Nutritional Influences on Reproduction: A Functional Approach

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32.1 Introduction

Reproduction is one of the most basic biological processes, yet it is also among the most mysterious. On one level, human reproduction merely requires the fusion of two haploid gametes, forming a diploid zygote. This zygote must then divide 40 times, amassing 1.4 trillion cells in the process (assuming the average weight of a newborn is 3250 g) [1]. The resulting conglomeration of cells is then ready to enter the world as a human infant. This newborn, however, is not merely a mass of molecules. It is a highly organized and immensely complicated network of other living organisms. Some of these organisms are endogenously derived (the 1.4 trillion human cells) [2], while others are acquired exogenously. Of those acquired, some are inherited (mitochondria), some are acquired within the womb, and still others are acquired as the fetus is exposed to the environment during and following childbirth [3].

Within the microenvironment, each of these cells has its own nutritional requirements, need for waste management, and defense against invaders. They all serve some unique purpose within the larger community that is a human organism. For endogenously derived cells, each cell's purpose is expressed through its phenotype. A cell that migrates to the heart will develop phenotypical characteristics of a cardiac cell, whereas a cell that migrates to the liver will develop characteristics of a hepatic cell. Despite clear phenotypical differences, both cells are genetically identical. The environment determines a cell's ultimate phenotypical expression, whether in the promotion of physiology or pathology.

The environment, therefore, is one of the key determinative factors in the health of an organism. Nutrients, as largely exogenous molecular influences, make up an important part of this environment, and variations in the type and quantity of such influences can significantly alter physiology. It is within this context that we will explore the dynamics of reproduction. The goal of this chapter is to help the reader understand the complexities inherent in reproduction and to create effective strategies for determining an appropriate nutritional intervention. This chapter is not, nor is it intended to be, a comprehensive catalogue of nutritional influences on reproduction.

32.2 Microenvironments and Complexity

Reproduction is a biological imperative and our bodies have evolved to survive and reproduce. As a result, the successful treatment of reproductive issues often has more to do with removing impediments to reproduction than directly facilitating conception. While both strategies merit consideration within any given case, it should be noted that the direct facilitation of conception through assisted reproductive technologies (ART), such as in vitro fertilization (IVF), even in the youngest and most fertile population, has a success rate of less than 50%. By the time a woman is 43 years old, she has a less than 4% chance of achieving a successful pregnancy through ART [4].

Interestingly, when ART techniques are combined with other modalities designed to address factors influencing the uterine environment, significant increases in pregnancies and live birth rates have been reported [5–7]. As we will explore, the uterine and ovarian microenvironments are essential factors in reproduction. The status of these microenvironments, however, is intimately entangled with the status of the relative macroenvironment of the organism. Indeed, many reproductive pathologies are merely one aspect of a larger clinical picture. For example, endometriosis is a condition that affects 10–15% of reproductive-age women and is associated with reduced fertility [8]. Researchers noted a significant association between endometriosis and pigmentary traits, including an increased number of cutaneous nevi, freckles, and those with sun-sensitive skin [9]. While the precise relationship between pigment and endometriosis has yet to be elucidated, it has been shown that women with endometriosis have a higher risk of melanoma [10]. Furthermore, both melanoma and endometriosis have been associated with environmental toxins, including PCB and organochlorine exposure [11]. One's ultimate toxic burden, while strongly correlated with the dose and type of toxic exposure, is also largely influenced by one's detoxification capacity for such toxins. In the case of PCBs, biotransformation occurs via the cytochrome P450 1A1 enzyme (CYP1A1) [12]. It was found that individuals with genetic polymorphisms in the gene that codes for CYP1A1 (A4889G) have significantly higher risks of cancer [13] and endometrial hyperplasia [14]. Similarly, genetic polymorphisms in other genes, such as the GSTM1 gene involved in the regulation of glutathione S-transferase (and thus protection from PCBs), were associated with an increased risk of endometriosis [15]. Because GSTM1 is also involved in detoxification of electrophilic compounds including carcinogens, therapeutic drugs, and other environmental toxins and products of oxidative damage, any findings related to issues in glutathione-mediated detoxification pathways warrant an inquiry into GSTM1 and other polymorphisms. In the case of GSTM1, the frequency of the particular polymorphism rs366631 in the general population is 50–78% (depending on race) [16]. Therefore, it is more likely than not that a patient presenting with endometriosis will develop a number of seemingly unrelated pathologies.

Endometriosis has also been shown to have a strong inflammatory component in both its pathogenesis and the resulting pathophysiology. Consequently, endometriosis has been associated with an increased risk of cardiovascular disease [17]. Vascular insult and atheromatous plaque progression are commonly found with endometriosis-associated coronary heart disease and can also be found in the general population of women with unexplained infertility [17–18]. While there are many systems affected by inflammation, an attempt to uncover the source of such inflammation should be made. As inflammation is an immune-mediated response, it comes as no surprise that endometriosis has been associated with infectious agents. Less intuitive is that infectious influence is not restricted to pathogens local to the reproductive tract. Take *Helicobacter pylori* (*H. pylori*), for example. *H. pylori* is not known to infect the genital tract or associated nervous or glandular structures, yet it is significantly more prevalent among infertile men and women than among healthy controls [20]. Extra-reproductive pathogens influencing reproduction are not limited to *H. pylori*. Periodontal disease, for example, was also significantly associated with endometriosis [20]. It has been subsequently hypothesized that systemic autoimmune disorders and possibly endometriosis may be an inflammatory response to seeded periodontal bacterial pathogens [20]. A variety of local pathogens have also been associated with an increased risk of developing endometriosis. Some of these include the human papillomavirus, *Escherichia coli*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* [21–22]. In addition to pathogens, inflammation can be induced by autoimmunity. In women with endometriosis, the presence of autoantibodies is a common feature [23].

Aside from the cardiovascular, toxicological, reproductive, and immune factors, endometriosis has perhaps most strongly been associated with endocrine pathology. Indeed, estrogen is often considered to be one of the most important factors in the pathogenesis of endometriosis [24]. What is less well known is that progesterone resistance may play an equally important role [25]. Progesterone resistance can result from various etiologies, one of the more important of which is via modulation of the endocannabinoid system (ECS). The cannabinoid receptor type 1 (CB1-R), for example, has been found to have essential reproductive functions [26] and appears to be responsible for progesterone's anti-inflammatory actions. Indeed, within the reproductive tract, the uterus contains the highest concentration of CB1-R ligands, and the activation of CB1-R seems to be directly involved in implantation. Altering the endocannabinoid system by inhibiting progesterone (a CB1-R ligand), or through direct exogenous ligand exposure (via cannabis use), resulted in reproductive malfunctions [25].

Other hormones have been associated with endometriosis as well. For example, low levels of vitamin D were found in women with endometriosis and associated pelvic pain [27]. Excessive exposure to thyroid hormone, for example, in Graves' disease, was also associated with endometriosis [28], as were genetic polymorphisms in the renin-angiotensin system [29].

Emotional factors were also found associated with endometriosis, with stress contributing to the development and severity [30]. Interestingly, endometriosis patients with high stress had lower salivary cortisol than controls, leading researchers to postulate that the hypocortisolism may be an adaptive response [31].

While there are many other factors that can influence endometriosis and reproduction in general, this example illustrates the importance of approaching infertility as a "nonrandom" occurrence. Different infertility etiologies are genetically and clinically linked with other diseases, and researchers suggest that we should be treating infertility problems using phenomics, rather than viewing infertility as an isolated and exclusive disease of the reproductive system or HPO/HPA axis [32].

As the previous example illustrates, there are many etiological and pathophysiological factors involved in reproductive pathology. Many of these factors overlap and form an interconnected web. Organizing the masses of information can be challenging. One useful model has its roots in Chinese medicine, where they describe all phenomena as some combination of three levels: material/structural, energy/function, and informational (which includes psychospiritual factors). While all phenomena will have some interaction with each of these factors, there tends to be a dominant factor. To illustrate this concept, let us examine a common reproductive pathology: uterine leiomyomas (fibroids).

A fibroid is a structural anomaly that can inhibit reproduction through a number of potential mechanisms, the primary of which is usually some form of physical obstruction. While hormone modulation and potentially certain phytochemicals can inhibit the growth and even regress the tumor [33], many of the therapeutic targets used to accomplish this are antagonistic to reproduction. Estrogen and progesterone, for example, are known growth factors for fibroids. Downregulation of ovarian steroid hormones using a GnRH agonist often results in tumor regression [34]; however, reproduction is not possible under such conditions and the therapy is only approved in the short term. Other hormonal and potentially nutraceutical therapies, such as epigallocatechin gallate (EGCG), work by modulating aromatase or directly inhibiting cellular reproduction [35–36]. In cases of infertility, inhibiting cellular reproduction would be counterproductive. As a result of a lack of options, fibroids suspected of causing infertility are often surgically excised, yet the 8-year recurrence rate for laparoscopic myomectomies is 76% [37]. Such a high recurrence rate may be the result of the failure to address antecedents or triggering events. Indeed, physical activity [38], lower BMI [39], intake of fruit, intake of preformed vitamin A [40], and sufficient sunlight exposure [41] have each been independently associated with lower incidence of fibroids. In animal models, activated vitamin D3 (1,25(OH)2D3) shrank uterine fibroids [42], lending further weight to the epidemiological data [41]. Genetic factors have also been found to play a role [429].

While a number of nutrients have been explored in the treatment of fibroids, human studies are lacking. As a general proposition, correlations between animal studies and human studies are largely disappointing. A review of the highest impact animal studies found only 10% resulted in a treatment approved for use in patients [43]. Thus, animal studies are not reliable predictors of human response. In addition, and as we'll see later in the chapter, many nutritional supplements seem to have dose-dependent biphasic effects: promoting or inhibiting the same function. Genistein, for example, was found either to proliferate or inhibit human uterine leiomyoma cells, depending on the dose [44].

In summary, uterine fibroids have a structural component, being the mass itself and the potential to physically obstruct important aspects of reproduction. They also have a functional component, which covers the etiology and pathophysiology of the fibroid and includes its antecedents, triggering events, and mediators. There are also psychological and informational aspects, including possible genetic and stress components.

As the aforementioned example illustrates, structural abnormalities are often the result of functional or informational problems. Therefore, when dealing with structural issues, an attempt should always be made to identify and address any confounding informational and functional issues.

32.3 Examining the Structural Layer

Structure dictates function. While this is a mantra of biology, as we will discuss, the converse is also true. Structural issues can present on a macroscale, such as a uterine fibroid, or on a microscale, such as improper protein structures or folding. Within reproductive pathophysiology we can roughly divide structural issues into direct and indirect.

Direct structural issues are gross anatomical abnormalities that can change how the reproductive process functions. Hydrosalpinx, ovarian cysts, endometriomas, fibroids, and polyps are all examples of masses that have potential for causing direct structural issues. Within male fertility, these may relate to varicoceles and other tumors, as well as morphological defects in sperm.

Indirect structural issues occur where structural damage or morphological anomalies interfere with cellular communication, often leading to over- or underproduction of hormones or other ligands. This form of structural issue has significant overlap with the energy/function level; however, if the structural level is not addressed, it is very difficult to correct the functional aspects. Therefore, the ideal therapeutic target is usually the structural abnormality and its antecedents. An example of this is a Leydig cell tumor (LT), which can secrete sex hormones resulting in reproductive problems. In men, an LT can lead to feminization, loss of libido, erectile dysfunction, and gynecomastia. In women, they can lead to masculinization, anovulation, amenorrhea, clitoromegaly, and increase in musculature. Treatments aimed at inhibiting the effects of estrogen or testosterone are of limited benefit and destruction of the tumors is necessary to stop the process [45].

Not all tumors, however, should be treated surgically. While a common procedure, aspiration of ovarian cysts has not been found to be effective at increasing fertility outcomes [46] and the "effects of surgical treatment are often more harmful than the cyst itself to the ovarian reserve" [47].

While tumors are one of the more common indirect structural issues, tissue damage is another. Head injuries, for example, can cause damage to the hypothalamus, resulting in hypopituitarism with elevated prolactin levels [48]. Scar tissue from abdominal surgeries or endometriosis can lead to pelvic adhesions and even infertility [49]. The formation of masses in the blood (i.e., clots) are also a common cause of reproductive problems [50]. These can inhibit blood flow or lead to ischemia and are a well-known risk factor in recurrent miscarriage and suspected factors in implantation failure [50]. Clots are an interesting subset of structural issues because nutritional intervention can be very effective. Nutraceuticals such as nattokinase, lumbrokinase, *Desmodium styracifolium*, and *Sargassum fulvellum* have strong fibrinolytic activity [51]. Many Chinese herbs have also been shown to inhibit a number of prothrombotic pathways [51]. Dietary factors can also influence clotting risk, with red and processed meats tending to increase thrombotic risk and fruit, vegetables, and fish decreasing risk [52]. Unfortunately, most studies incorporating meat are poorly designed. Red meat from grass-fed cows, for example, has a completely different nutritional profile than the same meat from grain-fed cows. An analysis done by the Weston A. Price Foundation with the University of Illinois found that "[t]he ratio of omega-6 to omega-3 fatty acids was over 16:1 for the grain-fed tallow but only 1.4:1 for the grass-fed tallow." It should be noted that a higher n6:n3 ratio has been found to be associated with higher thrombotic risk [53]. Therefore, studies discussing "meat" (or any other class of foods without specifying type or source) should be approached with significant skepticism.

Structural impingement of nerves or blood vessels may also result in altered function of a variety of systems. While high-quality data are lacking, biological mechanisms exist whereby spinal or other nerve impingement may negatively impact sexual and reproductive function [54]. Where such patho-mechanisms are suspected, manual manipulation such as massage, chiropractic, or osteopathic manipulation should be explored.

Finally, we have structural damage to DNA. The cause of such damage is often reactive oxygen species (ROS) or reactive nitrogen species (RNS). As will be discussed later in the chapter, this can cause damage leading to poor oocyte quality or oocyte destruction.

32.4 Examining the Functional Layer

Function is life. It is what separates an organism from an inanimate object. The term "function" is a concept. The means of executing that concept is energy. Therefore, energy is one of the most important and fundamental requirements for life and, as a consequence, for reproduction. Indeed, the body seems to have evolved to suppress reproductive function in response to energy deficits [55]. The energy cycle has four basic aspects: production, storage, delivery, and utilization. While energy storage and delivery can be important factors in reproduction, we will focus this discussion on production and utilization.

32.4.1 Energy Production

Efficient energy production occurs primarily through oxidative phosphorylation within the mitochondria. Indeed,