Menstruation, Perimenopause, and Chaos Theory

Paula S. Derry, PhD and Gregory N. Derry, PhD

This article first appeared in *Perspectives in Biology and Medicine*, vol. 55, no. 1 (Winter 2012), pages 26-42, Copyright © **2012** Johns Hopkins University Press.

ABSTRACT

This article argues that menstruation, including the transition to menopause, results from a specific kind of complex system, namely, one that is nonlinear, dynamical, and chaotic. A complexity-based perspective changes how we think about and research menstruation-related health problems and positive health. Chaotic systems are deterministic but not predictable, characterized by sensitivity to initial conditions and strange attractors. Chaos theory provides a coherent framework that qualitatively accounts for puzzling results from perimenopause research. It directs attention to variability within and between women, adaptation, lifespan development, and the need for complex explanations of disease. Whether the menstrual cycle is chaotic can be empirically tested, and a summary of our research on 20- to 40-year-old women is provided.

Introduction

Theoretical paradigms, the frameworks within which thinking occurs, never capture the complexity of reality and are necessarily selective. Factors most important to understanding the phenomenon in question will be included and explained in a coherent, meaningful manner. But facts and ideas inconsistent with underlying assumptions may then appear less plausible, and, indeed, may be systematically overlooked or ignored. Health-related paradigms have practical importance because they influence what counts as a fact, what theories appear plausible and important, what research questions should be pursued, and, therefore, what health-care interventions make sense. They also contain implicit underlying ideas about broader issues, such as the nature of the life course and the definitions of health and disease.

The dominant paradigm for medical care, the biomedical model of disease, focuses attention on discrete causal agents. This approach is exemplified by the germ theory, in which disease is "caused" by a pathogen. While no clinician would be surprised if two people were exposed to a pathogen and only one became ill, the factors beyond microbes that contribute to disease—physical susceptibility, lifestyle, psychosocial factors, environment, and so forth—are not incorporated into the biomedical model in a coherent conceptual perspective. The question is how to create a broader paradigm in which these other factors are cohesive, meaningful components, or in which conceptual bridges to them exist.

Some authors have suggested that a systems/complexity theory approach might provide a broader paradigm useful for understanding health and illness. The fundamental starting point here is that certain systems cannot be understood by breaking them down into their constituent parts. Instead, since the interacting parts of the system work as a whole, we must understand the characteristics and dynamics of the system as a whole. An approach of this sort calls attention to such things as multiple causes of disease, open systems, multiple interactions in a nonlinear modality, and the importance of time- or space-sensitive factors. One particular line of investigation in the general area of complexity science has focused on nonlinear dynamics and chaos. Recently, Varela, Ruiz-Esteban, and Mestre de Juan (2010) argued that chaos theory and fractal geometry lead to novel concepts of the pathophysiology underlying disease and, more broadly, the fundamental nature of disease (disease as a loss of complexity rather than disorder) and homeostasis. Others have similarly argued that chaos theory provides novel, useful approaches to health science that alter underlying paradigms (e.g., Ahn et al. 2006; Goldberger 2006; Higgins 2003). Of course, the suggestion is not that chaos theory replaces traditional work, but that different paradigms and methodologies will be relevant in different contexts and to answer different questions.

This article argues that chaos theory provides an important paradigm for explicating the nature of the menstrual cycle, especially perimenopause. It provides both a plausible explanation of confusing and unexpected endocrinological research results and a testable model of the physiological dynamics underlying the menstrual cycle. A chaos theory paradigm changes underlying concepts of what pathology is, distinctions between health and disease (for example, between pathology and normal variability), and broader underlying issues (for example, the relevance of individual differences and adaptation). The framework also focuses attention on the need to consider multiple factors and to regard those factors as intrinsically interconnected. Conceptual bridges can be made between physiology and its context (like life span development) when menstruation is regarded as the outcome of an open, actively adaptive system.

This article draws implications for understanding the nature of the healthy menstrual

cycle, and what might constitute pathology relative to this healthy baseline. We relate these considerations to general underlying concepts of the nature of the human life course, adaptation, and the role of variability. The current paradigm, focusing on homeostasis, closed systems, and regularly recurring cycles as underlying biological health, makes a broader discussion of health and illness more difficult. Menstruation and menopause in particular have had unclear boundaries between health and illness, as exemplified in questions such as when changes in the bleeding pattern require treatment. In contrast, chaos theory highlights the fact that variability in and of itself may not be an accurate measure of pathology—in fact, the opposite may be the case.

The format of the paper is as follows. We first provide an overview of the characteristics of chaotic systems and a brief review of research on the transition to menopause. We then describe our rationale for believing that the transition to menopause is the outcome of a chaotic process. We discuss the implications of this alternate framework for how we think about the underlying nature of perimenopause and, more broadly, for understanding menstruation throughout the lifespan. This leads to a discussion of how a complexity paradigm casts light on relationships between menstruation and health issues. While the emphasis of the paper is theoretical, presenting a plausible case for chaos theory and its implications, we also briefly summarize our published results providing empirical evidence that the menstrual cycle is the outcome of a chaotic system in 20- to 40-year-old women, along with our preliminary work on perimenopausal women.

An Introduction to Chaos Theory

Chaos theory calls attention to the variety that exists in nature. Certain systems generate

variability rather than predictable results, but the variability has specific characteristics. With regard to the menstrual cycle, for example, this could mean that the small differences commonly found in the number of days between one cycle and the next are not random fluctuations, or responses to environmental changes like diet, as envisioned by more traditional approaches. Instead, these differences may reflect the intrinsic working of a system that by its nature generates variability.

Reductionism, Determinism, and Linearity

Traditional approaches to understanding the biology of menstruation reflect basic ideas about the nature of scientific inquiry and the vision of reality that underlies it. One core assumption is reductionism, the idea that understanding consists of breaking a system into its constituent parts (such as hormones), finding cause-and-effect relationships (such as the specific effect of a specific hormone), and adding together all of the results thus discovered. The units are assumed to be independent of each other; in a complicated phenomenon, many cause-and-effect relationships will be studied, and the results of these studies added together to finally find a picture complex enough to explain the whole. Another core idea is determinism: scientists find patterns in nature and can make accurate predictions because an event is caused by certain conditions that cannot lead to any other outcome. The relationships found in scientific study are frequently taken to be linear and proportional; for example, if estrogen increases by a small amount, the effect it has on the uterine lining will be proportional, increasing the thickness of the lining by a small amount. Steady states and regularly recurring cycles are also outcomes of linearity typically studied by researchers.

Chaos Theory

Since the 1960s, there has been increasing recognition that many phenomena in the natural world obey different rules than those found in reductionist cause-and-effect analyses (Ahn et al. 2006; Bassingthwaighte, Liebovitch, and West 1994; Çambel 1993; Gleick 1987). Complexity theory assumes that certain systems cannot be understood by breaking them down into their constituent parts: the system has rules that are different from those that describe the behavior of its constituents (the whole is more than the sum of its parts) and is self-organizing or changing as a whole. Chaos theory describes a particular kind of complex system in which the complexity results not from large numbers of interacting agents, but rather from the nonlinear feedback interactions between relatively small numbers of agents. It provides a different way of explaining patterns in nature, a different way of thinking about what a system is and what rules it follows.

Chaos theory is perhaps unfortunately named, since in common English <u>chaos</u> means "disordered." Chaotic systems, on the other hand, are dynamical systems in which outcomes appear on the surface to be unpredictable or random but actually result from the workings of a coherent system: there is a hidden order that can be uncovered using certain mathematical techniques. In reductionism, <u>determinism</u> means that a small number of variables create an effect, and the effect is predictable. In chaotic systems, on the other hand, we have determinism—that is, a small number of factors or variables generate the complicated patterns that emerge—yet results are not predictable. This follows from other characteristics of chaos. First, the constituent units are not independent: they mutually interact with each other. In addition, each time they interact, the effects or output or the results thus generated reenter the system, helping to create a new round of activity. In a cause-and-effect system, small differences between two causes will result in similarly small differences between their effects: there is a straight-line relationship between what goes in and what comes out. Chaotic systems do not have these linear correspondences. "Sensitivity to initial conditions," also called the "butterfly effect," means that very small differences become larger and larger over time. This results in part from the output reentering the system—small differences between outputs become magnified as the system repeats over and over—and is in part what accounts for the variety and unpredictability generated by these systems.

The variability does have limits: despite a degree of unpredictability, there is still pattern. For example, the weather is unpredictable beyond a few days, yet I may say with confidence that it will not snow in August. Each snowflake is different, yet each will have six sides. The pattern may not be discernible when we look at a series of outcomes measured over time or predict what will happen next, but if we examine a very large number of these outcomes—for example, thousands of them—only some of the possible outcomes (only some of the possible values of the determining variables) will in fact be found. When a graphic plot is created of a very large number of these values (called a "phase space" diagram), the fact that some values never occur becomes clear. What emerges instead is a complicated, ordered pattern of where values do occur, called a "strange attractor." The strange attractor will have boundaries beyond which no point will be found but no point will repeat exactly. Rather than statistics like means and standard deviations, the mathematics that describe the strange attractor (and thus the chaotic system) are the mathematics of something called fractals.

Menopause Research

Menopause research was initially guided by the commonsense idea that senescence is the key to

understanding the biology of perimenopause: as we age, the reproductive system wears out, becoming less efficient, until the ovaries ultimately in effect stop working (P. Derry 2004; Voda 1997). In this view, perimenopause is a distinct process that begins when the system begins to change from its premenopausal functioning. For example, in 1996 the World Health Organization (WHO) defined menopause as the "cessation of menstruation associated with loss of ovarian function" (emphasis ours), emphasizing a loss, rather than a completion or change in function. WHO also defined the perimenopause as "the period immediately before menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause." In other words, if menopause is the breakdown of a system, the transition to menopause amounts to the process of breakdown (P. Derry 2004). In this view, understanding perimenopause meant identifying the ways in which the system was working differently, often less efficiently, understanding the mechanisms responsible for these observed changes, and especially understanding mechanisms initiating the process of change. Feedback relationships between hormones might be said to change because the ovary or pituitary gland have become "resistant" or otherwise less able to respond to previous hormonal signaling; deviations from the norm at younger ages, like increased menstrual cycle variability or increased numbers of anovulatory cycles, might be defined as "abnormal" (e.g., Santoro 2005; Sherman, West, and Korenman 1975).

As research began accumulating, especially since the 1980s and 1990s, the underlying physiological patterning was not what was expected (see summaries in Hale and Burger 2005; Prior 1998, 2005). After menopause, far lower amounts of estrogen and far higher amounts of follicle stimulating hormone (FSH) are found in a woman's body. As recently as the late 1990s, research was guided by a commonsense idea that that there would be a linear change (e.g.,

Rubinow, Schmidt, and Roca 1998): during perimenopause, estrogen would be declining and FSH on the rise, so that the perimenopause was therefore a low estrogen state. However, researchers found unexpected levels of hormones and unexpected and inexplicable relationships among them (Hale and Burger 2005; Prior 1998). Changes were not progressive and consistent: a change might be found one cycle but not the next. Instead of universal laws, hormone and other menstrual cycle changes were found to vary within and between women, apparently unpredictably. Instead of smooth increases or decreases in hormone levels, spikes were found where decreases were expected, as well as hormone levels that changed but then returned to premenopausal levels. Perhaps the most unexpected finding was that perimenopause was not, as had been assumed, a low estrogen state. In fact, estrogen levels were on average higher. Further, they could fluctuate, remain unchanged, or spike above rather than below those found earlier in life (Hale et al. 2007; Prior 1998). In addition, FSH levels were not, as expected, predictably higher, and they could be elevated one month and return to premenopausal levels the next. Feedback relationships between FSH and estrogen might no longer be inverse, and menstrual periods might be regular even when hormones varied. Luteinizing hormone (LH) also no longer reliably responded to estrogen. With regard to the idea that perimenopause is a distinct process with a specific physiological beginning, specific processes have not been found (Prior 1998). Understanding basic processes has therefore remained elusive.

It is perhaps not surprising that as more research on menopause was conducted, reality turned out to be more complicated than it had seemed when less was known. Recent research has explored more complicated dynamics, such as the role of additional hormones like inhibin B in causing observed dynamics, or changes in the ovary, such as numbers of remaining follicles or timing of ovarian events that may underlie observed dynamics (Burger et al. 2008; Hale and Burger 2005; Hale et al. 2009; Santoro 2005). One important trend in recent research is a greater emphasis on increased variability as a key characteristic of the transition to menopause. For example, Lisabeth, Harlow, and Qaqish (2004) found that an increase in the standard deviation of cycle length preceded a change in mean length by two to six years. Harlow, Lin, and Ho (2000) found a decreased correlation between the length of one period and the next, with greater numbers of both very short and very long cycles.

It is possible that continued research will resolve unanswered questions within the conventional paradigm. However, another possibility is that fundamental assumptions and paradigms need rethinking. We suggest that the fundamentally different approach to menstruation—indeed, to scientific theory and the underlying reality it describes—offered by chaos theory is relevant and useful.

Plausibility of Chaotic Dynamics in Perimenopause

Many biological systems have been found to exhibit chaotic dynamics (Bassingthwaighte, Liebovitch, and West 1994). While little studied in this regard, the reproductive endocrine system is the right kind of system to be chaotic. Systems with chaotic dynamics can arise when a number of variables interact, when output of parts of the system feed back into the system as input, and when the different parts of the system influence each other in nonlinear feedback loops. The reproductive system has just this kind of feedback. For example, estrogen levels are output when the ovary is stimulated by certain pituitary hormones, but then become input when the resulting estrogen then affects the functioning of the pituitary. These feedback loops are usually thought of in terms of closed systems, analogous to a thermostat, creating regularly recurring cyclic processes and preventing the system from deviating too far from its usual patterns.

However, if the effects of hormones are not linear, it is possible that chaotic processes exist that have hitherto not been tested for. Overviews of chaos theory typically suggest that certain patterns of results may signify chaos (Bassingthwaighte, Liebovitch, and West 1994; Çambel 1993; Gleick 1987; Liebovitch 1998). Gleick, in his history of chaos theory, summarizes these patterns by suggesting that unexpected noise, surprising fluctuations, and regularity mixing with irregularity all suggest the possibility of chaos. All of these have been found in perimenopause research, and the initially puzzling pattern of results makes conceptual sense if it is seen as the outcome of a chaotic system.

As noted above, the expectation that changes in estrogen and FSH levels would follow a linear, regular course during perimenopause, smoothly increasing or decreasing, was incorrect. At one time, Rubinow and Schmidt advocated that an elevated FSH level midway between premenopausal and postmenopausal levels should be used as part of the definition of perimenopause to make clinical research more rigorous, reproducible, and scientific (Rubinow, Schmidt, and Roca 1998). However, they found their research subjects might meet this criterion one month but not the next. While elevated FSH levels continue to be part of the recently developed Stages of Reproductive Aging Workshop (STRAW) definition of perimenopause, it is acknowledged that these levels are so variable and unpredictable that a particular FSH level cannot be a criterion for perimenopause (Soules et al. 2001). Burger et al. (2008) have concluded that changes in no one hormone typify or define perimenopause.

Regularity mixing with irregularity is another marker of chaotic dynamics (e.g., Cambel 1993), and this has also been found in perimenopause research. For example, Burger et al. (2008)

describe perimenopause as involving "erratic and unpredictable cycle characteristics, with normal ovulatory cycles continuing to occur episodically" (p. 603). In general, feedback relationships may change one month but then return to premenopausal, "normal," patterns, as when FSH and estrogen levels remain inverse at one time but not another.

Not only is the output of chaotic systems variable, the variability does not follow the distribution of values expected by a more typical approach, for example, falling on a normal curve. Instead, the variability can generate extreme values, odd oscillations, and other unexpected patterns. One of Gleick's (1987) examples was the eradication of rubella in Britain. After a program of inoculation was introduced, the rates of disease did not decrease smoothly. Though the long-term trend was downward, the rates oscillated and even had unexpected spikes, as predicted by chaos theory. The general shape of the rubella curve as described by Gleick seems surprisingly like what had been found for estrogen levels during perimenopause: the erratic output of estrogen, with some extreme high values, is qualitatively similar to what would be expected from a chaotic system.

A fundamental idea in more traditional approaches is that the statistical mean is a good way to describe a typical or "real" result, while standard deviations indicate differences around this composite (due either to errors in measuring variables, unknown complicating factors, or differences between individuals that don't alter the "real" result). But means and standard deviations are not good ways to describe outcomes in chaotic systems (e.g., Liebovitch 1998). Because of sensitivity to initial conditions and other characteristics of the system, statistical means do not represent a typical course. Again, we find in perimenopause research results that suggest chaos: individual data and group composite data (like means) about the course of menopause differ. Harlow, Lin, and Ho (2000) for example, found such differences, as did

Ferrell et al. (2005).

What Difference Does It Make If Perimenopause Is Chaotic?

Paradigms influence which problems appear important, how these problems are studied, and how research results are interpreted and applied to clinical practice. Facts and ideas inconsistent with underlying assumptions may appear less plausible, may not play a role in research and practice, and, indeed, may be systematically overlooked or ignored. Within a chaotic dynamics framework, factors such as variability, development, and adaptability become more prominent than in a traditional biomedical view. Thus, the change in perspective that results from a change in paradigm has implications for health care.

<u>Variability</u>

Chaos theory, importantly, directs our gaze to variability. Gleick (1987) suggests that when a chaos theory perspective is adopted, then previously overlooked variability can come into focus, because it now makes sense and appears important. When studying cause-and-effect systems, the assumption is that the statistical mean provides information about the "real" result. Small, inescapable variations, which can, for example, be measured as the standard deviation, will be found, but the assumption is that these variations are insignificant and not meaningful compared to the lawful regularities being studied. Universal stages, like developmental stages or staging systems for menstruation, also assume a universal "real" result, with variability a small, less meaningful, annoyance (Soules et al. 2001). However, variability and unpredictability are important facts during perimenopause. While universal stages have been sought (as in STRAW), each woman's path seems unique (Treloar 1981). Further, variability exists even before perimenopause. The idea that the normal menstrual cycle is cyclical, regular and repetitive, is a common premise, but scientific data inconsistent with this idea has existed for over 40 years. For example, in a landmark 1967 paper, Treloar and his colleagues reported on 30 years of research already accumulated at that time by their project, demonstrating variability within and between younger women. In a later paper, Treloar (1981) concluded that "[our] program has convincingly demonstrated [that] each woman in her menstrual cyclicity is a person apart" (p. 261). More recently, Lisabeth, Harlow, and Qaqish (2004) found that at ages 20 to 40, the time of greatest regularity, the correlation between the length of one period and the next averaged 0.30, a relatively low relationship. Gorrindo et al. (2007) found that lifelong menstrual histories were most typically erratic.

The idea that the mean result is the "real" result is intrinsic to the language of research reports. For example, a recent paper by Burger et al. (2008) states that menopause occurs "<u>at</u> 51.3 years" (p. 606, our emphasis). Obviously, very few women reach menopause at exactly 51.3 years, and it is well known there is a normal range, often considered to be 40 to 60 years, but the mean is reported as the "real" result. Similarly, these authors cite a study in which for "premenopausal women with regular cycles, cycle length <u>was</u> 26 days (95% CI: 21–34.)" (p. 605, our emphasis). Although variability was perceived by these authors, and even reported, it was not included as important information when drawing conclusions or making sense of data. This emphasis on average behavior is also seen when scientists identify "stages," reporting the results for "most people" and not explaining the patterns of those who deviate from these stages. Chaos theory suggests that we should attend to variability and take it into account when interpreting our results.

Development

Traditional research has often reflected an implicit view of development. The menstrual cycle is normal when it is regular, cyclic, and operating with efficiency (e.g., minimal anovulatory cycles). Variability means an immature system (in teenage girls), a system under stress (e.g., due to starvation or disease), or a system on the wane (perimenopause). In such a conceptualization, perimenopause implies a break with previous functioning. However, as discussed above, a sharp break is not what has been found. The STRAW system defines the beginning of perimenopause as when cycle variability increases by seven days (Soules et al. 2001). However, this clearly is not the beginning of perimenopause, since many changes occur before this. However, these previous changes (such as hot flashes) are variable, and the STRAW criterion privileges a consistent, measurable change. Changes dating to women in their 30s (like lighter menstrual flow) are sometimes identified as the beginnings of perimenopause (Mitchell, Woods and Mariella 2000), but this would mean we have a transition of up to 20 years in a system which premenopausally exists for about the same amount of time. Research is more consistent with a life course to menstruation, including increased variability at the beginning and end of menstrual life, and changes (like shortening of average cycle length) throughout the lifespan (Treloar 1981; Treloar et al. 1967).

Chaos theory is consistent with the data implying a lifespan arc to menstruation. In chaos theory, change is not seen as a consequence of a cause destabilizing a previously stable system: instead, "the dynamics of being in one condition itself causes the system to switch to another condition, the behavior of the system itself over time results in change" (Liebovitch 1998, p. 234). This view is not necessarily inconsistent with more traditional research. It would be consistent, for example, with ideas that changes in the ovarian follicle reserve or in hypothalamic set points are involved in perimenopausal dynamics. Importantly, it suggests that it is possible

that perimenopause is not the result of a system breaking down, of dynamics based on increased randomness or other senescence-based mechanisms. In the language of chaos theory, chaotic systems can change their dynamics (the shape of the strange attractor can change) when the system undergoes a "phase transition."

Anthropological and behavioral biology–based researchers have suggested that menopause as it exists in humans is unusual, perhaps unique, in the animal world (see P. Derry 2006; Ellison 2010). Pavelka and Fedigan (1991) point out that when compared to other primates, only humans have an end to menstruation that is universal, involves depletion of ovarian follicles, and occurs many years before the senescence of other body systems (which means that a period of healthy adulthood remains post-reproductively). If menopause and a postreproductive life stage are part of the human lifespan and body plan, we may infer that a lawful process may exist, and that chaotic dynamics might be involved. This speculation can be tested by researching whether chaotic dynamics exist premenopausally and during perimenopause, and, if so, comparing the shape of the strange attractor during each. More generally, our attention is directed to the idea that reproductive endocrinology be seen within the context of lifespan development to help define what is normal and what is not.

Adaptability

Chaos theory directs our attention to adaptability. Conrad (1986) has suggested that chaotic systems serve adaptability. In part, this is because such a system generates many alternatives. In addition, it turns out that a system with a little bit of irregularity is better able to return to stable functioning (remains within the strange attractor) when acted on by destabilizing influences, rather than developing an entirely new course (Liebovitch 1998). The reproductive endocrine system is often conceptualized as a closed system, maintaining regular, repetitive cycles (Burger et al. 2008). However, chaotic systems are open systems that respond to outside influences, yet paradoxically can remain stable. The idea that the reproductive endocrine system is an open system provides conceptual bridges to the idea that myriad influences, physical and sociopsychological, may be important to conceptualizing health and disease.

Taking into account flexibility and adaptability can encourage a different emphasis when conceptualizing menstrual cycle events. For example, if a woman who restricts her caloric intake, or is starving, develops anovulation, does this mean that her reproductive system is malfunctioning, or does it make sense biologically for women to become less fertile if food availability—and hence the potential support of an infant—is questionable? An emphasis on adaptation can also encourage openness about the direction of causality for other health problems. For example, polycystic ovary syndrome (PCOS) has been related to insulin resistance, and hence to a predisposition to diabetes. However, research now suggests a reverse direction of causality: endocrine disturbances resulting in insulin resistance (which, again, suggest a lack of health or robustness in the system) may be causing the reproductive system changes found in PCOS.

Other Implications for Health

Chaos theory encourages thinking differently about the menstrual cycle and its role in health and disease. This framework encourages viewing the cycle within the context of the whole organism and her life span, emphasizes an open system and adaptation, and draws attention to the variability that exists throughout life in the cycle.

Defining the boundaries between health and disease has been an issue with regard to the menstrual cycle. Variability or deviations from the norm have been seen as causes of problems or stresses on the system that can define pathology. Premenstrual problems, including mood

changes, menstrual migraine, and other problems, have been attributed to steep fluctuations in estrogen levels. Hot flashes, similarly, have been attributed to fluctuations in estrogen levels that affect a thermoregulatory center in the hypothalamus. However, it has become clear that, whatever role these fluctuations play, and however efficacious estrogen treatments may be, this does not explain the dynamics of problems. For example, estrogen levels do not differentiate between symptomatic and nonsymptomatic perimenopausal women, and other factors, both physiological and psychological, are known to be implicated. Perimenopausal women have been treated with hormone medications and surgery to make periods more regular and predictable or to correct changes like very heavy bleeding, but there is diversity of opinion within the medical community about when changes are normal and when they require treatment. The idea that perimenopause and menopause are related to the onset or worsening of chronic health problems, like heart or bone disease, may similarly derive a sense of plausibility from the underlying assumption that perimenopausal changes destabilize a normal, repetitive, predictable system.

However, if variability is part of the normal course of things, then identifying when variability is a cause for health concerns should be studied more specifically. Varying from patterns earlier in life, or from a statistical average, may not be a specific-enough criterion for determining when health problems exist, and identifying additional contributing criteria would then be important. If it is not seen as threatening the stability of a regularly recurring system, increased variability may not as automatically be theorized to be causing a stress on that system. For example, if some nonovulatory cycles (some variability) is typical, then maximally efficient functioning (ovulating every month) may not define normality. In other words, a chaos perspective helps direct attention to the idea that variations from the norm do not necessarily constitute pathology, and that multiple factors and more complex patterns should be studied to understand problems. Perhaps severe problems would be better conceptualized as "complications" or "disorders," rather than simply as symptoms of the premenstrual or perimenopausal time. Furthermore, if the cycle is chaotic, it is even possible that too <u>much</u> regularity may be a sign of health problems (analogous to findings for heart-rate variability). If so, then birth control pills, for example, said to have been created to mimic a 28-day cycle to create a feeling of normalcy in women, may require more thought.

While women need guidance about when cycle characteristics indicate a problem, they also need to develop a self-image of whether their body functioning is "normal," and a sense of comfort with their bodies. If a model of strict cyclical regularity is taught, girls may be concerned that small amounts of menstrual irregularity are abnormal and a cause for concern, and women may expect that they "should" be able to predict cycle-related changes. However, a chaos theory perspective encourages a woman to understand her own reproductive system as having a unique, personal course, in which some variability from month to month can be expected. If perimenopausal cycle changes are the outcome of chaotic processes, it is possible that menstrual irregularity reflects the normal workings of a system and not, as women sometimes believe, a body malfunctioning and becoming unreliable. The basic idea that there is a life course to menstruation, and that it is related to the distinctive human life plan, might be an important part of educating girls and women about the workings of their bodies.

Research on the menstrual cycle as the outcome of a nonlinear, dynamical, chaotic system, might, in addition, address basic issues. Can we characterize the strange attractor preand perimenopausally? Does this give us insight into what kind of a process perimenopause is? Do health problems correlate with specific characteristics of chaotic systems, as has been found for heart-rate variability? If so, can we find novel numerical descriptors that give insight into distinctions between health and disease? Further, researchers who mathematically model the menstrual cycle understandably seek solutions in which their models predict a regularly recurring cycle. If the cycle is chaotic, then such models might instead need to predict variability.

Our Study

It is plausible to assert that the menstrual cycle is the outcome of a chaotic process, but is it true? Experimental methods exist with which to evaluate whether a system is chaotic. These methods involve computational analysis with the goal of demonstrating that the data has key mathematical characteristics of chaos. We have conducted such a study and found evidence for chaos, looking at whether chaotic dynamics are found among women aged 20 to 40 years (Derry and Derry 2010). This is the age range with the greatest regularity in the menstrual cycle, yet, as discussed above, even at this age range the cycle has intrinsic variability. Our research question was whether fluctuations in the number of days in the menstrual cycle over a long period of time are chaotic or random. Does the average menstrual cycle length vary with small, meaningless, random fluctuations, or do variations have the attributes of a chaotic system? If the latter, this would imply that the biological system producing the cycle is similarly chaotic: that the myriad hormones and other components of the reproductive system act together as a chaotic system.

Time Series Analysis

We applied the established method of time series analysis to menstrual cycle data (Sprott 2003). As stated above, if a system is chaotic, we can't see a pattern when we look at a series of outcomes. However, if we look at a very large number of these outcomes, it turns out that only some of the possible outcomes in fact occur. By contrast, if a system is random, then points are

equally likely to occur anywhere. If a phase space plot, a multidimensional graph of chaotic data, is created, a complicated, ordered pattern of where values do occur will emerge—the strange attractor. The strange attractor will have boundaries beyond which no point will be found, but no point will repeat exactly. The characteristics of the attractor—such as sensitivity to initial conditions, behavior that never repeats—result in the mathematical qualities of the attractor having a fractal structure. Fractals are mathematical entities with certain characteristics, particularly self-similarity (it looks the same on different length scales). A fractal can be characterized by a number referred to as its <u>dimension</u>, which is related to the amount of information needed to specify the position of a point on an attractor. Dimension, oddly, will not be an integer in a fractal.

A problem in time series analysis is that we have data for only one variable in a system that is the outcome of many variables. It turns out that we will find a strange attractor that is mathematically equivalent if we use multiple sets of data from a single time series instead of the actual values of every variable involved. Through this "mathematical trick," time series analysis allows us to study whether the system we are interested in has the signatures of chaos. Mathematical procedures exist that allow us to determine if we have a non-integer dimension and other characteristics indicating that we have a fractal strange attractor, hence a chaotic system. For example, if we examine how many variables are needed to generate the output of a system (or how many axes a phase diagram would need), a chaotic system will have a relatively small number of variables; a random system, a very large number.

The Study

We were given permission to use data from the Tremin Research Program on Women's Health (Mansfield and Bracken 2003), an ongoing longitudinal study begun in 1934; the Cohort I and II subject pool contains data records for 3,717 women. In this research, women prospectively recorded which days they were menstruating and which not on calendar cards, so that there are no problems with inaccurate memory recall. The women were primarily white, middle-class, and from the Midwestern United States. We randomly chose 38 women for whom data was available for the entire 20- to 40-year-old age range. For this initial study, we followed Tremin norms for defining premenopause and whether a true menstrual cycle existed (Treloar et al. 1967). This gave us 7,438 menstrual cycle data points to analyze.

We developed procedures to make the data appropriate for time series analysis and for combining the cycle lengths from many women. In addition to conducting time series analysis, we did a number of analyses to determine whether these procedures had created erroneous results. Our data provided evidence that menstrual cycle length is chaotic among our sample of 20- to 40-year-olds. (The details of the mathematical tests are reported in Derry and Derry 2010). We found evidence for sensitivity to initial conditions and a fractal dimension (i.e., the dimension was low and non-integer). We tested for reproducibility by rerunning the analyses on subsets of the data, and we also tested for problems introduced by stringing together individual records. We employed several different dimension estimators and tested carefully for artifacts (we constructed a surrogate data set and performed the same analysis on it). We thus found evidence for a strange attractor, and analyses of the data suggested that the simplifying assumptions that allowed us to conduct the research had not artifactually produced our results.

Preliminary results for a sample of perimenopausal women (not yet published) also provided mathematical results indicating chaos, based on 4,112 data points from 65 women. We will analyze a larger sample to confirm and improve the precision of our results, allowing us to explore similarities and differences between premenopausal and perimenopausal women.

Conclusion

Chaos theory provides an alternative framework within which to consider research on the menstrual cycle and perimenopause in particular. Chaotic systems are complex, dynamical, nonlinear systems that are deterministic but not predictable, characterized by sensitivity to initial conditions and strange attractors. Chaos theory provides a coherent framework that qualitatively accounts for puzzling results from perimenopause research. Considering this possibility is also a useful exercise for sharpening sensitivity to implicit assumptions underlying more traditional research on the menstrual cycle.

Whether the menstrual cycle is chaotic can be empirically tested. Our data demonstrate chaos in menstrual cycle length among women aged 20 to 40, the times of greatest menstrual regularity, and preliminary data also indicate chaos during the perimenopause. We are conducting additional research to replicate these results and to further elucidate what light chaos theory throws on the dynamics of menstrual life and perimenopause in particular. Future research may characterize important aspects of menstrual life by measures that describe qualities of strange attractors that have potential implications for health research. In a chaotic system, a small number of variables would be expected to be responsible for generating observed dynamics. Some variability would be normal and expected, so dynamics would need to be found that generate this variability rather than predictable results.

Chaos theory encourages thinking differently about the menstrual cycle and its role in health and disease. This framework encourages viewing the cycle within the context of the whole organism and her entire life span, emphasizes an open system and adaptation, and draws attention to the variability that exists throughout life in the cycle. This has implications for health education, such as a woman's understanding of her own reproductive system having a unique, personal course, in which some variability from month to month is not unexpected. It also has implications for understanding pathology, such as not assuming that variability or deviations from the norm are in and of themselves stresses on the system or causal agents instigating pathology. Instead, more nuanced understanding of more complex dynamics are encouraged. With regard to perimenopause and menopause, chaos theory may also provide language that is not grounded in imagery of pathology. This imagery has, for example, contributed to the plausibility of assumptions, in the absence of strong data, that menopause is linked to health problems like increased vulnerability to chronic illnesses. Further research is needed to establish whether the chaos framework will be able to fulfill this potential.

References

Ahn, A., et al. 2006. The clinical applications of a systems approach. PLoS Med 3:956-60.

Bassingthwaighte, J., L. Liebovitch, and A. West. 1994. <u>Fractal physiology</u>. Oxford: Oxford Univ. Press.

- Burger, H., et al. 2008. Cycle and hormone changes during the perimenopause: The key role of ovarian function. <u>Menopause</u> 15:603–12.
- Çambel, A. 1993. <u>Applied chaos theory: A paradigm for complexity</u>. San Diego: Harcourt Brace Jovanovich.
- Conrad, M. 1986. What is the use of chaos? In <u>Chaos</u>, ed. A. Holden, 1–36. Princeton: Princeton Univ. Press.
- Derry, G. N., and P. S. Derry. 2010. Characterization of chaotic dynamics in the human menstrual cycle. <u>Nonlinear Biomed Phys</u> 4.

http://www.nonlinearbiomedphys.com/content/4/1/5.

Derry, P. S. 2004. Coping with distress during perimenopause. Women Ther 27:165-77.

Derry, P. S. 2006. A lifespan biological model of menopause. Sex Roles 54:393-99.

- Ellison, P. 2010. Life historical perspectives on human reproductive aging. <u>Ann N Y Acad Sci</u> 1204:11–20.
- Ferrell, R., et al. 2005. Monitoring reproductive aging in a 5-year prospective study: Aggregate and individual changes in steroid hormones and menstrual cycle lengths with age. <u>Menopause</u> 12:567–77.
- Gleick, J. 1987. Chaos: Making a new science. New York: Viking.
- Goldberger, A. 2006. Complex systems. Proc Am Thorac Soc 3:467–72.
- Gorrindo, T., et al. 2007. Lifelong menstrual histories are typically erratic and trending: A taxonomy. <u>Menopause</u> 14:74–88.
- Hale, G., and H. Burger. 2005. Perimenopausal reproductive endocrinology. <u>Endocrinol Metab</u> <u>Clin North Am</u> 34:907–22.
- Hale, G., et al. 2007. Endocrine features of menstrual cycles in middle and late reproductive age and the menopausal transition classified according to the stages of reproductive aging workshop (STRAW) staging system. J Clin Endocrinol Metab 92:3060–67.
- Hale, G., et al. 2009. Atypical estradiol secretion and ovulation patterns caused by luteal out-ofphase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. <u>Menopause</u> 16:50–59.
- Harlow, S., X. Lin, and M. Ho. 2000. Analysis of menstrual diary data across the reproductive life span: Applicability of the bipartite model approach and the importance of withinwoman variance. <u>J Clin Epidemiol</u> 53:722–33.

Higgins, J. 2003. Nonlinear systems in medicine. <u>Yale J Biol Med</u> 75:247-60.

- Liebovitch, L. 1998. <u>Fractals and chaos simplified for the life sciences.</u> Oxford: Oxford Univ. Press.
- Lisabeth, L., S. Harlow, and B. Qaqish. 2004. A new statistical approach demonstrated menstrual patterns during the menopausal transition did not vary by age at menopause. <u>J Clin</u> <u>Epidemiol</u> 57:484–96.
- Mansfield, P. and S. Bracken. 2003. <u>Tremin: A history of the world's oldest ongoing study of</u> <u>menstruation and women's health</u>. Lemont, PA: East Rim.
- Mitchell, E., N. Woods, and A. Mariella. 2000. Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: Toward a more precise definition. Menopause 7:334–49.
- Pavelka, M., and L. Fedigan. 1991. Menopause: A comparative life history perspective. <u>Yearb</u> <u>Phys Anthropol</u> 34:13–38.
- Prior, J. 1998. Perimenopause: The complex endocrinology of the menopausal transition. <u>Endocr</u> <u>Rev</u> 19:397–428.
- Prior, J. 2005. Ovarian aging and the perimenopausal transition. Endocrine 26:297–300.
- Rubinow, D., P. Schmidt, and C. Roca. 1998. Hormone measures in reproductive endocrinerelated mood disorders: Diagnostic issues. <u>Psychopharmacol Bull</u> 34:289–90.

Santoro, N. 2005. The menopausal transition. Am J Med 118:8S-13S.

Sherman, B., J. West, and S. Korenman. 1975. The menopausal transition: Analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. <u>J</u> <u>Clin Endocrinol Metab</u> 42:629–36.

Soules, M., et al. 2001. Stages of reproductive aging workshop (STRAW). J Womens Health

Gend Based Med 10:843-48.

Sprott, J. C. 2003. Chaos and time series analysis. Oxford: Oxford Univ. Press.

Treloar, A. 1981. Menstrual cyclicity and the pre-menopause. Maturitas 3:249-64.

- Treloar, A., et al.1967. Variation of the human menstrual cycle through reproductive life. Int J Fertil 12:77–126.
- Varela, M., R. Ruiz-Esteban, and M. J. Mestre de Juan. 2010. Chaos, fractals, and our concept of disease. <u>Perspect Biol Med</u> 53:584–95.

Voda, A. 1997. Menopause, me and you. Binghamton, NY: Haworth.

World Health Organization (WHO). 1996. <u>Research on the menopause in the 1990s: A report of</u> <u>the WHO Scientific Group.</u> Geneva: WHO.