such

an approach does there lie a cure as opposed to the symptomatic treatment currently available.

Acknowledgements

We are very grateful to the two reviewers of this paper for their insights and suggestions.

References

1. Stein, I. F. and Leventhal, M. L., Amenorrhea associated with bilateral polycystic ovaries. *Am. J. Obs. Gyn.*, 29, 181-191, 1935.

2. Franks, S., Medical progress article: polycystic ovary syndrome, *New Engl. J. Med.*, 333, 853-861, 1995.

3. Balen, A., Pathogenesis of polycystic ovary syndrome – the enigma unravels? *Lancet*, 354, 966-967, 1999.

4. Wijeyaratne, C.N., Balen, A.H., Barth, J.H., and Belchetz, P.E. Clinical manifestations and insulin resistance (IR) in polycystic syndrome (PCOS) among South Asians and Caucasians: is there a difference? *Clin. Endocrin.*, 57, 343-350, 2002.

5. Hart, R., Hickey, M., and Franks, S., Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Pract. Res. Clin. Obs. Gyn.*, 18, 671-683, 2004.

6. De Leo, V., la Marca, A., and Petraglia, F., Insulin-lowering agents in the management of polycystic ovary syndrome, *Endocrin. Rev.*, 24, 633-667, 2003.

7. Balen, A. and Michelmore, K., What is polycystic ovary syndrome? Are national views important? *Hum. Reprod.*, 17, 2219-2227, 2002.

8. Livingstone, C. and Collison, M., Sex steroids and insulin resistance, *Clin. Sci.*, 102, 151-166, 2002.

9. Lui, Y. et al., Relative androgen excess and increased cardiovascular risk after menopause: a hypothesized relation, *Am. J. Epidem.*, 154, 489-494, 2001.

10. Pollard, T., Unwin, N.C., Fischbacher, C.M., and Chamley, J.K., Sex hormone-binding globulin and androgen levels in immigrant and Bristish-born premenopausal British Pakistani women: evidence of early life influences, *Am. J. Hum. Biol.*, 18, 741-747, 2006.

11. Kauffman, R.P., Baker, V.M., DiMarino, P., and Castracane, V.D., Hyperinsulinemia and circulating dehydroepiandrosterone sulfate in white and Mexican American women with polycystic ovary syndrome, *Fertil. Steril.*, 85, 1010-1016, 2006.

12. RCOG, Patient Information sheet http://www.rcog.org.uk/resources/public/pdf/pcos_patient_info_0106.pdf, 2005, downloaded 23/11/06.

13. ASRM, Patient Information sheet http://www.asrm.org/Patients/FactSheets/PCOS.pdf, 2005, downloaded 23/11/06.

14. Clayton, R.N. et al., How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? *Clin. Endocrin.*, 37, 127-134, 1992.

15. Rodin, DA, Bano, G., Bland, JM., Taylor, K., and Nussey, S.S., Polycystic ovaries and associated metabolic abnormalities in Indian subcontinent Asian women, *Clin. Endocrin.*, 49, 91-99, 1998.

16. Wada, I. et al., High ovarian response in Yoruba African women during ovulation indiction for assisted conception, *Hum. Reprod.*, 9, 1077-1080, 1994.

17. Kousta, E. et al., The prevalence of polycystic ovaries in women with infertility, *Hum. Reprod.*, 14, 2720-2723, 1999.

18. Diamanti-Kandarakis, E. et al., A survey of the polycystic ovary syndrome in the Greek Island of Lesbos: hormonal and metabolic profile, *J. Clin. Endocrin. Metab.*, 84, 4006-4011, 1999.

19. Williamson, K., Gunn, A.J., Johnson, N., and Milsom, S.R. The impact of ethnicity on the presentation of polycystic ovarian syndrome. *Aust. New Zeal. J. Obs. Gyn.*, 41, 202-206, 2001.

20. Davis, S.R. et al., Preliminary indication of a high prevalence of polycystic ovary syndrome in indigenous Australian women, *Gyn. Endocrin.*, 16, 443-446, 2002.

21. Solomon, C.G., The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks, *Endocrinol. Metab. Clin. North Am.*, 28, 247–263, 1999.

22. Goodarzi, M.O. et al., Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance, *Fertil. Steril.*, 84, 766-9, 2005.

23. Carmina, E. et al., Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? *Am. J. Obs. Gyn.*, 167, 1807-1812, 2002.

24. Kauffman, R.P. et al., Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations, *Am. J. Obs. Gyn.*, 187, 1362-1369, 2002.

25. Welt, C.K. et al., Defining constant versus variable phenotypic features of women with polycystic ovary syndrome using different ethnic groups and populations. *J. Clin. Endocrinol. Metab.*, 91, 4361 – 4368, 2006.

26. Al-Fozan, H., Al-Futaisi, A., Morris, D., and Tulandi, T., Insulin responses to the oral glucose tolerance test in women of different ethnicity with polycystic ovary syndrome. *J. Obs. Gyn. Can.*, 27, 33-37, 2005.

27. Franks, S. et al., The genetic basis of polycystic ovary syndrome, *Hum. Reprod.*, 12, 2641-2648, 1997.

28. Franks, S., Genetic and environmental origins of obesity relevant to reproduction, *Reprod. Biomed. Online*, 12, 526-531, 2006.

29. Vink, J.M., Sadrzadeh, S., Lambalk, C.B., and Boomsma, D.I., Heritability of polycystic ovary syndrome (PCOS) in a Dutch twin-family study, *J. Clin. Endocrinol. Metab.*, 91, 2100-2104, 2006.

30. Jahanfar, S. et al., A twin study of polycystic ovary syndrome, *Fertil. Steril.*, 63, 478–86, 1995.

31. Ehrmann, D.A. et al., Relationship of calpain-10 genotype to phenotypic features of polycystic ovary syndrome, *J. Clin. Endocrin. Metab.*, 87, 1669-1673, 2002.

32. Haddad, L. et al., Variation within the type 2 diabetes susceptibility gene calpain-10 and polycystic ovary syndrome, *J. Clin. Endocrin. Metab.*, 87, 2606-2610, 2002.

33. Hara, M. et al., Insulin resistance is attenuated in women with polycystic ovary syndrome with the $Pro^{12}Ala$ polymorphism in the PPARγ gene, *J. Clin. Endocrin. Metab.*, 87, 772-775, 2002.

34. Sir-Petermann, T. et al., G972R polymorphism of IRS-1 in women with polycystic ovary syndrome. *Diabetologia* 44: 1200-1201, 2001.

35. El Mkadem, S.A. et al., Role of allelic variants Gly972Arg of IRS-1 and Gly1057Asp of IRS-2 in moderate-to-severe insulin resistance of women with polycystic ovary syndrome, *Diabetes*, 50, 2164-2168, 2001.

36. Lin, T-C. et al., Abnormal glucose tolerance and insulin resistance in polycystic ovary syndrome amongst the Taiwanese population – not correlated with insulin receptor substrate-1 Gly972Arg/Ala513Pro polymorphism, *BMC Med. Genet.*, 7, 36, 2006.

37. Urbanek, M. et al., Candidate gene region for polycystic ovary syndrome on chromosome 19p13.2, *J. Clin. Endocrinol. Metab.*, 90, 6623-6629, 2005.

38. Ibanez, L., Potau, N., Francois, I., and de Zegher, F., Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth, *J. Clin. Endocrin. Metab.*, 83, 3558-3562, 1998.

39. Laitinen, J. et al., Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms, *Int. J. Obes.*, 27, 710-715, 2003.

40. Hales, C.N. et al., Fetal and infant growth and impaired glucose tolerance at age 64, *BMJ*, 303, 1019-1022, 1991.

41. Barker, D.J.P. et al., Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth, *Diabetologia*, 36, 62-67, 1993.

42. Hales, C.N. and Barker, D.J.P., Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis, *Diabetologia*, 35, 595-601, 1992.

43. Birch, R., Robinson, J.E., Hardy, K., and Franks, S., Morphological differences in preantral follicle distribution between normal and androgenised ovine ovaries, *Endocr. Abst.*, 2, P74, 2001.

44. Abbott, D.H., Foong, S.C., Barnett, D.K., and Dumesic, D.A., Nonhuman primates contribute unique understanding to anovulatory infertility in women, *Inst. Lab. Anim. Resour. J.*, 45, 116-131, 2004.

45. Holte, J., Polycystic ovary syndrome and insulin resistance: thrifty genes struggling with over-feeding and a sedentary lifestyle? *J. Endocrin. Invest.*, 21, 589-601, 1998.

46. Gleicher, N., Barad, D., An evolutionary concept of polycystic ovarian disease: does evolution favour reproductive success over survival? *Reprod. Biomed. Online*, 12, 587-589, 2006.

47. Wood, L.E.P., Obesity, waist-hip ratio and hunter-gatherers, *BJOG*, 113, 1110-1116, 2006.

48. Neel, J.V., Diabetes mellitus: a ‘thrifty’ genotype rendered detrimental by ‘progress’? *Am. J. Hum. Genet.*, 14, 353-362, 1962.

49. Bindon, J.R. and Baker, P.T., Bergmann’s rule and the thrifty genotype, *Am. J. Phys. Anthropol.*, 104, 201-210, 1997.

50. Baschetti, R., Diabetes susceptibility. *CMAJ*, 174, 1597-1598, 2006.

51. Gerstein, H.C. and Waltman, L., Why don’t pigs get diabetes? Explanations for variations in diabetes susceptibility in human populations living in a diabetogenic environment, *CMAJ*, 174, 25-26, 2006.

52. Foley, R.A., The influence of seasonality on hominid evolution, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 17-37.

53. Johnston, F.E. (1993). Seasonality and human biology, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 5-16.

54. Rosetta, L., Seasonality and fertility, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 65-75.

55. Ulijaszek, S.J. (1993). Seasonality of reproductive performance in rural Gambia, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 76-88.

56. Rosetta, L., Biological aspects of fertility among Third World populations, in *Fertility and Resources*, Landers, J. and Reynolds, V., Eds., Cambridge University Press, Cambridge, 1990, 18-34.

57. Shintani, T., Hughes, C.K., Beckham, S., and O'Connor, H.K., Obesity and cardiovascular risk intervention through the *ad libitum* feeding of traditional Hawaiian diet, *Am. J. Clin. Nutr.*, 53, 1647S-1651S, 1991.

58. Saris, W.H.M., Very-low-calorie diets and sustained weight loss, *Obstet. Res.*, 9, 295S-301S, 2001.

59. Clark, A.M. et al., Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment, *Hum. Reprod.* 13, 1502-1505, 1998.

60. Norman, R.J., Davies, M.J., Lord, J., and Moran, L.J. The role of lifestyle modification in polycystic ovary syndrome, *Trends Endocrin. Metab.*, 13, 251-257, 2002.

61. Moran, L.J. and Norman, R.J. The obese patient with infertility: a practical approach to diagnosis and treatment, *Nutr. Clin. Care*, 5, 290-297, 2002.

62. Ferro-Luzzi, A. and Branca, F., Nutritional seasonality: the dimensions of the problem, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 149-165.

63. Butte, N.F. et al., Energy requirements during pregnancy based on total energy expenditure and energy deposition, *Am. J. Clin. Nutr.*, 79, 1078-1087, 2004.

64. Cole, T.J., Seasonal effects on physical growth and development, in *Seasonality and Human Ecology*, Ulijaszek, S.J. and Strickland, S.S., Eds., Cambridge University Press, Cambridge, 1993, 89-106.

65. Dyson, T., On the demography of South Asian famines: Part I, *Populat. Stud.*, 45, 5-25, 1991.

66. Gillman, M.W. et al., Maternal gestational diabetes, birth weight and adolescent obesity, *Pediatrics*, 111, e221-e226, 2003.

67. Yajnik, C.S. et al., Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study, *Int. J. Obes.*, 27, 173-180, 2002.

68. Razzaque, A., Alam, N., Wai, L., and Foster, A., Sustained effects of the 1974-5 famine on infant and child mortality in a rural area of Bangladesh, *Populat. Stud.*, 44, 145-154, 1990.

69. Scott, S., Duncan, S.R., and Duncan, C.J., Infant mortality and famine – a study in historical epidemiology in northern England, *J. Epidem. Comm. Health*, 49, 245-252, 1995.

70. Ellison, P.T. Energetics and reporductive effort. *Am. J. Hum. Biol.*, 15, 342-351, 2003.

71. Schenker, J.G., Meirow, D., Schenker, E., Stress and human reproduction, *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 45, 1-8, 1992.

72. Diamanti-Kandarakis, E. and Economou, F., Stress in women: metabolic syndrome and polycystic ovary syndrome, *Ann. N.Y. Acad. Sci.*, 1083, 54–62, 2006.

73. Ulijaszek, S.J., Potential seasonal ecological challenge of heat strain among Australian Aboriginal people practicing traditional subsistence methods: a computer simulation, *Am. J. Phys. Anthropol.*, 116, 236-245, 2001.

74. Barnett, D.K. and Abbott, D.H., Reproductive adaptations to a large-brained fetus open a vulnerability to anovulation similar to polycystic ovary syndrome, *Am. J. Hum. Biol.*, 15, 296-319, 2003.

75. Yuksel, O. et al., Relationship between bone mineral density and insulin resistance in polycystic ovary syndrome, *J. Bone Miner. Metab.*, 19, 257-262, 2001.

76. Kirchengast, S., Evolutionary and medical aspects of body composition characteristics in subfertile and infertile women, *Acta Med. Lituanica*, 12, 22-27, 2005.

77. Fox, D. The famished road, *New Scientist*, 2212, 38-43, 1999.

78. Adair, L.S. and Prentice, A.M., A critical evaluation of the fetal origins hypothesis and its implications for developing countries, *J. Nutr.*, 134, 191-193, 2004.

79. Barker, D.J.P., The fetal origins of coronary heart disease and stroke: evolutionary implications, in *Evolution in Health and Disease*, Stearns, S.C., Ed., Oxford University Press, Oxford, 1999, 246-250.

80. Wilson, D.S. and Sober, E. Reintroducing group selection to the human behavioural sciences. *Behav. Brain Sci.*, 17, 585-608, 1994.

81. Zahavi, A., Is group selection necessary to explain social adaptations in microorganisms? *Heredity*, 94, 143-144, 2005.

82. Kajioka, T., Tsuzuku, S., Shimokata, H., and Sato, Y., Effects of intentional weight cycling on non-obese young women, *Metabolism*, 51, 149-154, 2002.

83. Benyshek, D., Type 2 diabetes and fetal origins: the promise of prevention programs focusing on prenatal health in high prevalence Native American communities, *Hum. Organiz.*, 64, 192-200, 2005.

84. Choudhry, U.K. et al., Health promotion and participatory action research with South Asian women, *J. Nurs. Scholar.*, 34, 75-81, 2002.

85. Yajnik, C.S. et al., Adipocity and hyperinsulinaemia in Indians are present at birth, *J. Clin. Endocrinol. Metab.*, 87, 5575-5580, 2002.

	Population	% prevalence	Reference	Notes
PCO	General population (Western)	21-23%	Sources cited in [5]	
	British South Asian	52%	[15]	
PCOS	General population (Western)	8%	[5]	
	European New Zealanders	In proportion to general population	[19]	
	Maori New Zealanders	In proportion to general population	[19]	
	Pacific Island New Zealanders	In proportion to general population	[19]	
	Chinese New Zealanders	Under-represented	[19]	
	Indian New Zealanders	Over-represented	[19]	
	Aboriginal Australians	26%	[20]	Preliminary data
	Mexican Americans	13%	[22]	Self-reported
	Greeks (Lesbos)	7%	[18]	

Table 1: Prevalence of polycystic ovaries (PCO) and polycystic ovary syndome (PCOS) in different populations. Polycystic ovaries can be present without the associated syndrome. Current consensus on the diagnosis of polycystic ovary syndrome relies on the presence of at least two of the following in combination: identification of polycystic ovaries on ultrasound; oligo-/anovulation; biochemical evidence of androgen excess [5]. However, since the condition is nebulous, diagnoses have been made on the basis of other criteria, so the data reported here are not necessarily internally consistent or directly comparable.