Review Article

Could the theory of chaos contribute to the interpretation of pathogenesis of polycystic ovary syndrome?

D. K. Panidis, D. H. Rousso, A. I. Kourtis, K. V. Papathanasiou

Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki (Greece)

Summary

Polycystic ovary syndrome (PCOS) is a syndrome involving defects in primary cellular control mechanisms that result in the expression of chronic anovulation and hyperandrogenism. In this syndrome the relation between the various parameters is of particular interest. These relations constitute the cornerstone of the pathogenesis of PCOS. The fact that the pathogenesis of the PCOS has not yet been clarified, despite the plethora of relative information, may be the result of a general way of thinking in the interpretation of several scientific data, and especially those that refer to biochemical phenomena. The use of the various models of the theory of chaos, that permits a concrete approach for the interpretation of data, may constitute an optional procedure for the future understanding of the association of different parameters and their disturbances in the pathogenesis of PCOS.

Key words: PCOS; Pathogenesis of PCOS; Theory of chaos.

Introduction

Polycystic ovary syndrome is a syndrome involving defects in primary cellular control mechanisms that result in the expression of chronic anovulation and hyperandrogenism. This syndrome has for years been one of the most controversial entities in gynecological endocrinology. Since the initial report of Stein and Leventhal [1], our knowledge of the endocrine mechanism underlying the clinical signs of the syndrome is still fragmentary, incomplete and often confusing [2].

PCOS is a familial condition. Clinical genetic studies have pointed to an autosomal dominant mode of inheritance, but a complex trait with an oligogenic basis seems more likely. Evidence has been found, so far, for the involvement of two key genes in the etiology of PCOS. The results of both linkage and association studies suggest that the steroid synthesis gene CYP11α and insulin VNTR regulatory polymorphism are important factors in the genetic basis of PCOS and may explain, in part, the heterogeneity of the syndrome. Thus, differences in expression of CYP11α could account for variation in androgen production in women who have polycystic ovaries. It is postulated that those subjects carrying class III alleles at the insulin gene VNTR locus are more likely to be hyperinsulinemic and to suffer from menstrual disturbances, and may be at higher than normal risk of NIDMM [3].

Three major pathophysiologic hypotheses have been proposed to explain the clinical findings of PCOS related to three major laboratory findings. The three interlinked and not necessary mutually exclusive hypotheses are as follows: (a) *The LH Hypothesis:* A primary neuroendocrine defect leading to exaggerated LH pulse frequency and amplitude results in ovarian hyperandrogenism and anovulation. (b) *The Insulin Hypothesis:* A unique defect in insulin action leading to hyperinsulinemia results in excess androgen secretion and anovulation. (c) *The Ovarian Hypothesis:* A primary defect of sex steroid synthesis or metabolism results in exaggerated ovarian androgen secretion and anovulation [4].

A fourth hypothesis for a primary defect at the level of the ovary comes from the classic polycystic ovarian morphology seen histologically or by pelvic ultrasonography. Although the presence of many small follicles with a high androgen to estrogen ratio was first thought to represent a high rate of follicular atresia in polycystic ovaries, recent studies have demonstrated that granulossa cells are viable and able to respond to FSH

stimulation with normal increases in estradiol production. Thus, new evidence has arisen that FSH activity is somehow blocked at the ovarian level [4].

Polycystic ovary syndrome is a syndrome in which the relation between the various parameters is of particular interest. Thus, an increase of the LH/FSH ratio, bioactive/immunoactive LH, estrone/estradiol, and intraovarian androgens/intra-ovarian estrogens, as well as a decrease in the maximum anteroposterior diameter of the uterine fundus/longitudinal diameter of the larger ovary, significantly contribute to the diagnostic approach of the syndrome.

The above relations constitute the cornerstone of the pathogenesis of PCOS; for example, it is well known that wedged resection of the ovaries in the past, and ovarian electrocautery nowadays, have an obvious therapeutic effect in most PCOS cases [5]. The only possible explanation for this therapeutic result is precisely an alteration in the relation between the various parameters, which is achieved through these interventions.

Science does not try to explain, hardly even tries to interpret, and mainly makes models. By a model a mathematical construct is intended, which, with the addition of certain verbal interpretations, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.

The paragon of a complex dynamical system and to many scientists, therefore, the touchstone of any approach to complexity is the human body. No object of study available to physicists offers such a cacophony of counterrhythmic motion on scales from macroscopic to microscopic: motion of muscles, of fluids, of currents, of fibers, of cells. No physical system has lent itself to such an obsessive branch of reductionism: every organ has its own microstructure and its own chemistry. In the 1980s chaos brought to life a new kind of physiology, built on the idea that mathematical tools could help scientists understand global complex systems independent of local detail. Researchers increasingly recognized the body as a place of motion and oscillation, and they developed methods of listening to its variegated drumbeat. They studied chaos in respiratory disorders. They explored feedback mechanisms in the control of red and white blood cells. Cancer specialists speculated about periodicity and irregularity in the cycle of cell growth. Psychiatrists explored a multidimensional approach to the prescription of antidepressant drugs. But surprising findings about one organ dominated the rise of this new physiology, and that was the heart, whose animated rhythms, stable or unstable, healthy or pathological, so precisely measured the difference between life and death.

Ordinarily the eye is a remarkably smart instrument. A healthy person's eyes stay locked on moving targets without the least conscious thought; moving images stay frozen in place on the retina. But a schizophrenic's eyes jump about disruptively in small increments, overshooting or undershooting the target and creating a constant haze of extraneous movements. No one knows why. Some physicists formed a hypothesis and made a modest model. They thought in the crudest possible way about the mechanics of the eye and wrote down an equation. There was a term for the amplitude of the swinging pendulum and a term for its frequency. There was a term for the eye's inertia. There was a term for damping, or friction. And there were terms for error correction, to give the eye a way of locking in on the target. In the model, the erratic behavior had nothing to do with any outside signal. It was an inevitable consequence of too much nonlinearity in the system. A nonlinearity that could either stabilize the system or disrupt it, depending on whether the nonlinearity was weak or strong, might correspond to a single genetic trait. Periodic oscillations, aperiodic oscillations, all sorts of dynamical behavior could be found in the data by anyone who cared to go back and apply the tools of chaos.

Physiologists have begun to see chaos as health. It has long been understood that nonlinearity in feedback processes serves to regulate and control. Simply put, a linear process, given a slight nudge, tends to remain slightly off track. A nonlinear process, given the same nudge, tends to return to its starting point. Some psychiatrists went even further on the role of chaos in physiology. "Is it possible that mathematical pathology, i.e. chaos, is health? And that mathematical health, which is the predictability and differentiability of this kind of a structure, is disease?" The discoveries of chaos dictate a shift in clinical approaches to treating psychiatric disorders. By any objective measure, the modern business of "psychopharmacology" – the use of drugs to treat everything from anxiety and insomnia to schizophrenia itself – has to be judged a failure.

Modeling any one piece of the heart's behavior would strain a super computer; modeling the whole interwoven cycle would be impossible. Only in the mid-1980s, when some mathematicians applied new

computer modeling techniques to the problem, did the design of heart valves begin to take full advantage of available technology. Their computer made motion pictures of a beating heart, two-dimensional but vividly recognizable. Even subtler, and far deadlier, was the problem of arrhythmias. Ventricular fibrillation causes hundreds of thousands of sudden deaths each year. At autopsy the muscle tissue may reveal no damage at all. That is one reason chaos experts believed that a new, global approach was necessary: the parts of a fibrillating heart seem to be working, yet the whole goes fatally awry. Fibrillation is a disorder of a complex system, just as mental disorders – whether or not they have chemical roots – are disorders of a complex system. Why should the laws of chaos apply to the heart, with its peculiar tissue-cells forming interconnected branching fibers, transporting ions of calcium, potassium and sodium? Scientists carried out one of the most talked-about lines of research in the whole short history of nonlinear dynamics. They summed up their findings this way in *Science* in 1981: "Exotic dynamic behavior that was previously seen in mathematical studies and in experiments in the physical sciences may in general be present when biological oscillators are periodically perturbed" [6].

Many other scientists began to apply the formalisms of chaos to research in artificial intelligence. The dynamics of systems wandering between basins of attraction, for example, appealed to those looking for a way to model symbols and memories. A physicist thinking of *ideas* as regions with fuzzy boundaries, separate yet overlapping, pulling like magnets and yet letting go, would naturally turn to the image of a phase space with "basins of attraction". Such models seemed to have the right features: points of stability mixed with instability, and regions with changeable boundaries. Their fractal structure offered the kind of infinitely self-referential quality that seems so central the mind's ability to bloom with ideas, decisions, emotions, and all the other artifacts of consciousness. With or without chaos, serious cognitive scientists can no longer model the mind as a static structure. They recognize a hierarchy of scales, from neuron upward, providing an opportunity for the interplay of microscale and macroscale so characteristic of fluid turbulence and other complex dynamical processes. A pattern born amid formlessness: that is biology's basic beauty and its basic mystery. Life sucks order from a sea of disorder.

The fact that the pathogenesis of polycystic ovary syndrome has not yet been clarified, despite the plethora of relative information, may be the result of a general way of thinking in the interpretation of several scientific data, and especially those that refer to biochemical phenomena. The dominant model today can be described as "a detailed study of the tree and the concomitant loss of the forest". Aerial photography has solved the problem as far as the "forest" is concerned. It seems likely that, from the mid seventies, there is a corresponding procedure for the interpretation of complex phenomena, which could be used in the study of normal or abnormal folliculogenesis. This corresponding procedure is the theory of chaos that has already led to the inference of remarkable conclusions in other sections of biomedicine, e.g., disturbances of ocular movements in schizophrenia and disturbances of cardiac rhythm [7]. The use of the various models of the theory of chaos, that permits a concrete approach for the interpretation of data, may constitute an optional procedure for a future understanding of the association of different parameters and their disturbances in the pathogenesis of polycystic ovary syndrome.

References

[1] Stein I.F., Leventhal M.L.: "Amenorrhea associated with bilateral polycystic ovaries". *Am. J. Obstet. Gynecol.,* 1935, *29,* 181.
[2] Insler V., Lunenfeld B.: "Pathophysiology of polycystic ovarian disease: new insights". *Hum. Reprod.,* 1991, *6,* 1025.
[3] Franks S., Gharani N., Waterworth D., Batty S., White D., Williamson R., McCarthy M.: "Current developments in the molecular genetics of the polycystic ovary syndrome". *Trends. Endocrinol. Metab.,* 1998, *9,* 51.
[4] Taylor A.: "Polycystic ovary syndrome". *Endocrinol. Metab. Clin.,* 1998, *27,* 877.
[5] Gjonaess H.: "Ovarian electrocautery in the treatment of women with polycystic ovary syndrome (PCOS)". *Acta Obstet. Gynecol. Scand.,* 1994, *73,* 407.
[6] Guevara R., Glass L., Shrier A.: "Phase locking, period-doubling bifurcations, and irregular dynamics in periodically stimulated cardiac cells". *Science,* 1981, *214,* 1350.
[7] Gleick J.: "Inner Rhythms". In: Chaos. Viking Penguin eds., Portland, 1998, 273.

Address reprint requests to:
D. ROUSSO, M.D.
46-48, Mitropoleos Street
54623 Thessaloniki (Greece)