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Stress and Other Environmental Factors Affecting Fertility in Men and Women: Overview

by Andrés Negro-Vilar

To understand how environmental factors contribute to fertility or infertility in humans, it is first necessary to define environment. A view that will guide this review is that environment represents the "external milieu," analogous to the well-defined concept of "internal milieu" first introduced by Claude Bernard. Within this context, the environment provides both positive and adverse influences on reproductive health and development. Environmental factors can then be classified into categories such as physical, chemical, biological, behavioral, and socioeconomic. In many circumstances, multiple environmental factors may contribute to adversely modify human health. It has been suspected and in some cases demonstrated that stress can adversely affect reproductive function. Both animal and human data support this contention; however, the human data are clear in extreme situations (e.g., inmates of concentration camps) but less so under less drastic conditions. In recent years many advances have been made concerning the neurochemical mechanisms that mediate the effects of stress on reproductive functions and on the identification of "stress hormones" that may not only be involved in the stress response but also serve as biochemical markers to identify and correlate stress with different fertility parameters. Nutrition also plays an important role in infertility, and undernutrition or nutrition disorders are associated with stress in infertility. Environmental factors are often invoked as contributing to many cases of unexplained infertility. However, the direct causal relationship between those factors and the ensuing infertility of the couple are seldom well established and remain largely anecdotal. Several problems contribute to this state of affairs: *a*) the multifactorial nature of the contributing factors; *b*) the poor design of many of the studies; *c*) the diversity of parameters evaluated and whether they measure outcome (i.e., pregnancy rates) or intermediate events (semen values, ovulation, etc.); and *d*) the difficulty in monitoring exposure in terms of time and degree of intensity. Until unified criteria are applied consistently and systematically to evaluate environmental influences on human reproductive health, many cases of infertility will remain unexplained.

Introduction

The interaction between man and environment is continuous and certainly has influenced the process of evolution of the species. This interaction is in certain cases beneficial but in many it is hostile. Indeed, mankind has introduced elements into the environment that either pollute or modify environmental conditions with resulting negative effects on human health. Conversely, adverse environmental conditions not controlled or influenced by man can also affect human health and behavior. This is a continuously evolving process, with some elements that remain fairly constant over a relatively long period of time (decades or centuries) and others that can rapidly progress or change in a much shorter time frame (environmental disasters). Before attempting to evaluate environmental influences on adult reproductive functions in the human male and female, it is necessary to provide some definitions to focus the terms and the scope of the problem.

Environment: A Definition

To understand how environmental factors contribute to fertility or infertility, it is first necessary to define "environment". I propose here that environment represents the "external milieu" by analogy with the well defined concept of "internal milieu" introduced by the French physiologist Claude Bernard. Using this concept, the following definition is proposed:

> *Environment* represents the totality of physical, chemical, biological, behavioral and socioeconomic factors or conditions that constitute the external milieu surrounding the human organism.

Laboratory of Molecular and Integrative Neuroscience, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

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Table 1. Categories of environmental factors.

Category	Examples
Physical	Light, temperature, altitude, radiation
Chemical	Natural or man-made
Biological	Viruses, microorganisms
Behavioral	Stress, drug addiction
Socioeconomic	Nutrition, habitat, occupation, hygiene, education

Within this context, it is clear that this external milieu provides and conveys both positive and adverse influences that can affect every aspect of human health and development. This broad definition needs to be complemented by a description of the different categories that may serve to classify the different types of environmental factors affecting human health. As seen in Table 1, environmental factors can be divided into several categories: physical, chemical, biological, behavioral, and socioeconomical. Several key examples are given, but the list is by no means all-inclusive. In some cases the distinction between some of these categories is clear, whereas in others it is blurred. In looking at some of the latter (e.g., stress, socioeconomic) it becomes obvious that several if not many environmental factors may often be associated thus making it more difficult to ascertain the importance of their relative contribution.

The definition of reproductive health given by the World Health Organization (WHO) also has a broad scope, suggesting that multifactorial environmental inputs may introduce disorders of an organic, functional, or psychological nature. How is reproductive dysfunction evaluated, then? This is one of the complex aspects of the problem, and it has certainly contributed to the present state of confusion in the field. If one is going to evaluate the fertility potential of a couple, outcome (pregnancy) is obviously the gold standard. Other parameters, such as semen quality, ovulation, etc., although important markers for potential dysfunction, are not reliable measures of outcome. Evaluation of conception rates is obviously a desired parameter to ascertain the impact of a given environmental factor. Yet, if one is to analyze the impact of that same factor on an individual man or woman, less precise or reliable parameters (other than pregnancy) have to be used to quantitate and characterize the effect. Even pregnancy itself is a somewhat misleading parameter when applied to an individual couple, since subfertility induced by an environmental agent may still exist although pregnancy is achieved at a given time. It appears from the above that well-controlled, large population studies can provide reliable data on the influence of specific environmental factors on infertility. However, these studies are not without problems because levels of exposure, length of exposure, and preexisting or coexisting conditions may clearly affect the degree of damage to the reproductive capacity of the couple. In the case of environmental disasters, many of the above conditions could be more closely controlled, and, thus, lessons can be learned from those occurrences. In most other instances, however, analysis of the impact of an environmental agent or toxin needs to be conducted using different indexes of reproductive performance in addition to pregnancy. The above caveats notwithstanding, what do we know and not know about environmental influences on adult reproductive health?

Table 2. Links and targets for environmental agents.

System	Role
Nervous system	Sensory systems target for all environmental factors; impact affects neural control of reproduction
Endocrine system	Links environment to the human genome; controls reproduction
Immune system	Protects and adapts or affects cellular responses to agents; can influence reproduction
Respiratory, gastrointestinal, skin	Route for entry/exit
Receptors, enzymes, second messengers, genes	Ultimate targets for agents/toxins affecting reproductive functions

Organ Systems and Targets for Environmental Noxious Agents

Environmental agents interact with and/or affect reproductive tissues and functions through a variety of receptors linked to different organ systems. These interactions are outlined in Table 2. Briefly, a number of sensory systems linked to the nervous system transduce environmental signals such as light, noise, temperature, smell, and touch into chemical signals that affect the function of the neuroendocrine system, which controls reproductive functions and sexual behavior (*1*). Psychological and behavioral influences on reproduction are also mediated by the nervous and neuroendocrine systems (*1*). The neuroendocrine system controls every aspect of reproductive function (*2*), and hormonal factors are the chemical links between the environment and the human genome (*3*).

The immune system reacts and responds to antigenic exposures and, in turn, can modulate or adversely affect reproductive events. The respiratory and gastrointestinal systems as well as the skin act as routes of entry/exit for many environmental factors and biologically active agents. The ultimate target of environmental factors are the receptors, enzymes, and second messenger systems as well as the genes that are involved in the regulation of cellular development, differentiation, and function in reproductive tissues. These targets also include enzyme systems responsible for the metabolism, inactivation, and detoxification of any biologically active substance or toxin. These concepts clearly indicate that reproductive health can be impaired not only by agents or toxins that directly affect reproductive tissues but also by substances or factors that affect a number of other tissues or systems which indirectly regulate or support reproductive functions.

Stress, Nutrition, and Behavioral Effects on Reproductive Functions

Stress affects a large number of biological systems, including the reproductive system. Defined by Selye (*8*) more than half a century ago, the term "stress" has been used to include a variety of responses elicited by noxious or

potentially noxious stimuli. Many of these stimuli originate in the environment, some are derived from the response of the individual to environmental factors, and some are psychogenic and in certain cases may be the result of the interaction of what the individual perceives from the environment and the elicited response. Cultural, occupational, and many other behavioral differences can modify or sensitize the stress response and the ensuing change in reproductive function.

Experimental data in animals and humans suggests that chronic or severe stress leads to anovulation and amenorrhea in women (*4*) and to decrease in sperm count, motility, and morphology (*5,6*) in men. However, in many instances, stress has a more subtle, less-defined influence or is associated with other factors that make the interpretation of the observed effects more difficult. In addition, stress affects many endocrine and other regulatory systems, and thus the resulting effects are usually not limited to changes in reproductive function. Nevertheless, there are some well-defined syndromes associated or induced by stress that result in abnormal reproductive functions. Moreover, the neuroendocrine mechanisms triggering the stress response as well as the chemical signals mediating these responses are now better known.

Neuroendocrine Events during Stress

The hypothalamic-pituitary-adrenal (HPA) axis has been known to be involved in the stress response for many years (*8*), and a large number of reports have contributed information with animal and human data (*7*). The main players in this axis are corticotropin-releasing hormone or factor (CRF), adrenocorticotropin hormone (ACTH), and cortisol. Since the discovery of the structure of CRF by Vale and colleagues (*9*), many advances have been made to enhance our understanding of the mechanisms mediating activation of the HPA axis by stress (*10*) and the subsequent changes in reproductive function. In addition to CRF, several other brain neurotransmitters such as vasopressin, oxytocin, β-endorphin, angiotensin II, epinephrine, norepinephrine, and serotonin, among others are known to be involved in the mediating and integrated response to stressful stimuli (*10–12*). Several of these have been called "stress hormones" to indicate their primary role in stress responses. In many instances, secretion or activation of these hormonal systems serves as a biochemical marker to measure the stress response. In general, increased CRF secretion is almost always associated with an activation of the HPA axis. Concomitant increases in vasopressin secretion also occur in many instances, although there are a few situations in which either CRF or vasopressin secretion can be enhanced without changes in the other.

Catecholaminergic and serotoninergic systems are also markers for HPA activation during stress responses, and interference with the action of these amines can result in blunted or nullified stress responses. A close association also exists between the activation of CRF and central opioid (β-endorphin) systems. Secretion of CRF, vasopressin, and some of the amines into the pituitary portal vasculature leads to an increased activation of the corticotrophs in the anterior pituitary and to an enhanced release of ACTH and β-endorphin (*10,11*). The elevated levels of ACTH increase cortisol secretion from the adrenal gland, which leads to a number of adaptive changes in metabolic activity. In addition to this neurohormonal pathway, there is also a direct neural stimulation of the adrenal medulla, which results in enhanced secretion of adrenaline. This hormone contributes to the well known "fight or flight" reaction involving a number of endocrine, metabolic, and autonomic reflexes. Under chronic stress situations, changes in the steady-state levels of hormones and in their metabolic clearance may occur and part of the process of adaptation may involve sacrificing certain functions, such as reproduction, in order to maintain other vital functions.

Recent work has clearly demonstrated that enhanced CRF activity, i.e., increased release within the brain and into the pituitary portal circulation, leads to a suppression of gonadotropin secretion and, thereby, to decreased gonadal function. The intrinsic mechanism mediating this response is a direct inhibition by CRF of the activity of the luteinizing hormone-releasing hormone (LHRH) neurons that control gonadotropin secretion. CRF has been shown to shut down electrical activity of the LHRH pulse generator in rhesus monkeys (*16*) and to decrease release of LHRH in the hypophyseal portal circulation (*17*). Direct evidence for an inhibitory effect of CRF on gonadotropin secretion in the human has been provided by Barbarino et al. (*18*). These authors showed that CRF infusion to normal women reduced plasma levels of LH and follicle-stimulating hormone (FSH). This effect is abolished by the administration of naloxone, an opioid receptor blocker, suggesting that opioid peptides are involved in mediating the effects of CRF on LHRH and gonadotropin release, both in animals (*19*) and in the human (*18*). The accompanying acute increase in cortisol levels does not appear to be involved in mediating the inhibitory response (*16,18*). However, chronic increases in cortisol secretion such as those seen during prolonged stress may lead to inhibition of gonadotropin release, as recent studies in the rhesus monkey demonstrate (*20*). The mechanism appears to be a decreased function or activity of the LHRH pulse generator, which leads to decreased gonadotropin secretion and disruption of the normal gonadotropin pulsatility pattern.

Evidence is still lacking to support a clear, direct effect of corticosteroids on the gonads to suppress gonadal function, although it is conceivable that some of the effects may be mediated locally. However, more research is needed to clarify this issue.

Stress and Female Infertility

There is good evidence to support that excessive emotional stress, alone or in combination with changes in eating and nutrition patterns and exercise, can cause chronic anovulation. This disorder usually falls under the classification of hypothalamic amenorrhea, but in reality it represents a wide spectrum of reproductive disorders, which are summarized in Table 3. Chronic anovulation

Table 3. Stress-related disorders in women.

Chronic anovulation
Psychogenic amenorrhea
Pseudocyesis
Stress-related eating disorders
Anorexia nervosa
Bulimia
Exercise and menstrual dysfunction
Hyperprolactinemia and amenorrhea
Early pregnancy failure

Table 4. Stress-related disorders in men.

Decreased sperm count
Decreased sperm motility
Altered sperm morphology
Impotence
Ejaculatory disorders
Decreased serum lutinizing hormone and testosterone

associated with hypothalamic (or psychogenic) amenorrhea is more frequently seen and detected, although the direct link to stress is not always easy to establish (*4,21,22*). Elevated cortisol levels are associated with amenorrhea in these women (*21,22*), and abnormal responses to CRF have also been established (*22*). Circadian changes have been noted as well. For instance, the cortisol and prolactin responses to the noon-time meal are blunted in these women (*21*).

Psychologic distress is generally recognized as a contributing factor to infertility (*23*), and psychologic distress has been found to be high in infertile couples. Psychologic amenorrhea is more common in women that have stressful lives and occupations, are usually underweight, single, and have a history of using psychoactive drugs. Disrupted circadian patterns of cortisol secretion (*24*) and changes in opioid tone (*25*) have been reported in these patients.

A close association between stress and eating disorders is frequently found in female patients presenting with anovulation and amenorrhea. This is not surprising since both conditions lead to a slow-down of the LHRH pulse generator and, consequently, of gonadotropin secretion and gonadal function (*13–18,26,27*). Severe eating disorders, such as anorexia nervosa and bulimia, clearly involve several of the same systems that are affected by stress, such as CRF, LHRH opioid peptides, and aminergic systems. These systems are normally involved in the control of many functions, including reproduction, feeding, or eating behavior and autonomic functions, and these explain the frequent association of these disorders with infertility.

Exercise also evokes activation of many of the central pathways mentioned above, notably the opioid systems as well as aminergic and CRF systems. Therefore, exercise is frequently one of the components of the triad (i.e., stress, diet, exercise) that often is associated with infertility. Intense exercise clearly can cause amenorrhea in women athletes (*28*), and several other disorders have been described in female athletes including delayed onset of menarche, oligomenorrhea, anovulation, inadequate luteal phase, and secondary amenorrhea (*29*). The menstrual cycle disorders associated with malnutrition and exercise are often reversible, functional hypothalamic amenorrheas that have as a common denominator a slow-down of the LHRH pulse generator and, consequently, of pulsatile gonadotropin secretion.

Many of the brain hormones involved in stress responses and reproductive functions (e.g., CRF, LHRH, opioids) are also present in the placenta and can affect placental hormone secretion and function. It is not surprising, then, that claims have been raised concerning the role of stress in early pregnancy failure (*4*). However, although this is an intriguing hypothesis, it is difficult to evaluate in the human, and the available animal data are still too limited to arrive at a conclusion.

Stress and Male Infertility

Many of the concepts discussed above in relation to stress and female infertility also apply to the male (Table 4), particularly in terms of the neurohormones involved in mediating the effects. As indicated above, stress has been reported to decrease sperm count, motility, and morphology in men (*5,6*). Other disturbances, such as impotence, sham ejaculation, retrograde ejaculation, and oligospermia, have been reported to be associated with psychological factors in male infertility (*30*).

A variety of occupational activities with high levels of stress, including business, combat or combat training, have been reported to decrease plasma testosterone levels (*5,31*). Emotional stress associated with the evaluation or treatment for infertility of couples has also been associated with oligospermia (*6*), and may contribute to the variations in semen quality observed during evaluation.

Physical stress leads to low testosterone levels due to a reduction in LH pulse frequency (*32*). It is not yet known whether these effects are mediated only centrally by CRF/opioid systems or whether peripheral actions of ACTH/cortisol at the testicular level may also play an important role in the observed effects on semen quality. Recently, CRF (*33*) and β-endorphin (*34*) have been shown to be present in the testis, where they may play an important paracrine role. Since these are "stress peptides," it is plausible to think that changes in the intratesticular levels of these two peptides may contribute to alterations in gametogenic and endocrine functions of the testis.

As is the case in the female, diet and exercise also play a role in male infertility, and they are also frequently associated with stress situations. Decreases in gonadotropin and testosterone levels and gonadal atrophy have been reported in adult men as well as in adolescents (*35*) after chronic malnutrition. Short-term food withdrawal in male rhesus monkeys produces a significant reduction in LH and testosterone pulse frequency, even when body weight changes minimally (*36*). The opioid system also appears to be involved in the mediation of these effects. A similar pattern of changes and of the mechanisms involved appears to occur during exercise and physical activity.

Therefore, it appears that in both women and men the influence of the triad of stress, diet, and physical activity can exert similar individual and, more often, complemen-

tary effects on the reproductive system that lead to infertility. All three of these factors have their effects mediated by activation of similar neuroendocrine pathways involving CRF, β-endorphin, and the catecholaminergic systems (noradrenaline, adrenaline, and dopamine). These systems, in turn, control reproductive functions (by interacting with the LHRH neuronal system) as well as modulating eating behavior and autonomic mechanisms involved in responses to exercise and metabolism.

Future Needs

In the area of stress and infertility, our knowledge of the basic mechanisms mediating stress responses has progressed substantially, and this will allow interested researchers to formulate well-designed paradigms to evaluate the impact of stressful agents or situations on reproductive performance. The combination of psychological tests to measure stress levels with biochemical parameters to quantitate stress hormone responses should provide a good framework in which to address specific questions on fertility parameters. A more challenging problem still remains in trying to isolate confounding variables because stress situations as discussed above are often associated with other types of disorders. A fruitful area of research is emerging in the interplay between the neuroendocrine and the immune systems, particularly to ascertain how chronic stress modifies immune system function and what contribution this has to infertility.

In general, environmental factors are often invoked as contributing to many cases of otherwise unexplained infertility. However, the direct causal relationship between those factors and the ensuing infertility of couples is seldom well established and remains largely anecdotal. Several problems contribute to maintain this relatively confusing state of affairs: *a*) the multifactorial nature of the contributing factors; *b*) the poor design of many of the studies; *c*) the diversity of parameters evaluated and whether they measure outcome (i.e., pregnancy rates) or intermediate events (semen values, ovulation, etc.) and *d*) the difficulty in monitoring exposure both in terms of time and degree of intensity. Until unified criteria are applied consistently and systematically to evaluate environmental influences on human reproductive health, many of the cases of female or male infertility will remain unexplained.

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