Hypothesis

An evolutionary concept of polycystic ovarian disease: does evolution favour reproductive success over survival?

Dr Norbert Gleicher founded the Centre for Human Reproduction (CHR) in 1981. He is a graduate of Tel Aviv Medical School in Israel and completed his residency at Mount Sinai School of Medicine in New York. Dr Gleicher has published hundreds of scientific papers and book chapters in the areas of reproductive endocrinology and infertility, and high risk obstetrics. He has edited some of the most prestigious textbooks in these specialties and is also editor-in-chief of two scientific journals. Dr Gleicher divides his time between CHR's New York and Chicago practices and serves as Medical Director of CHR-NY.

Dr Norbert Gleicher

Norbert Gleicher[1,2,3], David Barad[1,2]
[1]Center for Human Reproduction, 21 East 69th Street, New York, NY 10021, USA; [2]Foundation for Reproductive Medicine, Chicago, IL, USA
[3]Correspondence: Tel. +1 212 994 4400; e-mail: ngleicher@thechr.com

Abstract

Polycystic ovarian disease (PCOD) is currently considered as possibly the most frequent cause of female infertility. It is also closely associated with syndrome XX, which, in turn, is closely linked with premature and excessive mortality. Considering these adverse effects on reproductive success and human survival, the evolutionary survival of PCOD, itself considered by many to be a genetically transmitted condition, would, on first glance, appear surprising, since evolution usually discriminates against both of these traits. However, an analysis of some recently reported characteristics of the condition calls for the reconsideration of PCOD as a condition which, from an evolutionary viewpoint, favours decreased reproductive success. Indeed, the reported observations that patients with PCOD will resume spontaneous ovulation with even relatively minor weight loss, and experience later menopause than controls, suggests exactly the opposite. Under an evolutionary concept, PCOD can thus be seen as a 'fertility storage condition' which in fact favours human reproductive success and allows the human species to maintain fertility even during adverse environmental circumstances, such as famines.

Keywords: *anovulation, infertility, polycystic ovarian disease*

Introduction

Polycystic ovarian disease (PCOD) is considered by many to be the most frequent cause of female infertility. Its prevalence within populations of different ethnicity varies. However, with practically all racial backgrounds, the condition can be found to be highly prevalent (Knockenhauer *et al*., 1998; Kousta *et al*., 1999).

PCOD has in many ways remained an enigma. The condition is clearly familial in inheritance (Lunde *et al*., 1989), but a precise genetic definition has been lacking. Investigators have, more recently, suggested a Mendelian inheritance pattern for at least some affected patients (Govind *et al*., 1999). The consensus has been that PCOD represents not only one condition but, most likely, the end stage of many different aetiologies. Some authorities have therefore suggested that the terminology of PCOD be abandoned and in its place a condition of persistent anovulation, including specific clinical manifestations, such as insulin resistance, hyperinsulinaemia and hyperandrogenism, be considered (Speroff *et al*., 1999).

As a consequence of an unprecedented obesity epidemic which is sweeping the world, the prevalence of PCOD may be on the rise (Ehrman, 2005). Yet, since the condition is so highly heterogeneous, and may be caused by different underlying aetiologies, its clinical presentation can vary to a significant degree. Amongst various associations, PCOD is clinically characterized in many patients by an increased risk of developing the so-called metabolic syndrome X, which includes obesity, insulin resistance and diabetes mellitus, hypercoagulability and hyperlipidaemia, together with hypertension and atherosclerotic heart disease. The syndrome is also strongly associated with premature, and overall increased, mortality. The term syndrome

XX has been suggested for the clinical association with PCOD (Ehrman, 2005). As noted before, PCOD is, of course, also characterized by anovulation and infertility (Speroff *et al.*, 1999; American College of Obstetrics and Gynecology, 2002).

It has previously been suggested that infertility, from an evolutionary viewpoint, may be seen as Nature's way to minimize the genetic transmission into future generations of undesirable medical traits and/or conditions (Gleicher, 2003). Infertility, in conjunction with PCOD, would, of course, prevent the inheritance of the detrimental effects of the metabolic syndrome. This kind of evolutionary viewpoint also allowed speculation that, as a consequence of improved treatment outcomes with modern infertility care, an increase in the prevalence of diabetes mellitus (and other metabolic syndrome X-related abnormalities) may be witnessed in future generations, which, indeed, already appears to be borne out by epidemiological data worldwide (Gleicher, 2003).

One of the most intriguing questions raised by such an evolutionary concept is why PCOD has been able to maintain such a high prevalence, worldwide, over thousands of years. As a condition closely linked to the metabolic syndrome X, and therefore to premature and increased mortality, one would expect evolution to select aggressively *against* such a genetic predisposition.

Reproductive success versus death

Evolution traditionally favours reproductive success over continuity of life. This means, when having to make a choice, Nature will value the creation of new over the maintenance of old life. With PCOD being widely considered a condition that causes infertility, it, on first glance, would *not* appear to qualify as supportive of reproductive success. Consequently, evolution should have in all ethnic populations selected against its survival.

A more careful review of recent literature may, however, lead to some rethinking of this premise. In the process, it may also result in a better understanding of PCOD as a very common medical condition in humans.

PCOD is, of course, characterized by the formation of large numbers of small follicles which generally fail to ovulate spontaneously (American College of Obstetrics and Gynecology, 2002; Ehrman, 2005). The increase in small size follicles has, in part, been suggested to be the consequence of high androgen concentrations which sensitize FSH receptors (Franks *et al.*, 2000). Such a mechanism is also supported by the recent observation that exogenous administration of androgens to older women can increase oocyte yield and will convert the ovary sonographically into a PCOD-like appearance (Barad and Gleicher, 2005).

PCOD patients, in principle, thus produce increased oocyte yields in comparison with other women; however, because of infrequent ovulation, this increase in oocyte production does not translate into enhanced fertility. In fact, as is known, it frequently translates phenotypically into infertility. Yet, anovulation in many PCOD patients is closely linked to obesity and even a rather minor weight loss can lead to spontaneous ovulation in previously anovulatory women (American College of Obstetrics and Gynecology, 2002).

PCOD can therefore, from an evolutionary point of view, be seen as a 'fertility storage condition', which will guarantee survival of the species even during periods of distress and famine.

The hypothesis can be seen as a conceptual cousin of the so-called thrifty phenotype hypothesis, first proposed in 1982, which suggested that the epidemiological association between poor fetal and infant growth and later development of type 2 diabetes mellitus (and the metabolic syndrome) are the consequence of poor nutrition in early life which permanently affects the individual's glucose–insulin metabolism (Hales and Barker, 2001). At the same time these two hypotheses are, however, also distinctively at variance.

In support of this hypothesis, it has been recently suggested that women with PCOD demonstrate later menopause than controls (Nikolalaou and Gilling-Smith, 2004). Since hard data confirming this fact are still lacking, any confirmation of later menopause in PCOD would greatly strengthen the hypothesis because it would further suggest that PCOD expands the potential fertile, reproductive years for affected women, and such an expansion, once again, has to be seen as an overall fertility-enhancing characteristic of PCOD which, in adverse times, clearly benefits the survival of the species.

Even though widely seen as a condition of infertility and, indeed, in most text books quoted as possibly the most frequent cause of female infertility (Speroff *et al.*, 1999), paradoxically, in an evolutionary sense, PCOD may therefore represent exactly the opposite: it may be a principal guarantor of reproductive success for the human species.

As society prospers (and women gain weight), endogenous androgens in women increase. Based on their hormonal effects on ovaries (Franks *et al.*, 2000), women may then indeed become temporarily infertile due to anovulation. Historically, such periods of overabundance rarely lasted for long. Indeed, frequently they were followed by famines. Even only minor weight loss, as the infertility literature well demonstrates, will then often reverse a PCOD patient's anovulation and return her fertility (American College of Obstetrics and Gynecology, 2002).

Paradoxically, PCOD may therefore only very recently, as a consequence of better economic conditions, have become a high prevalence condition, associated with infertility. Indeed, this may be the principal explanation for why evolution has not eliminated the condition and why it actually appears to be increasing in prevalence. This concept also explains why evolution would allow a condition, which so obviously reduces life expectancy, to survive at such a high prevalence. When given the choice, Nature always favours successful reproduction over survival. PCOD appears to represent only one, amongst many, example of this principle.

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