

Nutritional aspects related to endometriosis

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SUMMARY

This literature review analyzed the evidence on nutritional aspects related to the pathogenesis and progression of endometriosis. Diets deficient in nutrients result in changes in lipid metabolism, oxidative stress and promote epigenetic abnormalities, that may be involved in the genesis and progression of the disease. Foods rich in omega 3 with anti-inflammatory effects, supplementation with N-acetylcysteine, vitamin D and resveratrol, in addition to the increased consumption of fruits, vegetables (preferably organic) and whole grains exert a protective effect, reducing the risk of development and possible regression of disease. Dietary re-education seems to be a promising tool in the prevention and treatment of endometriosis.

Keywords: endometriosis, fatty acids, omega-3, diet, feeding, food habits, vitamin D.

INTRODUCTION

Changes in eating habits occurring since the domestication of animals, by the end of the nomadic era and with the advent of agriculture, have brought consequences for the health of humankind in general, especially if we consider that the human body is still metabolically programmed to the hunter-gatherer diet (lean meat of wild animals and uncultivated plants) and a more active lifestyle.¹

In recent decades, there has been a change in the dietary pattern, once rich in natural foods with mono and polyunsaturated fatty acids, fiber, vitamins, minerals, antioxidants and phytochemicals to refined, processed and canned foods, with a large amount of pesticides, colorants, preservatives, acidulants, flavorings and stabilizers. Western diets often have a high energy and low nutritional content (high intake of refined foods, fast food and low consumption of fruits, vegetables and whole grains).²

Factors such as anxiety, stress, pollution, sedentary lifestyle, environmental toxins, pesticides, dioxins and phthalates, polychlorinated biphenyls (PCB's) and xenobiotics, among others, generate imbalances in the body, as they increase circulating free radicals, favoring oxidative stress with increased nutritional demand. Given that the current diet is already deficient in nutrients, the established imbalance may contribute to the onset or worsening of diseases, such as endometriosis, recurrent miscarriages, premature menopause, unexplained infertility, and more.²

Copious evidence suggests that oxidative stress is involved both in the pathogenesis and the pathophysiology of endometriosis.³ Genetic, environmental and lifestyle factors appear to be associated with the development and maintenance of endometriosis. Among the environmental aspects, nutrition has been little studied, despite evidence showing its impact on the origin and progression of the disease.^{4,5}

The first scientific article that addresses the subject was published in 2004, by Parazzini et al. The authors evaluated 504 women aged between 20 and 65 years, using a food frequency questionnaire. They found that the highest weekly intake of fruits and vegetables was inversely associated with risk of developing the disease (vegetables: RR 0.3; 95CI 0.2-0.5, p=0.002; and fruits: RR 0.6; 95%CI 0.4-0.8, p=0.002). In contrast, consumption of red meat, cold cuts and sausages has been identified as a risk factor for the development of the disease.⁶

In this field, studies have faced difficulties arising from differences in dietary habits in different regions, the different composition of the same food in certain countries and a lack of homogenization to evaluate eating habits (food frequency questionnaire, habitual recall, seven-day recall, weighing of food, etc.).⁴ Another obstacle is the influence of pain on the eating habits of women affected by changing appetite, and consequently the choice of diet.

Despite the difficulties and disagreements among authors, the objective of this study was to assess recent evidence on nutrition and eating habits in relation to endometriosis.

METHODS

The largest medical information databases (Medline-Pubmed, Lilacs and Cochrane Library) were searched for the keywords “endometriosis” AND “nutrition” OR “diet” AND “oxidative stress” OR “inflammation” OR “Omega” OR “fatty acids” OR “antioxidants” OR “epigenetics” OR “n-acetylcysteine” OR “vitamin D” OR “resveratrol”, over the last 10 years.

Of the 113 articles retrieved, 31 were selected in English, French or Spanish based on title and abstract. By reading the abstracts and articles, we selected 21 articles deemed most relevant to this review. Articles related to molecular biology and case reports, which would not have practical applicability, were excluded.

We analyzed 10 case-control studies, 2 prospective studies, 1 randomized prospective study, 1 cohort study, 6 review articles, 2 communications and 2 book chapters.

PATHOPHYSIOLOGY AND NUTRITION

In the typical lesions of the disease, the cells grow, differentiate out of the uterus, and retain their ability to respond to hormonal proliferative stimuli. Furthermore, excess estrogen stimulates the formation of large amounts of prostaglandins (from the even series), promoting inflammation and, consequently, a painful stimulus.^{7,8}

During the progression of the disease, changes occur resulting in abnormal immunological antigen-antibody reactions, contributing to the increase of pro-inflammatory agents.⁷ Women with endometriosis have a higher concentration of lipid peroxidation markers in the blood and peritoneal fluid, which promotes cell adhesion and activation of macrophages. These, in turn, release reactive oxygen and nitrogen species, leading to oxidative stress.⁹

Nutrient (folic acid, vitamin B12, zinc and choline) deficiency may interfere with DNA methylation, resulting in epigenetic abnormalities, given that it alters the expression or silencing of certain CpG (cytosine-phosphate-guanine) genes. In endometriosis, CpG hypomethylation can lead to overexpression of steroidogenic factor 1 (SF1) or estrogen receptor β (ER- β), with a consequent increase in the levels of estradiol and prostaglandin E2 (PGE2), favoring inflammation and cell growth.⁸ Furthermore, the change in methylation of five-week embryos may predispose them to the development of endometriosis in adulthood.⁸

Various types of food demonstrate the ability to interfere in these stages of the pathophysiology. Among those that decrease the risk of developing the disease, we cite vegetables, legumes and whole grains, rich in nutrients (folate, methionine, vitamin B6, vitamins A, C and E) that act on the genome by changing the gene expression and influencing DNA methylation. Diets deficient in these nutrients show alterations in lipid metabolism, oxidative stress and epigenetic abnormalities.⁴

Although controversial, in 2011, Trabert et al. found that the higher consumption of fruits (2 servings or more *versus* one serving or less a day), the greater the risk of developing the disease (RR=1.5, 95CI 1.2-2.3, p= 0.04). With regard to vegetables, the authors found no association. This data can be justified considering that currently pesticides (organochlorines, organophosphates, bipyridines) and dioxins are used in the cultivation of fruit – these pesticides generate reactive oxygen species and reduce the antioxidant capacity of fruits and vegetables, an effect that may be reversed through the consumption of organic fruit. In addition to interfering in the antioxidant capacity of fruits, organochlorine interferes with hormonal pathways, acting on estrogen and androgen receptors.^{5,10}

It is noteworthy that the presence of organochlorine and pesticides in fruits should not contraindicate their consumption. This is merely a warning for prescribers and consumers, who should prefer organic ingredients and, whenever possible, remove the skin from foods that are usually contaminated.

In addition to being a source of nutrient antioxidants, fruits and vegetables favor the increase of estrogen excretion, contributing to hormonal regulation,¹¹ as these foods contain a significant amount of fiber and nutrients.

Nutrients such as calcium, zinc, selenium, vitamin C, vitamin E and bioactive compounds in foods (such as phytochemicals – carotenoids, flavonoids, indoles, isothiocyanates) influence health, interfering with processes closely related to the pathophysiology of endometriosis, as well as hormonal balance, cell signaling, control of cell growth, apoptosis and so on.¹²

Polyphenols (anthocyanins, hydroxybenzoic acids, flavones, isoflavones, lignans, resveratrol) are compounds present in foods that have the ability to modulate the activity of enzymes, as well as strong antioxidant properties.¹³

Resveratrol, a polyphenol found in the skin of dark grapes and *jaboticaba* (*Myrciaria cauliflora*, also known as Brazilian grape) has demonstrated antineoplastic, anti-inflammatory and antioxidant action. The administration of 10mg/kg/day of resveratrol in a rat model (compared

with saline solution) reduced the size of endometrial implants, as well as the levels of vascular endothelial growth factor (VEGF) in the plasma and peritoneal fluid, and of monocyte chemotactic protein (MCP-1) in the peritoneal fluid. Furthermore, it increased suppression of VEGF in endometrial tissue and favored histological changes in the focal point of the disease after treatment.¹⁴

Red meats are associated with higher concentrations of estradiol and estrone sulfate, and their consumption contributes to increased levels of circulating steroids, collaborating with the maintenance of the disease.⁶ It is a food that contains arachidonic acid (omega 6) which, in excess, increases pro-inflammatory substances, and contains dioxins – xenobiotics that act as endocrine disruptors.⁵

Arachidonic acid, an omega-6 polyunsaturated fatty acid ($\omega 6$) – derived from animal foods and decomposed from vegetable oils – is a substrate for the synthesis of prostaglandins and even-series leukotrienes (PGE and LTB4) with marked inflammatory action. Omega 3 ($\omega 3$) – eicosapentaenoic and docosahexaenoic acid – (fish oil, chia oil and flaxseed oil) is a substrate for the synthesis of odd-series chemical mediators (PGE3 and LTB5) with less inflammatory activity.^{15,16}

Both omega 3 and arachidonic acid are synthesized by delta 5 and delta 6 desaturase, so the more omega 3, the less inflammatory substances are synthesized.^{15,16} Although there is no consensus, a ratio of around 2:1 to 4:1 ($\omega 6:\omega 3$) is suggested. A few decades ago (the period before the age of industrialization) the $\omega 6:\omega 3$ ratio was around 1:1 to 2:1, as a result of the greater consumption of vegetables and seafood. In recent years, these indexes have achieved ratios between 10:1 to 20:1 and even 50:1, due to increased consumption of refined vegetable oils, lower consumption of seafood products and reduced consumption of fruits and vegetables.¹⁵

The change in the $\omega 6:\omega 3$ ratio is associated with increased menstrual pain and hormonal and autoimmune disorders in women with endometriosis.¹⁷ In 2011, Savaris and Amaral found that women with endometriosis had a lower consumption of polyunsaturated fatty acids ($\omega 3$ and $\omega 6$) than the control group and lower than recommended, resulting in an imbalance in the formation of long chain polyunsaturated fatty acids ($\omega 3$).

Some authors suggest that supplementation with omega 3 can slow the growth of endometrial implants, reduce pain and inflammation, and improve the quality of life of women with stage III and IV endometriosis.¹⁶ In 2008, Natsu et al. found that supplementation with EPA (eicosapentaenoic acid) led to a reduction in the thick-

ness of the endometrial tissue interstitium, suggesting that the inflammatory process of endometriosis must be concentrated in this region.

Trans fat intake was assessed by the Nurses Health Study II.¹⁸ Women who consumed foods containing hydrogenated vegetable fat the most (margarine, some breads and cookies, snack foods, fried foods, processed products) were 48% more likely to develop the disease than those who consumed less (RR=1.48 – 95CI 1.17-1.88 p=0,001). This type of fat is associated with metabolic molecules that participate in inflammatory processes (TNF, TNF receptor, IL-6, CRP).

Further considering the population of the Nurses Health Study, the authors found that food (not supplements) rich in thiamine, folate, vitamin C and vitamin E were related to a lower rate of diagnosis of endometriosis. It is believed that supplements do not exert the same effect as food because various nutrients and bioactive compounds that interact with each other are found in the diet.¹⁹

Vitamins A, C and E are antioxidant nutrients that prevent lipid peroxidation, a phenomenon that contributes to the development and progression of chronic diseases with inflammatory characteristics.²⁰ Corroborating these data, Mier-Cabrera et al.⁹ found a reduction in markers of oxidative stress in patients with endometriosis with administration of a diet rich in vitamins A, C and E for four months.

In recent years, vitamin D has been extensively studied for its anti-inflammatory, immunomodulatory and antiproliferative action in addition to its known action on bone metabolism.

Lymphocytes CD4, CD8, macrophages and dendritic cells express receptors and enzymes that metabolize and activate vitamin D, suggesting that 1,25-dihydroxyvitamin D (metabolically active form) can be produced locally, performing an autocrine and paracrine role in the endometriosis focus or lesion²¹.

In the endometrium, the active form of vitamin D reduces the synthesis of IL-6, TNF 20 and prostaglandins by suppressing COX-2 expression. Besides increasing prostaglandin inactivation of 15-hydroxy prostaglandin dehydrogenase, high concentrations of 1.25(OH)-D inhibit PG (prostaglandin)²¹ receptor expression.

When a group of women with dysmenorrhea received a dose of 300,000 IU of vitamin D before the menstrual cycle there was a reduction of pain and nonsteroidal anti-inflammatory (NSAIDs) use during the two-month study, compared to the placebo group. Response was greater in patients who reported worst pain severity at the start of the study.²¹

Ngô et al. found that N-acetylcysteine (found in foods with red pigments, garlic, onions, broccoli, Brussels sprouts, oatmeal and wheat germ) regulates cell proliferation and activation of ERK 1/2 in endometriotic cells, and reduces the production of hydrogen peroxide by reducing oxidative stress.²²

N-acetylcysteine (NAC) is the acetylated form of cysteine (amino acid) which, when supplemented, has been shown to reduce the size of the *endometrioma*, replacing proliferative behavior with differentiating behavior, and decreasing the inflammatory and invasive activity.²³

In a case-control study, Porpora et al. assessed the diameter and volume of *endometrioma* in women supplemented with 1800mg of NAC (600 mg/3 times a day or placebo).²⁴ This supplementation was given for 3 days in a week, with a washout of 4 days, for a period of 3 months. A reduction in the diameter of the cyst was seen in treated patients compared to the untreated ones (-1.5mm x 6.6mm, p=0.001).

CONCLUSION

There are few studies on the nutritional aspects related to endometriosis; however, as in a number of chronic diseases, the role of nutrients in the pathophysiology of such diseases has received more attention. For the treatment and control of endometriosis, hormonal medications are the only options currently available, often without therapeutic success and with numerous side effects.

This review allows us to conclude that there is evidence that food and nutrients influence both the pathogenesis and progression of the disease, leading to the possibility of alternative, adjuvant treatments to those suffering from the disease.

It is known that the treatment of endometriosis is multidisciplinary. As such, interferences in this field through the incorporation of nutritionists into teams may, in the coming years, assume an important role in preventive and therapeutic results for combating the disease.

RESUMO

Aspectos nutricionais relacionados à endometriose

Esta revisão de literatura analisou as evidências sobre aspectos nutricionais relacionados com a etiopatogenia e a progressão da endometriose. Dietas deficientes em nutrientes refletem-se em alterações no metabolismo lipídico, estresse oxidativo e favorecem anormalidades epigenéticas que podem estar envolvidas na gênese e na progressão da doença. Alimentos ricos em ômega-3, com

efeito anti-inflamatório, suplementação com N-acetilcisteína, vitamina D e resveratrol, além do maior consumo de frutas, verduras (preferencialmente orgânicas) e cereais integrais, exercem efeito protetor, com redução no risco de desenvolvimento e possível regressão da doença. A reeducação alimentar parece ser uma ferramenta promissora na prevenção e no tratamento da endometriose.

Palavras-chave: endometriose, ácidos graxos ômega-3, dieta, alimentação, hábitos alimentares, vitamina D.

REFERENCES

- O'Keefe JH, Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our paleolithic genome: how to become a 21st. century hunter-gatherer. *Mayo Clin Proc.* 2004; 27:101-8.
- Halpern G. Nutrição e (In) fertilidade. In: Melamed RM, Seger L, Borges Jr E. *Psicologia e reprodução humana assistida - uma abordagem multidisciplinar.* São Paulo: Gen, 2009.
- Augoulea A, Alexandrou A, Creatsa M, Vrachnis N, Lambrinouadaki I. Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress. *Arch Gynecol Obstet.* 2012; 286:99-103.
- Parazzini F, Viganò P, Candiani M, Felede L. Diet and endometriosis risk: a literature review. *Reprod BioMed Online.* 2013; 26:323-36.
- Paris K, Aris A. [Hypothetical link between endometriosis and accumulation of xenobiotics associated with genetically modified foods]. *Gynecol Obstet Fertil.* 2010; 38:747-53.
- Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V, et al. Selected food intake and risk of endometriosis. *Hum Reprod.* 2004; 19:1755-9.
- Savaris AL, do Amaral VF. Nutrient intake, anthropometric data and correlations with the systemic antioxidant capacity of women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2011; 158:314-8.
- Bulun SE. Endometriosis. *N Engl J Med.* 2009; 360:368-79.
- Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, Jiménez-Zamudio L, Tolentino MC, Casanueva E, et al. Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. *Reprod Biol Endocrinol.* 2009; 7:54.
- Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. *Br J Nutr.* 2011; 105:459-67.
- Fjerbaek A, Knudsen UB. Endometriosis, dysmenorrhea and diet--what is the evidence? *Eur J Obstet Gynecol Reprod Biol.* 2007; 132:140-7.
- Trujillo E, Davis C, Milner J. Nutrigenomics, proteomics, metabolomics, and the practice of dietetics. *J Am Diet Assoc.* 2006; 106:403-13.
- Fonseca ABBL, Paschoal V. Nutrifito alimentos coadjuvantes dos fitoterápicos. In: Kalluf LJH. *Fitoterapia funcional.* São Paulo: Valeria Paschoal, 2008. p.224-59.
- Ergenoglu AM, Yeniel AÖ, Erbas O, Aktug H, Yildirim N, Ulukus M, et al. Regression of endometrial implants by resveratrol in an experimentally induced endometriosis model in rats. *Reprod Sci.* 2013; 20:1230-6.
- Martin CA, Almeida VV, Ruiz MR, Visentainer JEL, Matshushita M, Souza NE, et al. Ácidos graxos poliinsaturados ômega-3 e ômega-6: importância e ocorrência em alimentos. *Rev Nutr.* 2006; 19:761-70.
- Khanaki K, Nouri M, Ardekani AM, Ghassemzadeh A, Shahnazi V, Sadeghi MR, et al. Evaluation of the relationship between endometriosis and omega-3 and omega-6 polyunsaturated fatty acids. *Iran Biomed J.* 2012; 16:38-43.
- Netsu S, Konno R, Odagiri K, Soma M, Fujiwara H, Suzuki M. Oral eicosapentaenoic acid supplementation as possible therapy for endometriosis. *Fertil Steril.* 2008; 90(4 Suppl):1496-502.
- Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod.* 2010; 25:1528-35.
- Darling AM, Chavarro JE, Malspeis S, Harris HR, Missmer SA. A prospective cohort study of vitamins B, C, E, and multivitamin intake and endometriosis. *J Endometr.* 2013; 5:17-26.

20. Gentilini D, Busacca M, Di Francesco S, Vignali M, Viganò P, Di Blasio AM. PI3K/Akt and ERK1/2 signalling pathways are involved in endometrial cell migration induced by 17beta-estradiol and growth factors. *Mol Hum Reprod.* 2007; 13:317-22.
21. Lasco A, Catalano A, Benvenega S. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: results of a randomized, double-blind, placebo-controlled study. *Arch Intern Med.* 2012; 172:366-7.
22. Ngô C, Chéreau C, Nicco C, Weill B, Chapron C, Batteux F. Reactive oxygen species controls endometriosis progression. *Am J Pathol.* 2009; 175:225-34.
23. Pittaluga E, Costa G, Krasnowska E, Brunelli R, Lundeberg T, Porpora MG, et al. More than antioxidant: N-acetyl-L-cysteine in a murine model of endometriosis. *Fertil Steril.* 2010; 94:2905-8.
24. Porpora MG, Brunelli R, Costa G, Imperiale L, Krasnowska EK, Lundeberg T, et al. A Promise in the treatment of endometriosis: An observational cohort study on ovarian endometrioma reduction by N-Acetylcysteine. *Evid Based Complement Alternat Med.* 2013; 2013:240702.