Stress, Immune Function, and Women's Reproduction

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ABSTRACT: Only 23% of women will begin a successful pregnancy during the first menstrual cycle in their attempt to conceive.[1] A large number of these failed reproductive attempts are attributed to a broad set of pathologies, but across studies an important proportion of unsuccessful cycles is consistently left unexplained. Stress has become a commonly cited factor when discussing unexplained reproductive failures. Early research on the effect of stress on reproduction was plagued with methodological problems and lacked a solid theoretical framework. However, recent experimental, clinical and population-based research provides new evidence and suggests novel biological mechanisms, which merit a fresh evaluation of the purported association. Here we briefly review the latest advancements in the study of the interplay between stress, the immune system and women's reproduction, discuss a proposed evolutionary origin for their relationship and examine the biological pathways that may mediate the connection between these three systems.

KEYWORDS: stress; immune function; reproductive function; evolution

STRESS AS A MODULATOR OF REPRODUCTIVE FUNCTION

Reproduction is a particularly onerous endeavor for females of eutherian mammal species. Intrauterine gestation demands significant physiologic and immune changes, which result in increased health risks for the mother. Furthermore, in several species maternal investment can continue considerably after

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parturition. In the case of humans, maternal investment continues for almost the entire life span. Also important, a mother's ability to invest in reproduction also affects the survival and future reproduction of her offspring.

Given the extensive costs involved, the timing of each reproductive venture can critically affect females' lifetime reproductive success. Therefore, being able to time reproductive events would be a valuable adaptation. Such ability requires two mechanisms: one to ascertain the quality of the current reproductive environment relative to its potential quality in the near future; another to suppress reproductive function when convenient. The convenience of reproducing now versus later might be assessed through environmental cues. Increases in environmental unpredictability or deteriorations of the social or physical environment, such as the loss of a social network member, a period of negative energetic balance due to famine, a natural disaster, or the development of an infection, are all challenges that will increase the risks associated with pregnancy as well as threaten a female's ability to invest in reproduction postnatally. The organism perceives all of those challenges as stressors. Consequently, stress has been proposed to be one of the mechanisms used by organisms to assess the appropriateness of their current context for initiating a reproductive venture. Consistent with the proposed hypothesis, the activation of the stress axis has been found to trigger reproductive suppression mechanisms both in humans and nonhuman mammals.[2–9]

STRESS AND REPRODUCTION IN HUMANS

Current understanding of the relationship between stress and reproductive function in women is mainly based on fertility of patients. Various studies based on interview data have shown psychological stress to be associated with reduced fecundability (probability of conceiving in a given cycle), increased risk of early pregnancy loss, and even infertility. For example, some prospective studies focused on women undergoing fertility treatment suggest that those with perceived or actually higher workload are less likely to conceive, and among those who conceive the likelihood of successful pregnancy completion is reduced.[10] In contrast, a small prospective study of six cycles among Danish women failed to find a relation between work demands and control, and pregnancy outcome. However, when restricting the sample to those with idiopathic infertility, job strain did predict miscarriage.[11] Importantly, consistent with what has been observed among fertility patients, healthy, nulliparous women with low scores of psychosomatic symptoms, few negative life events, no fluctuations in body weight prior to pregnancy, and regular religious practice have been reported to prospectively predict higher than average fertility.[12]

Until recently hormonal evidence for the relationship between stress and reproductive suppression was mainly restricted to clinical studies of individual stressors or studies focused on subgroups of women affected by similar

stressors, such as athletes[13] or individuals who shared a professional context.[14] In the last few years, however, Nepomnaschy *et al*. began reporting results from a long-term, prospective study including periodical physiologic data on both stress and reproductive biomarkers. They followed the daily lives of 61 participant Mayan women for 1 year. This society frequently endures psychological, immunologic, and energetic challenges, such as intervals of restricted food supply, infectious diseases, and social violence. Longitudinal analyses of their data uncovered several interesting relationships. First, participants' most critical concerns, identified through the analyses of open-ended interviews, were found to be accurate predictors of increases in each woman's cortisol levels.[15] As discussed below, cortisol is a key mediator in the body's response to stress and, consequently, is frequently used as a marker of stress.[6,16] Second, increases in cortisol levels were associated with significant changes in the profiles of the participants' reproductive hormones during their menstrual cycles.[8] Specifically, increased cortisol levels were tied to increases in gonadotrophin and progestin levels during the follicular phase. Increased cortisol levels were also associated with significantly lower progestin levels during the middle of the luteal phase. These untimely changes in gonadotrophins and gonadal steroids have been previously found to affect a female's chances to conceive.[17,18] Finally, in the case of conceptive cycles, increases in cortisol during the first 3 weeks of gestation were predictive of miscarriage.[3] Their results are consistent with the hypothesis that stress levels may be used by a woman's body to assess the quality of her environment and regulate her investment on reproduction accordingly.[3,8]

BIOLOGICAL PATHWAYS

Three "super-systems"—the endocrine, immune, and nervous systems—engage in multiple interactions during the body's response to acute and chronic stress. Each of these systems is also individually vulnerable and responds to stressors.[19,20] Communication between systems is possible because they use a common "chemical language," sharing respective ligands and their cognate receptors.[21,22] Next, we briefly discuss some of the salient aspects of what has been learned so far regarding each one of these three systems and their interplay.

Physiologically, the term stress describes the response of an organism to challenges to its dynamic equilibrium or homeostasis. Stress activates the hypothalamic-pituitary-adrenal axis (HPA), the adrenergic and the autonomic nervous systems. The principal central nervous system regulators of the HPA axis are corticotrophin-releasing hormone (CRH) and antidiuretic hormone (AVP). Further, peripheral mediators of the stress response, such as glucocorticoids (GCs), catecholamines, and neurotrophins are activated.[23,24] Apart from the central nervous system, CRH has been found in the adrenal

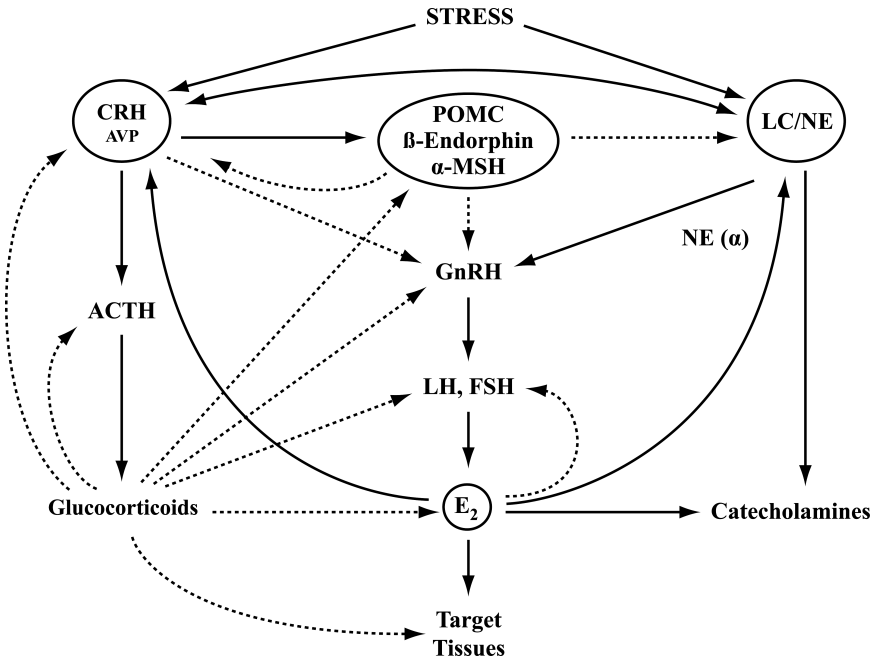

FIGURE 1. Heuristic representation of the interplay among the HPA axis, the LC/NE sympathetic system, and the HPG axis. POMC = proopiomelanocortin; α-MSH = α-melanocyte-stimulating hormone. The dotted lines represent inhibition while the solid lines represent stimulation.

medulla, ovaries, myometrium, endometrium, placenta, testis, and elsewhere. The "stress system" in the brain (the CRH neurons in the paraventricular nucleus of hypothalamus and other brain areas; locus ceruleus/norepinephrine system, central sympathetic system in the brainstem) collaborates with its peripheral components (HPA, and peripheral sympathetic nervous system).[25] CRH and its receptors are found in many extrahypothalamic sites in the brain. CRH secretion is complex and is based on reciprocal interactions among the various parts of the stress system. HPA axis activation inhibits the reproductive axis at all levels[26] either directly or through β-endorphin secreted from the arcuate proopiomelanocortin (POMC) neuron as well as through catecholamines. CRH suppresses the GnRH neurons of the arcuate and preoptic nuclei in the medial preoptic area (FIG. 1).[27,28] Glucocorticoids exert inhibitory effects on GnRH neurons, the pituitary gonadotrophs, influencing primarily the secretion of LH, and the gonads themselves while they render target tissues of sex steroids resistant to these hormones (FIG. 1).[29] The interaction between CRH and the reproductive axis is bidirectional, probably exerted via estrogen-responsive elements (ERE) in the promoter area of the CRH gene.[30] In the monkey, systemic administration of CRH rapidly decreases plasma LH levels.

The response of the hypothalamic-pituitary-gonadal (HPG) axis to stress is potentially biphasic. Humans and intact rodents exposed to acute stress respond with a small and often short-lived increase in plasma LH levels while prolonged stress inhibits LH release and blocks ovulation.

In premenstrual syndrome urinary-free cortisol excretion is normal in both phases of the cycle but adrenocorticotropic hormone (ACTH) responses to ovine (o)CRH stimulation are abnormal. Thus, in these women the HPA axis is perturbed but retains the ability to normalize its time-integrated function. Furthermore, suppression of gonadal function, caused by chronic HPA axis activation that is stimulated by the inflammatory cytokines (IL-1, TNF-α, IL-6), is observed in highly trained individuals or those sustaining anorexia nervosa or starvation.[25,31] These subjects have increased evening plasma cortisol and ACTH levels, increased urinary-free cortisol excretion, blunted ACTH responses to exogenous CRH, and present hypogonadotrophic hypogonadism and oligoamenorrhea.[32]

The actions of the stress system and the female reproductive system are bidirectionally interrelated.[26] Gonadal dysfunction and deregulation of the HPG axis are very common in Cushing syndrome and congenital adrenal hyperplasia.[33] In Cushing syndrome hypercortisolism-induced suppression of the HPG axis in women can lead to secondary amenorrhea. Furthermore, increased activity of the HPA axis, could probably be involved in the pathogenesis of the polycystic ovary syndrome (PCOS) characterized by chronic anovulation and hyperandrogenism (ovarian and adrenal). In PCOS increased activity of the enzyme (P450c17a) responsible for the conversion of progesterone to 17-hydroprogesterone and Δ4-androstedione within the adrenal cortex is associated with increased activity of the same enzyme within the ovaries. Increased adrenal production of 17-hydroxysteroids associated with the increased levels of the adrenarche indicator DHEA-S accounts only for 20% of the patients.[31]

Additionally, the presence of CRH has been demonstrated in the theca and stroma cells as well as in cells of the corpora lutea of rat and human ovaries.[34] CRH exerts an inhibitory effect on ovarian steroidogenesis, mediated through CRH-and interleukin-1-receptors, and may be linked to follicular atresia and luteolysis.[35] Also, the epithelial cells of human and rodent endometrium produce CRH throughout the menstrual cycle, while the stroma needs to undergo decasualization in order to produce CRH.[36]

Maternal HPA Axis during Pregnancy, Parturition, and Postpartum

Circulating CRH in plasma, produced by the placenta, decidua, and fetal membranes, increases exponentially in the last 2 months of gestation.[37] Amniotic fluid CRH-binding protein (CRHbp) levels fall approaching term.[38] The unbound CRH stimulates maternal ACTH secretion, which rises within normal limits.[39] The circadian rhythm of maternal CRH is maintained probably

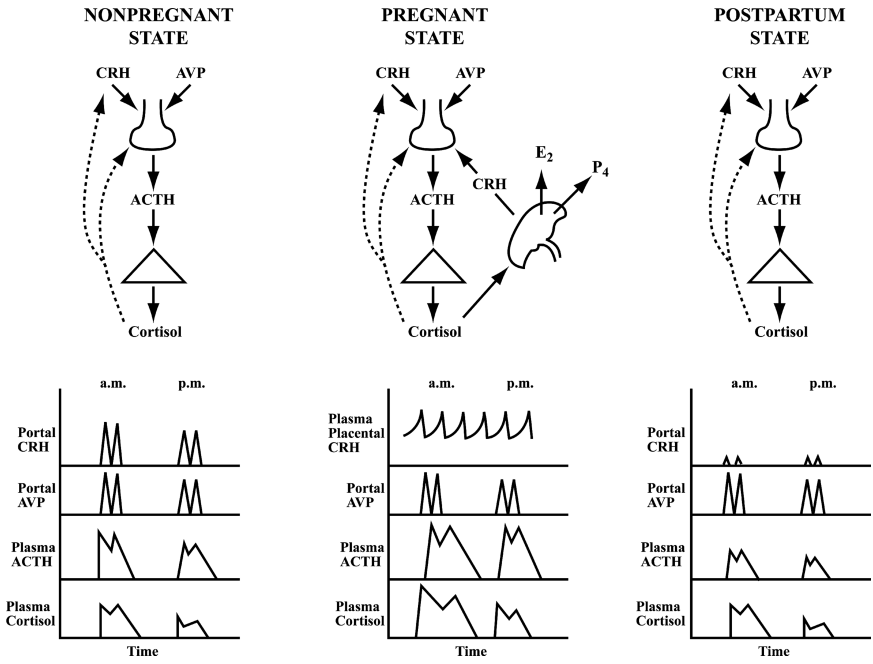

FIGURE 2. Heuristic model of the hypothalamic-pituitary-adrenal axis in the nonpregnant, pregnant, and postpartum state. The dotted lines represent inhibition while the solid lines represent stimulation.

due to the circadian AVP secretion by the parvicellular neuron of the PVN.[40] Maternal adrenal glands gradually become hypertrophic and free plasma cortisol rises during the third trimester reaching three times nonpregnant values (FIG. 2).

In sheep, placental CRH stimulates fetal ACTH production at term that in turn leads to a surge of fetal cortisol secretion precipitating parturition.[41] Activation of the HPA axis and increase of CRH during parturition have also been observed in primates. Cortisol competes with the action of progesterone in the regulation of placental CRH gene at the end of gestation. The fetal adrenal responds to the fetal pituitary ACTH and placental CRH with DHEAS production. The latter is aromatized in the placenta to estrogen promoting myometrial contractility. When labor does not progress satisfactorily in primiparous women delivering vaginally (spontaneously) ACTH levels increase. Women with preterm labor show significantly higher IL-1 levels than those of same gestational age with normal pregnancies. In women with preterm labor IL-1 and CRH levels are positively correlated suggesting that IL-1 acts directly and/or indirectly as a biological effector on placental CRH release. It seems, however, that critical levels of CRH should be achieved for the initiation of

labor.[41] The HPA axis during pregnancy may function as a biological clock, "counting" from the early stages of gestation with placental CRH presumed to be the timing "starter," determining the course of pregnancy.[42]

During postpartum maternal plasma cortisol levels show a decline toward normal levels. Dynamic testing of the HPA axis shows transiently suppressed hypothalamic CRH secretion until 6 weeks postpartum. Although suppressed ACTH responses to oCRH stimulation are noted during postpartum, total plasma cortisol levels remain within normal range, probably due to the adrenal glands hypertrophy. The latter results from the maternal HPA axis hyperactivity during pregnancy.[32] Almost half of postpartum women develop a short-lived dysthymic disorder, called the "postpartum blues," while overt postpartum depression is common and occurs in up to 18% of newly delivered mothers.[43] Women who have postpartum blues or postpartum depression show more blunted ACTH responses to oCRH stimulation testing than euthymic women. Thus, the gradual recuperation of the HPA axis in the postpartum may be implicated in this period's mood disorders. Although the causal mechanism of this attenuated HPA axis response has yet to be elucidated, a role of estrogen on CRH expression can be speculated, exerted via EREs on the promoter area of the human CRH gene.[44] Estrogen given at high doses during the postpartum period is effective as an antidepressant possibly acting to reestablish normal CRH and norepinephrine responses to stressors.[32,45] In animal studies prolactin was shown to suppress HPA axis responses to stress. The HPA axis seems to influence the mother's psychological status and the mother–infant relationship/bonding.

Stress, Immune Function, and Pregnancy

Why women's immune systems generally do not reject the fetus in spite of spatial adjacencies of fetal "histoincompatible" tissue is still unclear. Such spatial adjacencies at the interface of fetal and maternal tissues-—the so-called fetomaternal interface-—guarantee nourishment of the fetus.[46] Hence, fetal tolerance is fundamental for successful pregnancy maintenance. Plural tolerance at the fetomaternal interface may be mediated via immune adaptation mechanisms evolving during early pregnancy. Such mechanisms include the predominance of anti-inflammatory, Th2 cytokines over proinflammatory Th1 cytokines in the decidua[47,48]; the expression of indoleamine 2, 3-dioxygenase (IDO), an enzyme that famishes immune rejection by depriving the T cells of tryptophan and by inhibiting lymphocyte proliferation[49,50]; and the presence of $CD4^{+}CD25^{bright}$ regulatory T (Treg) cells, which suppress an aggressive allogeneic response directed against the fetus in humans[51] and mice.[52] Further, an elaborate homeostasis between stimulatory and inhibitory signals promotes immune privilege at the fetomaternal interface.[53,54] Additionally, signal

transducers and activators of transcription (STAT)3[55] and transforming growth factor (TGF)-β1[56] are involved in the regulation of fetal immune tolerance, likely by inhibiting the expression of proinflammatory mediators and promoting the synthesis of immunosuppressive factors. In addition, dendritic cells (DC) may be an essential cell subset for the regulation of the innate immune response mediating tolerance at the fetomaternal interface.[57] Furthermore, early in pregnancy, endometrial CRH at the implantation sites induces the expression of Fas ligand, which induces apoptosis, in the invading embryonic trophoblast and the maternal decidual cells on the fetal–maternal interface promoting thus, apoptosis of activated T lymphocytes participating in both the implantation and the tolerance process of pregnancy.[58] Pyrrolopyridine compounds have been developed as CRH receptor antagonists. Antalarmin (a pyrrolopyridine antagonist) prevented implantation in rats, by reducing the inflammatory-like reaction of the endometrium to the invading blastocyst. Consequently, antalarmin and its analogues might represent a new class of nonsteroidal inhibitors of early pregnancy.[58]

In view of the enormous complexity of the regulatory immune mechanisms involved in pregnancy maintenance, it is evident that pregnancy failure is most likely the result of complex deregulation. This deregulation can be initiated or aggravated by stress.[9] Rodent models have been particularly instructive to understand failing immune adaptation in response to stress during pregnancy.[58] Failure to sustain fetal immune tolerance during pregnancy in response to stress must be seen in the context of a neuroendocrine–immune disequilibrium. As previously outlined, stress activates the HPA axis. The upregulation of stress hormones, such as CRH and ACTH and peripheral mediators of stress response, such as GCs, catecholamines, and neurotrophins, may in turn strongly alter the immune response.[19,21,22] For example, GCs inhibit the production of proinflammatory cytokines, such as interleukin (IL)-12, interferon- (IFN-)γ, and tumor necrosis factor (TNF) and upregulate the production of IL-4, IL-10, and IL-13 by Th2 cells,[59] subsequently inducing a selective suppression of the Th1-mediated cellular immunity and a skew toward Th2-mediated humoral immunity. Interestingly, it has been postulated that this Th2 shift may actually protect the organism from systemic 'overshooting' with Th1/proinflammatory cytokines with tissue-damaging potential.[60]

The notion that stress represents a threat to pregnancy maintenance may appear to be in contradiction with the understanding that high levels of GC promote fetal tolerance by protecting pregnant women from overshooting abortogenic Th1/proinflammatory cytokines. However, this hypothesis can be rejected: besides the often-quoted immunosuppressive effects of GCs, relevant examples of proinflammatory actions of CRH —which triggers the release of GC–have been introduced.[61] In addition, as already described, neuroendocrine responses to stress also include activation of the sympathetic nervous system.[23] Lymphoid organs are prominently innervated by noradrenergic nerves

fibers[62] and the immune system appears to be regulated via the sympathetic nervous system/catecholamines at regional, local, and systemic levels.[19–22,63] Lymphocytes express adrenergic receptors, and respond to stress-induced catecholamines with lymphocytosis, and distinct changes in lymphocyte trafficking, circulation, proliferation, and production of proinflammatory Th1-like, all of which can interfere with fetal tolerance.[64,65]

Besides the cardinal stress mediators, neurotrophin nerve growth factor (NGF) is progressively appreciated as a pivotal regulator involved in the stress response.[66] In addition to functioning as a trophic factor for peptidergic and sympathetic neurons and axon sprouting, NGF acts as a strong immunomodulator, endorsing interaction between neuronal, glia, and immune cells and facilitating cell migration through vascular endothelium.[67] Moreover, stress-triggered fetal rejection has been prevented by neutralizing NGF in mice.[68]

Apart from neurohormones and neurotrophins, progesterone mediates the onset, development, and maintenance of pregnancy.[69,70] Stress has been linked to decreased levels of progesterone in human[8] and nonhuman mammals.[70–73] Progesterone replacement abrogates effects of stress exposure by decreasing the levels of the abortogenic proinflammatory cytokines.[69] Such endocrine-immune cross-talk is exceedingly dependent on a specific $CD8^+$ T cell population, since depletion of CD8 leads to termination of the protective effect of progesterone on pregnancy.[69]

Uterine DC may serve as a switchboard between fetal rejection and tolerance.[57,74,75] DC are the most potent antigen-presenting cells (APCs) involved in the defense of the body and in the maintenance of the immune tolerance. The endogenous regulation of DC function is still poorly understood, yet their maturation, migration, and their expression of stimulatory and costimulatory molecules have major consequences on the immune response.[57] Vasoactive intestinal peptide (VIP), produced by decidual lymphocytes during the early postimplantation period[76] has been shown to decrease in mucosal tissue in response to stress in rats.[77] VIP presents potent anti-inflammatory actions and affects the early stages of DC differentiation and results in the generation of DC that cannot mature following inflammatory stimuli.[78] These DC exhibit a tolerogenic phenotype and are characterized by low expression of co-stimulatory molecules (CD40, CD80, and CD86), low production of pro-inflammatory, Th1-like cytokines, increased production of anti-inflammatory cytokines such as IL-10, and capacity to induce regulatory T cells with suppressive actions, all of which will promote fetal tolerance.[57] What remains to be elucidated is whether stress alters VIP expression at the fetomaternal interface.

Immature DC reside in the decidua during early pregnancy[57,74,75] and possibly serve as sentinel cells of the tissue environment for potential danger signals. In mice, the majority of decidual DC during early gestation is immature, and the highest percentage of immature DC occurs during blastocyst adhesion and early implantation.[79] However, in pregnancies with high abortion

risk, for example, induced by exposure to experimental stressors, an increase of mature APC can be observed.[57] By blocking crucial ligands required on APC to induce T cell activation, mechanisms of fetal tolerance are restored in stress-challenged pregnancies.[54,57] Besides VIP, stress hormones and/or progesterone may initiate a considerable plasticity of DC phenotype and future research is likely to provide detailed insights on the impact of hormones on DC phenotype, for example, at the fetomaternal interface.

CONCLUDING REMARKS

Evidence continues to accumulate indicating that stress can lead to reproductive suppression. The relationship between stress, immune function, and reproduction may have arisen through natural selection due to its value in preventing or stopping pregnancy in dire circumstances. However, in modern industrialized environments stress-triggered mechanisms of reproductive suppression may have lost some of their original adaptive value and may even result in, or aggravate, reproductive pathologies.

Our understanding of the biologic mechanisms mediating the interplay between the stress, immune, and reproductive functions has advanced. There are, however, various aspects of their relationship that still require further research. Animal research is revealing some of the neuroendocrine–immune pathways linking reproductive suppression and stress. Translation of those results to human applications is, however, a complex process. The patient population in clinical studies is generally self-selected and stress "quantification" is difficult. Tissue collection can often only be performed retrospectively, leaving much room for discussions of cause versus effect. Clinicians and basic scientists should join efforts to elucidate hierarchical, temporal, and spatial interactions of key parameters during central and peripheral responses to stress, so that a list of candidate targets for clinically useful therapeutic interventions could be identified. Also, in order to understand the relationship between stress and reproduction in healthy women, more population-based prospective studies will be needed. We still have much to learn about basic important issues, such as how the effects of stress may change as gestation progresses or the role of the HPA axis during the transition between lactation amenorrhea and eumenorrhea. Only longitudinal studies will provide answers to those questions.

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