IMMUNOLOGICAL AND NON-IMMUNOLOGICAL APPROACHES TO DIETETIC INTERVENTIONS IN INFERTILITY TREATMENT

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Summary
Studies of recent years show that diet intervention can be a supportive therapy in management of certain reproductive system disorders, including infertility. A review of literature about mechanisms of fertility affected by systemic effects of food allergy, gluten sensitivity, lectins, and biologically active peptides derived from food involved in opioid regulation of reproductive physiology is presented in this paper. Additionally, lifestyle and dietary habits leading to a change in body mass, underweight or obesity, and metabolic deregulation resulting in subfertility have been discussed.

INTRODUCTION
Diet-dependent diseases are an increasing epidemiological problem in the world. Diet therapy can be a part of the management of many diseases including food allergies and intolerance, diabetes mellitus, obesity, hypercholesterolemia, hypertension, osteoporosis, renal diseases, autism, and others. Studies of recent years show that diet intervention can be a supportive therapy in management of certain reproductive system disorders, including infertility. Despite the increasing number of studies, the connection between fertility and nutrition is still underestimated. Infertility is classically defined as the inability to conceive after one year of regular intercourse without contraception [1]. In Europe the prevalence of infertility is estimated to be above 15%. Evaluation of infertility usually identifies different causes, including male infertility (30%), female infertility (35%), the combination of both (20%), and finally unexplained or “idiopathic” infertility (15%). The etiology of reproductive failure may be very complex owing to a neuroendocrine-immune association [2].

The aim of the article: a review of literature about mechanisms of fertility affected by systemic effects of food allergy, gluten sensitivity or by activity of exorphins, lectins, and biologically active peptides derived from diet involved in opioid regulation of reproductive physiology is presented in this paper. Additionally, lifestyle and dietary habits leading to a change in body mass, underweight or obesity, and metabolic deregulation resulting in subfertility have been discussed.

SOURCES AND WORK METHODS
Food allergy and allergic diseases. A food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [3]. Food allergens are defined as those specific components of food or ingredients within food (typically proteins, but sometimes also chemical haptens) that are recognized by allergen-specific immune cells and elicit specific immunologic reactions resulting in characteristic symptoms [4]. Despite the risk of severe allergic reactions there is no current treatment for food allergy; the disease can only be managed by allergen avoidance or treatment of symptoms. A long list of symptoms of food-induced allergic reactions includes uterine contractions as a symptom from the reproductive tract when the uterine muscle is the site of an allergic reaction [3]. A skin puncture test, allergen-specific serum IgE, and atopy patch tests in combination with a food elimination diet can be helpful in identifying foods responsible for clinical reactions.

IgE-dependent food allergies (type I hypersensitivity) are a part of the atopic response. Atopy is the genetic tendency to produce IgE in response to common environmental proteins such as house dust mites, grass pollen, and food allergens. The classic allergic diseases (atopic triad) include atopic dermatitis, allergic rhinitis (hay fever), and asthma. Enhanced Th2 cell activity (the lower index of the Th1/Th2 cells) is characteristic atopic diseases as well as physiological pregnancy, while in-
creased Th1 immune response and/or Th2 hypoactivity are associated with recurrent miscarriage and infertility [2, 5]. There are also therapies that modulate the Th1/Th2 ratio in infertile women to improve their reproductive outcomes [6]. Nowadays there is not enough evidence if an association between atopy and infertility exists and there are conflicting reports on this topic [7-8]. For example, allergies and asthma were found to be more common in women with endometriosis [9].

Most research on the relationship between allergy and infertility focuses on IgE reactions. Although they constitute about 50% of all immunologic food reactions, there are other reactions which are often unrecognized. Among these reactions are those to gluten.

**Gluten sensitivity (celiac disease).** It has been shown that reproductive disorders may be the first symptoms of celiac disease in both women and men [10-11]. Celiac disease is not a food allergy but an autoimmune disease. Food allergies, including wheat allergy, are conditions that people can grow out of. This is not the case with celiac disease. Although more than 200 signs and symptoms have been reported in association with gluten sensitivity it is possible that no symptoms may manifest. Such a condition is called silent or latent celiac disease [12]. Diagnosis of celiac disease is based on serological and histological findings with symptomatic and histological improvement upon gluten withdrawal. Serological testing has become the main mode of determining who will undergo biopsy. Tests for IgA endomyosal antibodies and IgA tissue transglutaminase antibodies have approximately 90% sensitivity and specificity [13]. Histological abnormalities in duodenal biopsies consisting of inflammatory damage of small intestine mucosa include: intraepithelial lymphocytosis, crypt hyperplasia, and various degrees of villous height reduction (so called microscopic enteritis [14]. Chronic nutritional deficiencies in celiac disease are involved in mechanisms of reproductive disorders. Deficiencies and malabsorption especially of zinc, selenium, iron, and folate may interfere with embryogenesis, fetal nutrition, and growth [11]. Selective nutrient deficiencies may result in endocrine derangements. Women diagnosed with celiac disease are at higher risk of recurrent spontaneous miscarriage, delayed menarche, and early menopause or amenorrhea. Aguiar et al. in 2009 published the first report on the prevalence of celiac disease among women with endometriosis which seems to be clinically relevant. Prevalence was found to be about 2.5% [15].

Celiac disease is a common disorder occurring in 0.5% to 1% of the general population in most countries [16]. In a study by Kumar, the seroprevalence of transglutaminase IgA was 6.70% in the group with recurrent abortion, 5.70% in the group with stillbirth, 5.65% in the group with infertility, 9.33% in the group with intrauterine growth restriction (IUGR), and 1.30% in the control group [11]. Celiac disease also affects the ability of men to produce sperm in sufficient quantities and with proper motility and morphology. A growing number of observations propose that screening for celiac disease should be a part of the diagnostic scheme in unexplained infertility because treatment of celiac disease is suggested to be a major predictor for favorable pregnancy outcome [17].

**Dietary lectins.** Some adverse effects to foods are due to lectins which are carbohydrate-binding proteins found in most plants. They have numerous effects on cells and tissues and some are toxic. Lectin-induced diseases include diabetes, arthritis, nephritis, IgE-type allergy as well as infertility and teratogenesis. The list of lectin sources includes wheat germ, beans, lentils, tomatoes, potatoes, and soy beans. Wheat germ, soy beans, and peanuts are considered to contribute the most in pathologies of the reproductive system [18-20]. Lectins and wheat germ in particular bind avidly to human spermatozoa (sperm agglutination), mucus, human ova, and human endometrium which likewise has a high avidity to lectin, and may be involved in mechanisms of infertility. Diet therapy is an avoidance diet of suspected foods and it is important to know that all cereals are similar to each other and contain lectins.

**Opiate-like activity of food derived peptides.** The opioid system is a biological communication system whose activity is mediated by the so-called endogenous opioid peptides which encompass three main groups: enkephalins, endorphins, and dynorphins. The opioid system operates as a multi-messenger system and can participate in the regulation of female and male reproductive physiology at multiple levels: by central effects (with inhibitory effects on GnRH release) and peripheral effects (e.g., at the level of the testes and at the level of the sperm) [21]. Endogenous opioid peptides exert their actions through opioid receptors; there are three principal types of opioid receptors (the δ-opioid, the μ-opioid and the κ-opioid receptors) which are present in different organs and tissues of the female and male reproductive systems. In the testis, endogenous opioid peptides are mainly synthesized de novo by Leydig and Sertoli cells and appear to be able to inhibit Sertoli cell function in an autocrine and paracrine manner [22]. The opioid system is involved in the control of GnRH release
and thus the sex hormones follicle stimulating hormone (FSH) and luteinizing hormone (LH). Opioid activity appears to be altered in women with PCOS, both centrally and peripherally [23]. Because PCOS patients are recognized as having elevated peripheral &-endorphin levels, a dysregulated opioid system seems to be partially responsible for hyperinsulinemia and insulin resistance seen in PCOS [24]. Opioid antagonists (naltrexone, naloxone) have been used in the management of PCOS-related Infertility [23]. Administration of opioid antagonists such as naltrexone in men can improve symptoms of hypogonadism and improve erectile function even though the antagonist did not increase testosterone or LH levels. This suggests regulation at the central rather than the peripheral level [25].

Opioid activity can be demonstrated by peptides derived from food (milk, gluten, rice, spinach): these peptides are called ‘exorphins’ because of their exogenous (alimentary) origin and opioid-like activity [26-27]. Gluten exorphins can be released in vivo after gluten ingestion and can also cross the intestinal barrier fully intact and are detectable in cerebrospinal fluid. In animal models, gluten exorphins have been shown to increase insulin and prolactin levels [28].

Milk proteins, both bovine and human, also make a rich source of biologically active peptides. The µ-opioid receptor agonist peptides, called beta-casomorphins (BCMs), are released from beta-casein. The cells of the digestive, immune, nervous, and endocrine systems are equipped with opioid receptors that modulate functioning of the organism by the activity of endogenous opioids.

**Underweight and overweight.** According to previous research, a woman needs a minimum of 17% of body fat to maintain a menstrual cycle and 22% of body fat would be optimal for reproductive capacity [29]. The Nurses’ Health Study II, which examined prospectively collected data on adiposity for 830 cases of incident ovulatory infertility and 26,125 pregnancies, revealed an increased risk for ovulatory infertility with a body mass index (BMI) below 20.0 or above 24.0 kg/m² [30]. Taken together, these findings demonstrate a U-shaped association between BMI and the relative risk for female infertility.

**Overweight and Obesity.** According to the Centers for Disease Control and Prevention classification of BMI is grouped as follows: normal weight (BMI <25 kg/m²), overweight (25 < BMI <30 kg/m²), and obese (BMI >30 kg/m²) [31]. The effects of diet and obesity have been implicated in disturbances of female reproductive function [32]. Obesity is associated with menstrual dysfunction, decreased fertility, increased risk of miscarriages, and increased risk of birth defects [33]. Menstrual irregularity in obese women correlates with increasing BMI. Infertility in obese women relates primarily to ovulatory dysfunction. Rich-Edwards et al. found a relationship between BMI of women at the age 18 and the risk of subsequent anovulatory infertility. In their study the relative risk (RR) for anovulatory infertility was 1.3 (95% confidence interval [CI] 1.2–1.6) among women having a BMI between 24 and 31 kg/m², and 2.7 (95% CI 2.0–3.7) for those with a BMI >32 kg/m² [34]. A Dutch study found that the probability of natural conception declined by 4% per kg/m² in women with a BMI >29 kg/m² (hazard ratio 0.96, 95% CI 0.91–0.99) [35]. Obesity and menstrual irregularity are common symptoms of polycystic ovary syndrome (PCOS) although not all women with PCOS are obese. Obesity decreases fecundity even in ovulatory women. For obese women, reduction in weight of 10% to 15% may release the hormonal blockage of the reproductive axis [36]. Weight loss may result in spontaneous ovulation, conception, and successful pregnancy; this diet
and exercise therapy is especially successful in women with polycystic ovary syndrome.

Although the mechanisms responsible for the lower fertility observed in obese women are unclear, attention has been focused primarily on the potential adverse effects of elevated insulin levels [33]. These effects are most pronounced in women diagnosed with PCOS. In women with PCOS, insulin stimulates ovarian androgen production both directly and indirectly (by SHBG), resulting in hyperandrogenism and menstrual cycle abnormalities [37]. Reduction in insulin concentrations and increasing levels of SHBG with improvement of fertility can be achieved in these women by moderate weight loss during long-term dietary treatment (calorie restriction to 1000 kcal/day) [38]. It has been clearly established that obesity is associated with reduced gonadotropin secretion in men and women. In adolescent girls obesity is associated with an earlier onset of puberty and precocity, increased risk of chronic anovulation with menstrual irregularities, and greater likelihood of PCOS in adulthood.

A hypothalamic mechanism of the influence of diet and obesity on fecundity is suggested based on results of experimental studies [39-40]. According to a study by Wang, dietary-induced obesity in female mice can be associated with reduced fertility secondary to hypogonadism. This central mechanism of infertility is likely due to chronic hyperleptinemia caused by an accumulation of excess adipose tissue leading to central leptin resistance as manifested by the reduction in leptin receptor expression in the hypothalamus. The decreased leptin signaling, which normally suppresses neuropeptide Y (NPY) expression, leads to an elevated central NPY tone which then inhibits pulsatility of the GnRH neurons. Hyperleptinemia, central leptin resistance, NPY elevation, GnRH suppression, and subfertility associated with dietary-induced obesity in female DBA/2J mice appear reversible through dietary modification [40]. The role of hyperleptinemia in fertility was also assessed in human studies. In obese women leptin may inhibit ovarian follicular development and steroidogenesis and can be associated with reproductive abnormalities [41].

Obesity may adversely affect not only female but also male fertility even though anatomical defects, genetic diseases, and injuries, as well as testicular sperm and hormonal dysfunction, are considered the major causes of male infertility [21]. Obesity is associated with abnormal semen parameters; increased incidence of low sperm concentrations and low progressively motile sperm counts [42]. Obesity can cause male infertility by altered spermatogenesis due to hypoandrogenism (a decrease in serum levels of total and free testosterone) and sequelae of increased serum levels of E2, insulin, and leptin [42-43]. Based on these observations, treatment of infertility in obese couples should take into account treatment of obesity in both partners.

CONCLUSIONS

The awareness of nutritional impact on all aspects of human health and reproductive capacity is increasing. A gluten-free diet may result in conception and a favorable outcome of pregnancy in women diagnosed with celiac disease as well as in patients with symptoms of opioid activity gluten derived peptides (glutemorphin). Similarly, opioid activity derived from milk casein (casomorphins) may be reduced by applying a casein-free diet. Other foods are also potential sources of food-derived proteins; therefore, diet restriction can be enhanced pharmacologically by an opioid receptor antagonist (naltrexone). Given the detrimental influence of maternal overweight and obesity on reproductive and pregnancy outcomes for both mother and child, the American Dietetic Association and the American Society for Nutrition strongly suggest that all overweight and obese women of reproductive age should receive counseling prior to pregnancy, during pregnancy, and in the interconceptional period on the roles of diet and physical activity in reproductive health in order to prevent these adverse outcomes [44].

References


IMUNOLOGINIAI IR NEIMUNOLOGINIAI MECHANIZMAI, KURIAIS PAGRÁSTAS NEVAISINGUMO GYDYMAS DIETA

Santrauka

Pastarųjų metų studijos rodo, kad dieta gali turėti įtakos reprodukcinės sistemos sutrikimams, taip pat ir nevaisingumui. Šiame straipsnyje pateikiama literatūros apžvalga apie sisteminių alergijų maistui, jautrumu gaunamiusiems su maisto produktais glutenumą, lekiniams ir biologiniais atvejais poveikį įvairiems immunologiniams ir neimunologiniams mehanizmams. Aptariama ir gyvenimo būdo, maitinimo ir gyvenimo būdo paieška. Santrauka

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