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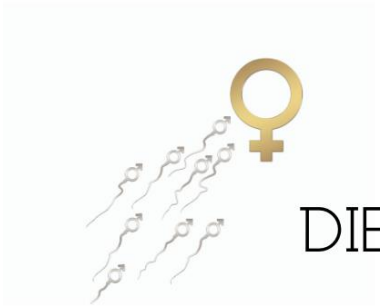
COMPENDIUM OF SCIENTIFIC ABSTRACTS



REGARDING

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OF FERTILITY PATIENTS WITH

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Content

Introduction 4

Fertility is impaired in women with endometriosis by a number of pathways 5

Endometriosis and Nutrition 7

Nutritional aspects related to endometriosis. 8

Self-management and Psychological-Sexological Interventions in Patients With Endometriosis: Strategies, Outcomes, and Integration Into Clinical Care 8

Influence of diet on the risk of developing endometriosis. 9

A Prospective Cohort Study of Meat and Fish Consumption and Endometriosis Risk 9

Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. 10

Different nutrient intake and prevalence of gastrointestinal comorbidities in women with endometriosis. 11

Magnesium deficit ? overlooked cause of low vitamin D status? 11

Magnesium in the gynecological practice: a literature review. 12

Zinc and endometriosis 12

The possible role of zinc in the etiopathogenesis of endometriosis. 12

Decreased zinc and increased lead blood levels are associated with endometriosis in Asian Women. 13

Oxidative stress and endometriosis 13

Oxidative Stress and Endometriosis: A Systematic Review of the Literature. 13

Markers of oxidative stress in follicular fluid of women with endometriosis and tubal infertility undergoing IVF. 14

Effects of oxidants and antioxidants on proliferation of endometrial stromal cells. 14

The Role of Oxidative Stress and Membrane Transport Systems during Endometriosis: A Fresh Look at a Busy Corner. 15

Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. 16

More than antioxidant: N-acetyl-L-cysteine in a murine model of endometriosis. 16

A promise in the treatment of endometriosis: an observational cohort study on ovarian endometrioma reduction by N-acetylcysteine 17

Oocyte Quality 17

Endometriosis Is a Cause of Infertility. Does Reactive Oxygen Damage to Gametes and Embryos Play a Key Role in the Pathogenesis of Infertility Caused by Endometriosis? 18

Oocyte Oxidative DNA Damage May Be Involved in Minimal/Mild Endometriosis-Related Infertility..... 19

Increased Concentration of 8-hydroxy-2'-deoxyguanosine in Follicular Fluid of Infertile Women With Endometriosis..... 19

Markers of Oxidative Stress in Follicular Fluid of Women With Endometriosis and Tubal Infertility Undergoing IVF..... 20

Dietary pain management..... 20

Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. 20

Oxidation-sensitive nociception involved in endometriosis-associated pain. 21

The Effect of Micronutrients on Pain Management of Primary Dysmenorrhea: A Systematic Review and Meta-Analysis..... 21

Polyunsaturated fatty acids and endometriosis..... 22

Serum Polyunsaturated Fatty Acids and Endometriosis. 22

The anti-inflammatory impact of omega-3 polyunsaturated Fatty acids during the establishment of endometriosis-like lesions. 22

Efficacies of vitamin D and omega-3 polyunsaturated fatty acids on experimental endometriosis. 23

Homocysteine levels in endometriosis..... 25

Homocysteine Level in the Blood and Follicular Fluid is Higher in Infertile Women with Endometriosis 25

Apoptosis inhibitors as therapeutic targets 26

The Role of Survivin in the Pathogenesis of Endometriosis 26

Survivin and VEGF as Novel Biomarkers in Diagnosis of Endometriosis. 26

Inhibitor of apoptosis proteins (IAPs) may be effective therapeutic targets for treating endometriosis. 27

Inhibitors of apoptosis proteins in experimental benign prostatic hyperplasia: effects of serenoa repens, selenium and lycopene. 28

Survivin and NAIP in Human Benign Prostatic Hyperplasia: Protective Role of the Association of Serenoa repens, Lycopene and Selenium from the Randomized Clinical Study. 29

Vitamin E succinate inhibits survivin and induces apoptosis in pancreatic cancer cells. 29

RRR-α-tocopheryl succinate induces apoptosis in human gastric cancer cells via the NF-κB signaling pathway. 30

Vitamin D Intake and its Protective Role in Multiple Sclerosis: The Checkmate to Survivin? 30

Survivin is associated with cell proliferation and has a role in 1a,25-dihydroxyvitamin D3 induced cell growth inhibition in prostate cancer..... 32

Fertilovit®F Endo..... 33

Gonadosan Distribution GmbH 33

References.....33

Introduction

Endometriosis is a gynecological chronic inflammatory disease characterized by the presence of endometrial tissue outside the uterine cavity (Matarese 2003). These endometriomas can be found in the ovaries, on the surfaces and inside the pelvic cavity organs (Remorgida et al., 2007), inside the myometrium as adenomyosis, (Kunz et al, 2005) and even in remote tissues like pleura, lungs and the spinal canal (Lombardo et al, 1968) Endometriosis, although not malignant, occurs spontaneously in women who menstruate. Estimates show that it affects an average of 10-20% of all women of reproductive age (Holoch et al, 2010).In infertile women the prevalence is estimated to be even higher in between 35% to 50% (Burney et al, 2012).

There are several theories about the ethiopathogenesis of endometriosis, the two most important ones of which suggest either development in situ by metaplasia or development as a consequence of the dissemination of endometrium. There is evidence to suggest that alterations in the immune response, whether genetically transmitted or environmentally induced, predispose women to the ectopic implantation of endometrial cells transported into the peritoneal cavity by way of retrograde menstruation. This predisposition may exist because of an impaired peritoneal clearing of endometrial cells and fragments or because of pathological angiogenesis (Gazvani et al, 2002).

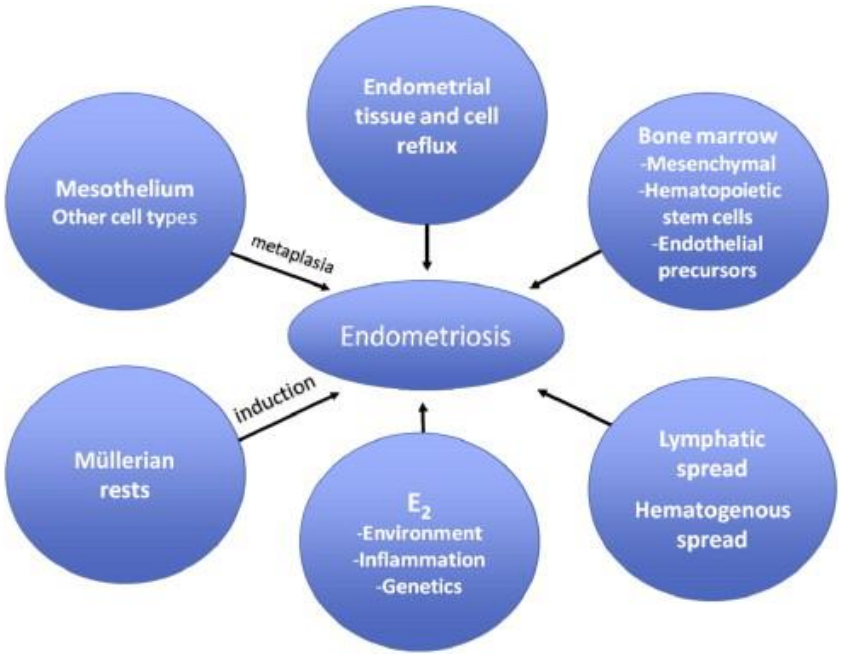

Figure 1: Hypotheses on the etiology of endometriosis. From: Burney; Fertility& Sterility Volume 98, Issue 3, September 2012, Pages 511–519

The main symptoms of endometriosis (though not always present) are pain and infertility (Allaire, 2006) other symptoms include dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding, and/or infertility (Burney et al, 2012).
Endometriosis appears to affect every part of a woman's reproductive tract. Many women with minimal, mild, or moderate endometriosis experience difficulties conceiving. An estimated 50% of endometriosis patients are subfertile (Bulletti et al., 2010).

Fertility is impaired in women with endometriosis by a number of pathways

In endometriosis, there is a dysfunction of the pituitary-ovarian axis altering feedback pathways resulting in abnormal patterns of LH secretion (Bancroft et al., 1992; Cahill et al., 1995). This can impair follicular growth, ovulation and corpus luteum development in the ovary. Impairment of folliculogenesis in women with endometriosis is found in terms of a reduction of the number of pre-ovulatory follicles, follicular growth, dominant follicle size and follicular estradiol concentrations (Cahill et al., 1995; Dlugi et al., 1989). In addition to this, the follicular fluid of patients with endometriosis has been reported to have altered hormone profiles including reduced estrogen, androgen and progesterone and increased activin (Cahill and Hull, 2000). Not surprisingly, altered luteal function has been noted in endometriosis patients, too (Cunha-Filho et al., 2003) and women with endometriosis who have a luteal deficiency are more likely to experience infertility (Cunha-Filho et al., 2001).
Apart from estrogen-dominance, another big issue in patients with endometriosis is cytokine mediated inflammation leading to an increase of reactive oxidative species (ROS) and therefore to increased oxidative stress on the developing oocytes, ultimately causing decreased oocyte quality. Changes in proteolytic enzymes (Ebisch et al., 2007; Smedts et al. 2006; Wunder et al. 2005), cytokines (Carlberg et al., 2000; Garrido et al., 2000; Pellicer et al., 1998; Wunder et al., 2006) and inflammatory molecules (Carlberg et al. 2000; Lachapelle et al., 1996; Wunder et al., 2006) have been reported.
So women with endometriosis in average not only ovulate fewer oocytes than healthy women (Al-Fadhli et al. 2006; Bergqvist and D'Hooghe 2002; Cahill and Hull 2000; Kumbak et al. 2008) but those oocytes ovulated by women with endometriosis are often compromised (Garrido et al. 2000, 2002, 2003; Navarro et al. 2003; Pellicer et al. 2000). One study has shown that women with endometriosis exhibit an increase in apoptosis of the cumulus cells surrounding the oocyte, which has been identified as a good indicator of poor oocyte quality (Díaz-Fontdevila et al. 2009).
The ROS and inflammation-mediating cytokines also have an impact on the fertilizing sperm after intercourse. They contribute to the failure of a spermatozoon to fertilize a potentially compromised oocyte. An increase in peritoneal macrophages during endometriosis can lead to increased phagocytosis of healthy spermatozoa that might have otherwise been able to fertilize the ovum (Muscato et al. 1983). Uterine/oviductal sperm transport is impaired in endometriosis (Kissler et al.2005, 2006, 2007; Leyendecker et al. 1996). Additionally, endometriosis negatively impacts sperm binding to the oviductal epithelium (Reeve et al. 2005). This impairment emerges even in the early stages of endometriosis (Kissler et al. 2007). The inflamma-

tory environment of the peritoneal fluid of patients with endometriosis had in vitro a negative impact on sperm binding to the zona pellucida of the oocyte (Coddington et al. 1992). Finally, inflammation and ROS have an impact on the genetic health of oocytes and sperms: Peritoneal fluid of women with endometriosis has been shown to increase DNA fragmentation in sperms from healthy donors (Mansour et al. 2009b). Interleukin-6 (IL-6) and its soluble receptor, which are present in the peritoneal fluid of women with endometriosis (Harada et al. 1997), reduce sperm motility (Iwabe et al. 2002; Yoshida et al. 2004).

Genetic health of the oocyte is crucial for good embryo development. Aberrant nuclear and cytoplasmic events in embryos from women with endometriosis are six times more likely compared with women without endometriosis (Brizek et al.1995), including cytoplasmic fragmentation (Brizek et al. 1995), darkened cytoplasm (Brizek et al. 1995), reduced cell numbers (Garrido et al. 2002; Pellicer et al. 1995; Tanbo et al. 1995) and increased frequency of arrested embryos (Garrido et al. 2000; Yanushpolsky et al. 1998). Exposure of the embryo to inflammatory cytokines in peritoneal fluid while in the reproductive tract has been suggested to cause these defects (Esfandiari et al. 2005; Furukubo et al.1998; Gomez-Torres et al. 2002).

Apoptosis or programmed cell death of the embryo can also occur through several mechanisms associated with endometriotic lesions such as increased concentrations of inflammatory cytokines or reactive oxygen species (ROS; Agic et al. 2006; Jana et al. 2010). Inflammatory cytokines such as tumor necrosis factor-a can activate caspase-dependent signaling pathways to increase apoptosis (Hu, 2003). ROS can cause mitochondrial damage and DNA strand breaks (Lao et al., 2009). This might also encourage the cell to undergo programmed cell death or apoptosis.

No cure is available for endometriosis and current treatments focus on reducing the pain associated with the disease often causing cessation or chemical alteration of the reproductive cycle. Also, surgical treatments are not curative and may cause detrimental side effects (Acién, Velasco, 2013).

Regarding fertility, the assisted reproductive therapies can help restore fertility in women with endometriosis but unfortunately produce inconsistent results. Some studies have shown that the pregnancy outcome with use of in vitro fertilization (IVF) is similar in women with and without endometriosis (Bergendal et al. 1998; Huang et al. 1997). Women with endometriosis undergoing IVF treatments involving oocytes from a non-affected individual show normal implantation and pregnancy rates (Simon et al. 1994). However, other workers have reported that fertilization and/or embryo cleavage rates after IVF, both in stimulated and unstimulated cycles, are significantly lower in endometriosis compared with controls (Cahill and Hull 2000; Harlow et al. 1996; Hull et al. 1998; Tanbo et al. 1995). Fertilization and embryo cleavage rates remain impaired in women with endometriosis after spermatozoa from their partners are substituted with spermatozoa from donors (Hull et al. 1998). Additionally, implantation rates of oocytes from donors with endometriosis are reduced in recipients who do not have endometriosis (Navarro et al. 2003).

Bringing things together, inflammation and increased ROS can be implicated as a main potential source of endometriosis-related infertility (Gupta, Agarwal 2006, Augoulea et al.2009). Studies have shown increased concentrations of ROS and lipid peroxides in the peritoneal fluid from women with endometriosis (Murphy et al. 1998; Zeller et al. 1987). More recent studies have demonstrated a decrease in the antioxidants present (Jackson et al. 2005), too. This suggests that antioxidant protection is decreased in the peritoneal fluid from women with endometriosis, an occurrence that could negatively affect embryo development (Augoulea et al., 2009).

Endometriosis and Nutrition

Generally, nutrition seems to play an important role in endometriosis. Beneficial effects have been recorded for a diet that takes into account individual intolerances (fructose malabsorption, sorbitol, lactose, histamine, and gluten intolerances are commonest) and aims to avoid pollutants, decrease estrogen dominance, alleviate inflammation, and lower oxidative stress. In addition to that, certain micronutrients targeting apoptosis inhibitors have been of interest as well.

Maintaining a healthy weight is crucial for endometriosis patients, as estrogen is not only produced in ovary, corpus luteum and adrenal cortex, but also in muscle, bone marrow and fat tissue. This is why overweight women tend to have higher estrogen levels than lean women. In addition to that, studies have shown that increased body weight can bring down the antioxidative capacity in endometriosis patients and to worsen the situation (Savaris, Amaral 2011).
A diet rich in antioxidants may be beneficial for overall wellbeing, support oocyte quality and also contribute to pain relief. A new study shows: Women who consume a lot of citrus fruits have a significantly lower risk being diagnosed with endometriosis (Harris et al, 2018). Citrus fruits are well known for their high content in antioxidants, such as vitamin C.

An important aspect of an endometriosis-adjusted meal plan is an anti-inflammatory diet. This consists of fruit, vegetables, herbs and healthy fats. Many patients report that they feel better when sticking to a low carb diet. Indeed, research has linked elevated insulin-levels, which are a consequence of a diet rich in carbohydrates, to increased levels of inflammation. Endometriosis patients are therefore recommended to prefer whole grain products with a low glycemic index.

An anti-inflammatory diet and lowering of oxidative stress often can make a big difference when it comes to pain in endometriosis. In addition to that, supplementing certain micronutrients can offer additional benefits: Magnesium helps to reduce muscular cramps, B-vitamins, selenium, zinc, iron and antioxidants have all been shown to provide a benefit for patients.

Additional aspects of a dietetic treatment include the observation that frequently, there is an increase in homocysteine levels in endometriosis patients (Ebisch et al 2006; Aidrus et al 2013) and on the other hand a lack of micronutrients such as selenium (Singh et al, 2013; Hernández Guerrero et al, 2006) or vitamin C, vitamin E and vitamin C as well as zinc and copper (Mier-Cabrera et al, 2009).

In recent years the use of specific supplements for women wishing to conceive has been proposed to improve success rates of fertility treatment and while there is still some controversy, there have been some promising studies (Agraval et al, 2011; Grajecki et al, 2012;).

Endometriosis patients, too, can be supported via an indication adjusted dietetic treatment. The following collection of abstracts provide an overview over the current state of research.

Endometriosis Pathoetiology and Pathophysiology: Roles of Vitamin A, Estrogen, Immunity, Adipocytes, Gut Microbiome and Melatonergic Pathway on Mitochondria Regulation.

Anderson G.

Endometriosis is a common, often painful, condition that has significant implications for a woman's fertility. Classically, endometriosis has been conceptualized as a local estrogen-mediated uterine condition driven by retrograde menstruation. However, recent work suggests that endometriosis may be a systemic condition modulated, if not driven, by prenatal processes. Although a diverse array of factors have been associated with endometriosis pathophysiology, recent data indicate that the low body mass index and decreased adipogenesis may be indicative of an early developmental etiology with alterations in metabolic function crucial to endometriosis pathoetiology. The present article reviews the data on the pathoetiology and pathophysiology of endometriosis, suggesting key roles for alterations in mitochondria functioning across a number of cell types and body systems, including the immune system and gut microbiome. These changes are importantly regulated by decreases in vitamin A and its retinoic acid metabolites as well as increases in mitochondria estrogen receptor-beta and the N-acetylserotonin/melatonin ratio across development. This has treatment and future research implications for this still poorly managed condition, as well as for the association of endometriosis with a number of cancers.

Biomol Concepts. 2019 Jul 19;10(1):133-149. doi: 10.1515/bmc-2019-0017.

Nutritional aspects related to endometriosis.

Halpern G, Schor E, Kopelman A.

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.

Rev Assoc Med Bras (1992). 2015 Nov-Dec;61(6):519-23. doi: 10.1590/1806-9282.61.06.519.

Self-management and Psychological-Sexological Interventions in Patients With Endometriosis: Strategies, Outcomes, and Integration Into Clinical Care

Laura Buggio, Giussy Barbara, Federica Facchin, Maria Pina Frattaruolo, Giorgio Aimi, Nicola Berlanda

Endometriosis has a multifactorial etiology. The onset and progression of the disease are believed to be related to different pathogenic mechanisms. Among them, the environment and lifestyle may play significant roles. Diet, dietary supplements, physical exercise, osteopathy, massage, acupuncture, transcutaneous electrical nerve stimulation, and Chinese herbal medicine may represent a complementary and feasible approach in the treatment of symptoms related to the disease. In this narrative review, we aimed to examine the most updated evidence on these alternative approaches implicated in the self-management of the disease. In addition, several studies have demonstrated that endometriosis may negatively impact mental health and quality of life, suggesting that affected women may have an increased risk of developing psychological suffering as well as sexual problems due to the presence of pain. In light of these findings, we discuss the importance of integrating psychological interventions (including psychotherapy) and sexual therapy in endometriosis treatment.

Int J Womens Health. 2017 May 2;9:281-293.

Influence of diet on the risk of developing endometriosis.

Jurkiewicz-Przondziono J, Lemm M, Kwiatkowska-Pamuła A, Ziółko E, Wójtowicz MK.

Endometriosis is a hormone-dependent chronic inflammatory disease characterized by the presence of endometrium beyond the uterine cavity. The disease affects 5-15% of women of child-bearing age, 30-50% of whom suffer from infertility. Understanding the role of dietary factors in the development of endometriosis is critical to development of effective dietary instructions for prevention. Existing studies concerning nutrition and endometriosis suggest that diet is a potentially modifiable risk factor for endometriosis. Fruits and vegetables, fish oils, dairy products rich in calcium and vitamin D, and Omega-3 fatty acids are likely connected with a lower risk of developing endometriosis. Risk factors that increase the risk of endometriosisinclude consumption of products rich in trans-unsaturated fatty acids, consumption of fats generally, and consumption of beef and other kinds of red meat and alcohol. Currently, there are no clear correlations between par-ticular food products and the riskof endometriosis. Further research is needed in order to fully understand the influence of consumed food products on the risk of development of this disease.

Ginekol Pol. 2017;88(2):96-102. doi: 10.5603/GP.a2017.0017.

A Prospective Cohort Study of Meat and Fish Consumption and Endometriosis Risk

Ayae Yamamoto, Holly R Harris, Allison F Vitonis, Jorge E Chavarro, Stacey A Missmer

Background: Only 2 case-control studies have examined the associations between consumption of meat products and endometriosis risk with inconsistent results. Consumption of animal products has the potential to influence endometriosis risk through effects on steroid hormones levels.

Objective: We sought to determine whether higher intake of red meat, poultry, fish, and seafood are associated with risk of laparoscopically confirmed endometriosis.

Study design: A total of 81,908 participants of the prospective Nurses' Health Study II were followed up from 1991 through 2013. Diet was assessed via food frequency questionnaire

every 4 years. Cox proportional hazards models were used to calculate rate ratios and 95% confidence intervals.

Results: During 1,019,294 person-years of follow-up, 3800 cases of incident laparoscopically confirmed endometriosis were reported. Women consuming >2 servings/d of red meat had a 56% higher risk of endometriosis (95% confidence interval, 1.22-1.99; Ptrend < .0001) compared to those consuming ≤1 serving/wk. This association was strongest for nonprocessed red meats (rate ratio, 1.57; 95% confidence interval, 1.35-1.83 for ≥2 servings/d vs ≤1 servings/wk; Ptrend < .0001), particularly among women who had not reported infertility (Pinteraction = .0004). Women in the highest category of processed red meat intake also had a higher risk of endometriosis (rate ratio, 1.20; 95% confidence interval, 1.06-1.37 for ≥5 servings/wk vs <1 serving/mo; Ptrend = .02). Intakes of poultry, fish, shellfish, and eggs were unrelated to endometriosis risk.

Conclusion: Our prospective analysis among premenopausal US nurses suggests that red meat consumption may be an important modifiable risk factor for endometriosis, particularly among women with endometriosis who had not reported infertility and thus were more likely to present with pain symptoms. Well-designed dietary intervention studies among women with endometriosis could help confirm this observation.

Am J Obstet Gynecol. 2018 Aug;219(2):178.e1-178.e10.

Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study.

Harris HR, Chavarro JE, Malspeis S, Willett WC, Missmer SA.

The etiology of endometriosis is poorly understood, and few modifiable risk factors have been identified. Dairy foods and some nutrients can modulate inflammatory and immune factors, which are altered in women with endometriosis. We investigated whether intake of dairy foods, nutrients concentrated in dairy foods, and predicted plasma 25-hydroxyvitamin D (25(OH)D) levels were associated with incident laparoscopically confirmed endometriosis among 70,556 US women in Nurses' Health Study II. Diet was assessed via food frequency questionnaire. A score for predicted 25(OH)D level was calculated for each participant. During 737,712 person-years of follow-up over a 14-year period (1991-2005), 1,385 cases of incident laparoscopically confirmed endometriosis were reported. Intakes of total and low-fat dairy foods were associated with a lower risk of endometriosis. Women consuming more than 3 servings of total dairy foods per day were 18% less likely to be diagnosed with endometriosis than those reporting 2 servings per day (rate ratio = 0.82, 95% confidence interval: 0.71, 0.95; P(trend) = 0.03). In addition, predicted plasma 25(OH)D level was inversely associated with endometriosis. Women in the highest quintile of predicted vitamin D level had a 24% lower risk of endometriosis than women in the lowest quintile (rate ratio = 0.76, 95% confidence interval: 0.60, 0.97; P(trend) = 0.004). Our findings suggest that greater predicted plasma 25(OH)D levels and higher intake of dairy foods are associated with a decreased risk of endometriosis.

Am J Epidemiol. 2013 Mar 1;177(5):420-30. doi: 10.1093/aje/kws247. Epub 2013 Feb 3.

Different nutrient intake and prevalence of gastrointestinal comorbidities in women with endometriosis.

Schink M, Konturek PC, Herbert SL, Renner SP, Burghaus S, Blum S, Fasching PA, Neurath MF, Zopf Y.

Even though endometriosis presents one of the most common gynaecological diseases, the pathogenesis is insufficiently studied. Besides immunologic, inflammatory or oxidative processes, recent studies also suggest an influence of nutrition on disease onset and progression. Because data about the actual nutrient intake of endometriosis patients are scarce, we aimed to examine the actual nutrient intake and potential influencing factors in these women. A total of 156 women with endometriosis (EM) and 52 age-matched controls were included in this retrospective case-control study. All women filled in a validated food frequency questionnaire to acquire the nutrient intake of the past 12 months and a disease-related questionnaire for the determination of disease status, clinical symptoms and comorbidities. Patients with endometriosis suffered significantly more from diet-related comorbidities like food intolerances (25.6% versus 7.7%; P = 0.009) and allergies (57% versus 31%; P < 0.001) compared to controls. Also gastrointestinal symptoms, including constipation, flatulence, pyrosis, diarrhea or frequent defecation, were higher in the EM group (77% versus 29%; P < 0.001). The nutrient intake of patients with endometriosis differed significantly compared to controls with a significantly lower ingestion of organic acids (P = 0.006), maltose (P = 0.0.16), glycogen (P = 0.035), tetradecenoic acid (P = 0.041), methionine (P = 0.046), lysine (P = 0.048), threonine (P = 0.046) and histidine (P = 0.049). The total intake of animal proteins was significantly lower in the EM group compared to the controls (P = 0.047). EM patients showed a decreased intake of vitamin C (P = 0.031), vitamin B12 (P = 0.008) and magnesium (P = 0.043) compared to controls. This study confirms a high association of endometriosis and gastrointestinal disorders accompanied by an altered nutrient intake. A dietary intervention by a professional nutritionist may help to reduce disease burden in the affected women.

J Physiol Pharmacol. 2019 Apr;70(2). doi: 10.26402/jpp.2019.2.09. Epub 2019 Aug 20.

Magnesium deficit ? overlooked cause of low vitamin D status?

Zittermann A.

Like vitamin D deficit, magnesium deficit is considered to be a risk factor for cardiovascular disease. Several steps in the vitamin D metabolism, such as vitamin D binding to its transport protein and the conversion of vitamin D into the hormonal form 1,25-dihydroxyvitamin D by hepatic and renal hydroxylation, depend on magnesium as a cofactor. A new analysis of two National Health and Nutrition Examination Surveys data sets, published in BMC Medicine, investigated potential interactions between magnesium intake, circulating 25-hydroxyvitamin D, which is the generally accepted indicator of vitamin D status, and mortality. Data indicate a reduced risk of insufficient/deficient vitamin D status at high magnesium intake and an inverse association between circulating 25-hydroxyvitamin D and mortality, particularly cardiovascular mortality, among those with magnesiumintake above the median. The study provides important findings concerning potential metabolic interactions
between magnesium and vitamin D and its clinical relevance. However, results should be considered preliminary since biochemical data on individual magnesium status were lacking,

confounding cannot be excluded and questions on the dose?response relationship still remain to be answered.

BMC Med. 2013 Oct 24;11:229. doi: 10.1186/1741-7015-11-229.

Magnesium in the gynecological practice: a literature review.

Parazzini F, Di Martino M, Pellegrino P.

A growing amount of evidence suggests that magnesium deficiency may play an important role in several clinical conditions concerning women health such as premenstrual syndrome, dysmenorrhea, and postmenopausal symptoms. A number of studies highlighted a positive correlation between magnesium administration and relief or prevention of these symptoms, thus suggesting that magnesium supplementation may represent a viable treatment for these conditions. Despite this amount of evidence describing the efficacy of magnesium, few and un-systematize data are available about the pharmacological mechanism of this ion for these conditions. Herein, we review and systematize the available evidence about the use of oral magnesium supplementation in several gynecological conditions and discuss the pharmacological mechanisms that characterize these interventions. The picture that emerges indicates that magnesium supplementation is effective in the prevention of dysmenorrhea, premenstrual syndrome, and menstrual migraine and in the prevention of climacteric symptoms.

Magnes Res. 2017 Feb 1;30(1):1-7. doi: 10.1684/mrh.2017.0419.

Zinc and endometriosis

The possible role of zinc in the etiopathogenesis of endometriosis.

Messalli EM, Schettino MT, Mainini G, Ercolano S, Fuschillo G, Falcone F, Esposito E, Di Donna MC, De Franciscis P, Torella M.

PURPOSE OF INVESTIGATION:

Aim of the study was to evaluate the possible involvement of zinc in the complex pathogenic process behind the onset and perpetuation of endometriotic lesions. To study the level of zinc serum between a group of patients affected by endometriosis and a group of healthy patients.

MATERIALS AND METHODS:

The study included 86 women: 42 patients whose histodiagnosis had revealed pelvic endometriosis and 44 healthy patients. The authors measured the serum zinc concentration for all patients.

RESULTS:
The group of patients with endometriosis presented serum zinc concentration of 1010 +/- 59.24 microg/l. The observation group presented a serum zinc concentration of 1294 +/- 62.22 microg/l.

CONCLUSION:
The results showed that serum zinc levels in women with endometriosis are decreased and this seems to actually confirm that this microelement can possibly affect the multifactorial pathogenesis of the disease. As a matter of fact, zinc interferes with many biological processes, among which inflammation and immunity, which seem to be the base of the development of the lesions. Therefore, the authors believe that this hypothesis requires more attention and further investigation to determine its reasonableness. If the results are confirmed, this study opens up future prospects as for the treatment of endometriosis, taking into account also the role of zinc in the onset of male sterility and the development of testicles. Zinc could in fact be used as marker to detect women at high risk of endometriosis and for the elaboration of a new treatment for sterility, from which these women often suffer.

Clin Exp Obstet Gynecol. 2014;41(5):541-6.

Decreased zinc and increased lead blood levels are associated with endometriosis in Asian Women.

Lai GL, Yeh CC, Yeh CY, Chen RY, Fu CL, Chen CH, Tzeng CR.
Endometriosis is an inflammatory disease associated with multiple pathogenic factors and studies regarding roles of trace metals in endometriosis have been inconsistent and limited. The aim of this cross-sectional study was to compare the blood levels of miscellaneous trace metals measured by inductively coupled plasma mass spectrometry in infertile women with and without endometriosis. Zinc level is associated with declining odds (adjusted OR=0.39, 95% CI=0.18-0.88) of endometriosis. By contrast, lead level is associated with increasing odds (adjusted OR=2.59, 95% CI=1.11-6.06) of endometriosis. The cadmium levels were higher in women with endometriosis, but the aOR was not significant. Zinc has anti-inflammatory characteristics and regulates homeostasis of zinc-containing superoxide dismutase. High lead levels might induce reactive oxygen species and deplete antioxidant defense mechanisms. Further prospective study is needed to test for their causal associations.

Reprod Toxicol. 2017 Dec;74:77-84. doi: 10.1016/j.reprotox.2017.09.001. Epub 2017 Sep 7.

Oxidative stress and endometriosis

Oxidative Stress and Endometriosis: A Systematic Review of the Literature.

Scutiero G, Iannone P, Bernardi G, Bonaccorsi G, Spadaro S, Volta CA, Greco P, Nappi L.

Endometriosis is one of the most common gynaecologic diseases in women of reproductive age. It is characterized by the presence of endometrial tissue outside the uterine cavity. The women affected suffer from pelvic pain and infertility. The complex etiology is still unclear and it is based on three main theories: retrograde menstruation, coelomic metaplasia, and induction theory. Genetics and epigenetics also play a role in the development of endometriosis. Recent studies have put the attention on the role of oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and antioxidants, which may be implicated in the pathophysiology of endometriosis causing a general inflammatory response in the peritoneal cavity. Reactive oxygen species are intermediaries produced by normal oxygen metabolism and are inflammatory mediators known to modulate cell proliferation and to have deleterious effects. A systematic review was performed in order to clarify the different roles of oxidative stress and its role in the development of endometriosis. Several issues have been investigated: iron metabolism, oxidative stress markers (in the serum, peritoneal fluid, follicular fluid, peritoneal environment, ovarian cortex, and eutopic and ectopic endometrial tissue), genes involved in oxidative stress, endometriosis-associated infertility, and cancer development.

Oxid Med Cell Longev. 2017;2017:7265238. doi: 10.1155/2017/7265238. Epub 2017 Sep 19.

Markers of oxidative stress in follicular fluid of women with endometriosis and tubal infertility undergoing IVF.

Singh AK, Chattopadhyay R, Chakravarty B, Chaudhury K.

Oxidative stress and trace elements in the oocytes environment is explored in endometriosis and impact on in vitro fertilization (IVF) outcome assessed. Follicular fluid was aspirated at the time of oocyte retrieval from endometriosis (n=200) and tubal infertility (n=140) and the analytes measured using spectroscopy and HPLC. Increased concentration of reactive oxygen species (ROS), nitric oxide (NO), lipid peroxidation (LPO), iron, lead, cadmium and reduced levels of total antioxidant capacity (TAC), superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase (GR), vitamins A, C, E, copper, zinc and selenium was observed compared to tubal infertility. Increased ROS and NO in endometriosis and tubal infertility associated with poor oocytes and embryo quality. Increased levels of ROS, NO, LPO, cadmium and lead were observed in women who did not become pregnant compared to women who did. Intrafollicular zinc levels were higher in women with endometriosis who subsequently became pregnant following IVF.

Reprod Toxicol. 2013 Dec;42:116-24. doi: 10.1016/j.reprotox.2013.08.005. Epub 2013 Aug 29.

Effects of oxidants and antioxidants on proliferation of endometrial stromal cells.

Foyouzi N, Berkkanoglu M, Arici A, Kwintkiewicz J, Izquierdo D, Duleba AJ.

OBJECTIVE: To evaluate the effects of oxidative stress and antioxidants on proliferation of endometrial stromal cells.
DESIGN: In vitro study.
SETTING: Academic laboratory.
PATIENT(S): Women, with and without endometriosis, of reproductive age.
INTERVENTION(S): Culture of endometrial stromal cells with antioxidants or with agents inducing oxidative stress.
MAIN OUTCOME MEASURE(S): Proliferation of endometrial stromal cells as determined by thymidine incorporation assay and 3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide (MTT) assay.
RESULT(S): Antioxidants induced a dose-dependent inhibition of thymidine incorporation: vitamin E succinate was inhibitory at 10-100 microM (by 43%-95%), ebselen at 10-30 microM (by 29%-77%), and N-acetylcysteine at 10-30 mM (by 52%-85%). In contrast, modest oxidative stress induced by hypoxanthine/xanthine oxidase (1 mM/3-30 microU/mL) stimulated proliferation by 40%-62%. H2O2 (1 microM) increased DNA synthesis by 56%. Comparable findings were obtained using MTT proliferation assay. Antioxidants inhibited proliferation: vitamin E succinate (100 microM) by 91%, ebselen (30 microM) by 81%, and N-acetylcysteine (30 mM) by 95%. Hypoxanthine/xanthine oxidase (1 mM/30 microU/mL) and H2O2 (1 microM) stimulated growth by 122% and 58%, respectively.
CONCLUSION(S): Reactive oxygen species may modulate growth of endometrial stroma. Under pathologic conditions such as endometriosis, increased oxidative stress and depletion of antioxidants may contribute to excessive growth of endometrial stromal cells.
Fertil Steril. 2004 Oct;82 Suppl 3:1019-22.

The Role of Oxidative Stress and Membrane Transport Systems during Endometriosis: A Fresh Look at a Busy Corner.

Vitale SG, Capriglione S, Peterlunger I, La Rosa VL, Vitagliano A, Noventa M, Valenti G, Sapia F, Angioli R, Lopez S, Sarpietro G, Rossetti D, Zito G.

Endometriosis is a condition characterized by the presence of endometrial tissue outside the uterine cavity, leading to a chronic inflammatory reaction. It is one of the most widespread gynecological diseases with a 10-15% prevalence in the general female population, rising up to 30-45% in patients with infertility. Although it was first described in 1860, its etiology and pathogenesis are still unclear. It is now accepted that inflammation plays a central role in the development and progression of endometriosis. In particular, it is marked by an inflammatory process associated with the overproduction of an array of inflammatory mediators such as prostaglandins, metalloproteinases, cytokines, and chemokines. In addition, the growth and adhesion of endometrial cells in the peritoneal cavity due to reactive oxygen species (ROS) and free radicals lead to disease onset, its ensuing symptoms-among which pain and infertility. The aim of our review is to evaluate the role of oxidative stress and ROS in the pathogenesis of endometriosis and the efficacy of antioxidant therapy in the treatment and mitigation of its symptoms.

Oxid Med Cell Longev. 2018 Mar 21;2018:7924021. doi: 10.1155/2018/7924021. eCollection 2018.

Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet.

Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, Jiménez-Zamudio L, Tolentino MC, Casanueva E, Hernández-Guerrero C.

BACKGROUND: Oxidative stress has been identified in the peritoneal fluid and peripheral blood of women with endometriosis. However, there is little information on the antioxidant intake for this group of women. The objectives of this work were 1) to compare the antioxidant intake among women with and without endometriosis and 2) to design and apply a high antioxidant diet to evaluate its capacity to reduce oxidative stress markers and improve antioxidant markers in the peripheral blood of womenwith endometriosis.
METHODS: Women with (WEN, n = 83) and without endometriosis (WWE, n = 80) were interviewed using a Food Frequency Questionnaire to compare their antioxidant intake (of vitamins and minerals). Then, the WEN participated in the application of a control (n = 35) and high antioxidant diet (n = 37) for four months. The high antioxidant diet (HAD) guaranteed the intake of 150% of the suggested daily intake of vitamin A (1050 microg retinol equivalents), 660% of the recommended daily intake (RDI) of vitamin C (500 mg) and 133% of the RDI of vitamin E (20 mg). Oxidative stress and antioxidant markers (vitamins and antioxidant enzymatic activity) were determined in plasma every month.
RESULTS: Comparison of antioxidant intake between WWE and WEN showed a lower intake of vitamins A, C, E, zinc, and copper by WEN ($p < 0.05$, Mann Whitney Rank test). The selenium intake was not statistically different between groups. During the study, the comparison of the 24-hour recalls between groups showed a higher intake of the three vitamins in the HAD group. An increase in the vitamin concentrations (serum retinol, alpha-tocopherol, leukocyte and plasma ascorbate) and antioxidantenzyme activity (superoxide dismutase and glutathione peroxidase) as well as a decrease in oxidative stress markers (malondialdehyde and lipid hydroperoxides) were observed in the HAD group after two months of intervention. These phenomena were not observed in the control group.
CONCLUSION: WEN had a lower intake of antioxidants in comparison to WWE. Peripheral oxidative stress markers diminished, and antioxidant markers were enhanced, in WEN after the application of the HAD.

Reprod Biol Endocrinol. 2009 May 28;7:54. doi: 10.1186/1477-7827-7-54.

More than antioxidant: N-acetyl-L-cysteine in a murine model of endometriosis.

Pittaluga E, Costa G, Krasnowska E, Brunelli R, Lundeberg T, Porpora MG, Santucci D, Parasassi T.

N-acetyl-L-cysteine exerts a complex action on endometrial cells, involving regulation of gene expression and protein activity and location, all converging into a decreased proliferation and a switch toward a differentiating, less invasive, and less inflammatory phenotype. Also considering the lack of undesired side effects, including unaffected fertility potential, this suggests a beneficial use of NAC in endometriosis clinical treatment.

Fertil Steril. 2010 Dec;94(7):2905-8. doi: 10.1016/j.fertnstert.2010.06.038. Epub 2010 Jul 23.

A promise in the treatment of endometriosis: an observational cohort study on ovarian endometrioma reduction by N-acetylcysteine.

Porpora MG, Brunelli R, Costa G, Imperiale L, Krasnowska EK, Lundeberg T, Nofroni I, Piccioni MG, Pittaluga E, Ticino A, Parasassi T.

Urged by the unmet medical needs in endometriosis treatment, often with undesirable side effects, and encouraged by N-acetylcysteine (NAC) efficacy in an animal model of endometriosis and by the virtual absence of toxicity of this natural compound, we performed an observational cohort study on ovarian endometriosis. NAC treatment or no treatment was offered to 92 consecutive Italian women referred to our university hospital with ultrasound confirmed diagnosis of ovarian endometriosisand scheduled to undergo laparoscopy 3 months later. According to patients acceptance or refusal, NAC-treated and untreated groups finally comprised 73 and 72 endometriomas, respectively. After 3 months, within NAC-treated patients cyst mean diameter was slightly reduced (-1.5 mm) versus a significant increase (+6.6 mm) in untreated patients (P = 0.001). Particularly, during NAC treatment, more cysts reduced and fewer cysts increased their size. Our results are better than those reported after hormonal treatments. Twenty-four NAC-treated patients-versus 1 within controls-cancelled scheduled laparoscopy due to cysts decrease/disappearance and/or relevant pain reduction (21 cases) or pregnancy (1 case). Eight pregnancies occurred in NAC-treated patients and 6 in untreated patients. We can conclude that NAC actually represents a simple effective treatment for endometriosis, without side effects, and a suitable approach for women desiring a pregnancy.

Evid Based Complement Alternat Med. 2013;2013:240702. doi: 10.1155/2013/240702. Epub 2013 May 7.

Oocyte Quality

N-Acetyl-Cysteine and l-Carnitine Prevent Meiotic Oocyte Damage Induced by Follicular Fluid From Infertile Women With Mild Endometriosis.

Giorgi VS, Da Broi MG, Paz CC, Ferriani RA, Navarro PA.

This study evaluated the potential protective effect of the antioxidants, l-carnitine (LC) and N-acetyl-cysteine (NAC), in preventing meiotic oocyte damage induced by follicular fluid (FF) from infertile women with mild endometriosis (ME). We performed an experimental study. The FF samples were obtained from 22 infertile women undergoing stimulated cycles for intracytoplasmic sperm injection (11 with ME and 11 without endometriosis). Immature bovine

oocytes were submitted to in vitro maturation (IVM) divided into 9 groups: no-FF (No-FF); with FF from control (CFF) or ME (EFF) groups; and with LC (C + LC and E + LC), NAC (C + NAC and E + NAC), or both antioxidants (C + 2Ao and E + 2Ao). After IVM, oocytes were immunostained for visualization of microtubules and chromatin by confocal microscopy. The percentage of meiotically normal metaphase II (MII) oocytes was significantly lower in the EFF group (51.35%) compared to No-FF (86.36%) and CFF (83.52%) groups. The E + NAC (62.22%), E + LC (80.61%), and E + 2Ao (61.40%) groups showed higher percentage of normal MII than EFF group. The E + LC group showed higher percentage of normal MII than E + NAC and E + 2Ao groups and a similar percentage to No-FF and CFF groups. Therefore, FF from infertile women with ME causes meiotic abnormalities in bovine oocytes, and, for the first time, we demonstrated that the use of NAC and LC prevents these damages. Our findings elucidate part of the pathogenic mechanisms involved in infertility associated with ME and open perspectives for further studies investigating whether the use of LC could improve the natural fertility and/or the results of in vitro fertilization of women with ME.

Reprod Sci. 2016 Mar;23(3):342-51. doi: 10.1177/1933719115602772. Epub 2015 Sep 3.

Endometriosis Is a Cause of Infertility. Does Reactive Oxygen Damage to Gametes and Embryos Play a Key Role in the Pathogenesis of Infertility Caused by Endometriosis?

Gábor Máté, Lori R Bernstein, Attila L Török

Approximately, 10-15% of women of reproductive age are affected by endometriosis, which often leads to infertility. Endometriosis often has an inherited component, and several causative predisposing factors are hypothesized to underlie the pathogenesis of endometriosis. One working hypothesis is the theory of retrograde menstruation. According to the theory of retrograde menstruation, components of refluxed blood, including apoptotic endometrial tissue, desquamated menstrual cells, lysed erythrocytes, and released iron, induce inflammation in the peritoneal cavity. This in turn activates macrophage release of reactive oxygen species (ROS), leading to oxidative stress via the respiratory burst. Refluxed blood promotes the Fenton reaction, terminating in the production of hydroxyl radical, the most potently destructive ROS. In this article, we review the papers that demonstrate decreased quantity and quality of oocytes and embryos retrieved from IVF/ICSI patients with endometriosis. We discuss literature data demonstrating that ROS are generated in endometriotic tissues that have physical proximity to gametes and embryos, and demonstrating adverse impacts on oocyte, sperm and embryo microtubule apparatus, chromosomes, and DNA. Data that addresses the notions that endometriosis causes oocyte and fetal aneuploidy and that these events are mediated by ROS species are also discussed. Literature data are also discussed that employ use of anti-oxidant molecules to evaluate the importance of ROS-mediated oxidative damage in the pathogenesis of endometriosis. Studies are discussed that have employed anti-oxidants compounds as therapeutics to improve oocyte and embryo quality in infertile subjects, and improve fertility in patients with endometriosis.

Front Endocrinol (Lausanne). 2018 Nov 29;9:725.doi: 10.3389/fendo.2018.00725. eCollection 2018.

Oocyte Oxidative DNA Damage May Be Involved in Minimal/Mild Endometriosis-Related Infertility

Michele G Da Broi, Alceu A Jordão Jr, Rui A Ferriani, Paula A Navarro

Early endometriosis is associated with infertility, and oxidative stress may play a role in the pathogenesis of disease-related infertility. This prospective case-control study aimed to compare the presence of oxidative stress markers in the follicular microenvironment and systemic circulation of infertile women with minimal/mild endometriosis (EI/II) versus individuals undergoing controlled ovarian stimulation for intracytoplasmic sperm injection (ICSI). Seventy-one blood samples (27 from infertile women with EI/II and 44 controls with tubal and/or male infertility factor) and 51 follicular fluid samples (19 EI/II and 32 controls) were obtained on the day of oocyte retrieval. Total hydroperoxides (FOX1), reduced glutathione, vitamin E, Superoxide dismutase, total antioxidant capacity, malondialdehyde, advanced oxidation protein products, and 8-hydroxy-2'-deoxyguanosine (8OHdG) concentrations were measured in both fluids. Women with EI/II showed higher FOX1 (8.48 ± 1.72 vs. 7.69 ± 1.71 µmol/g protein) and lower total antioxidant capacity (0.38 ± 0.18 vs. 0.46 ± 0.15 mEq Trolox/L) concentrations in serum, and higher 8OHdG concentrations (24.21 ± 8.56 vs. 17.22 ± 5.6 ng/ml) in follicular fluid compared with controls. These data implicate both systemic and follicular oxidative stress may in infertile women with EI/II undergoing controlled ovarian stimulation for ICSI. Furthermore, the elevated 8OHdG concentrations in follicular fluid of women with EI/II may be related to compromised oocyte quality.

Mol Reprod Dev. 2018 Feb;85(2):128-136. doi: 10.1002/mrd.22943. Epub 2018 Jan 17.

Increased Concentration of 8-hydroxy-2'-deoxyguanosine in Follicular Fluid of Infertile Women With Endometriosis

Michele G Da Broi , Felipe O de Albuquerque, Aline Z de Andrade, Rafaela L Cardoso, Alceu A Jordão Junior, Paula A Navarro

Impaired oocyte quality and oxidative stress might be involved in the pathogenesis of endometriosis-related infertility. To improve our understanding of the role of oxidative stress in this condition, we compare eight oxidative stress markers from each stage, including the simultaneous analysis of lipids, proteins and DNA damage, in the serum and follicular fluid of infertile women with endometriosis and infertile controls undergoing controlled ovarian stimulation for intracytoplasmic sperm injection. In total, 87 serum samples (43 with endometriosis, 44 controls) and 61 follicular fluid samples (29 with endometriosis, 32 controls) free of blood contamination upon visual inspection and presenting granulosa cells alone or granulosa cells plus a retrieved mature oocyte were collected on the day of oocyte retrieval. Total hydroperoxides, malondialdehyde, advanced oxidation protein products, glutathione, superoxide dismutase (SOD) and total antioxidant capacity (TAC) were determined by spectrophotometry, vitamin E by high-performance liquid chromatography and 8-hydroxy-2'-deoxyguanosine (8OHdG) by enzyme-linked immunosorbent assay. The endometriosis group showed higher serum concentrations of glutathione and SOD, lower serum concentrations of TAC and higher follicular concentrations of 8OHdG and vitamin E compared with infertile controls. These data indicate both systemic and follicular oxidative stress in infertile patients with endometriosis. For the first time, we demonstrate the presence of oxidative DNA damage, represented by higher 8OHdG concentrations in the follicular microenvironment of these patients, possibly related to compromised oocyte quality and associated with the pathogenesis of endometriosis-related infertility.

Cell Tissue Res. 2016 Oct;366(1):231-42. doi: 10.1007/s00441-016-2428-4. Epub 2016 Jun 1.

Markers of Oxidative Stress in Follicular Fluid of Women With Endometriosis and Tubal Infertility Undergoing IVF

Abhay K Singh, Ratna Chattopadhyay, Baidyanath Chakravarty, Koel Chaudhury

Oxidative stress and trace elements in the oocytes environment is explored in endometriosis and impact on in vitro fertilization (IVF) outcome assessed. Follicular fluid was aspirated at the time of oocyte retrieval from endometriosis (n=200) and tubal infertility (n=140) and the analytes measured using spectroscopy and HPLC. Increased concentration of reactive oxygen species (ROS), nitric oxide (NO), lipid peroxidation (LPO), iron, lead, cadmium and reduced levels of total antioxidant capacity (TAC), superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase (GR), vitamins A, C, E, copper, zinc and selenium was observed compared to tubal infertility. Increased ROS and NO in endometriosis and tubal infertility associated with poor oocytes and embryo quality. Increased levels of ROS, NO, LPO, cadmium and lead were observed in women who did not become pregnant compared to women who did. Intrafollicular zinc levels were higher in women with endometriosis who subsequently became pregnant following IVF.

Reprod Toxicol. 2013 Dec;42:116-24. doi: 10.1016/j.reprotox.2013.08.005. Epub 2013 Aug 29.

Dietary pain management

Antioxidant supplementation reduces endometriosis-related pelvic pain in humans.

Santanam N, Kavtaradze N, Murphy A, Dominguez C, Parthasarathy S.

We previously suggested that women with endometriosis have increased oxidative stress in the peritoneal cavity. To assess whether antioxidant supplementation would ameliorate endometriosis-associated symptoms, we performed a randomized, placebo-controlled trial of antioxidant vitamins (vitamins E and C) in women with pelvic pain and endometriosis. Fifty-nine women, ages 19 to 41 years, with pelvic pain and history of endometriosis or infertility were recruited for this study. Patients were randomly assigned to 2 groups: vitamin E (1200 IU) and vitamin C (1000 mg) combination or placebo daily for 8 weeks before surgery. Pain scales were administered at baseline and biweekly. Inflammatory markers were measured in the peritoneal fluid obtained from both groups of patients at the end of therapy. Our results indicated that after treatment with antioxidants, chronic pain ("everyday pain") improved in 43% of patients in the antioxidant treatment group ($P = 0.0055$) compared with the placebo group. In the same group, dysmenorrhea ("pain associated with menstruation") and dyspareunia ("pain with sex") decreased in 37% and 24% patients, respectively. In the placebo group, dysmenorrhea-associated pain decreased in 4 patients and no change was seen in chronic pain or dyspareunia. There was a significant decrease in peritoneal fluid inflammatory markers, regulated upon activation, normal T-cell expressed and secreted ($P \leq 0.002$), interleukin-6 ($P \leq 0.056$), and monocyte chemotactic protein-1 ($P \leq 0.016$) after antioxidant therapy compared with patients not taking antioxidants. The results of this clinical trial show that administration of antioxidants reduces chronic pelvic pain in women with endometriosis and inflammatory markers in the peritoneal fluid.

Transl Res. 2013 Mar;161(3):189-95. doi: 10.1016/j.trsl.2012.05.001. Epub 2012 May 31.

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Oxidation-sensitive nociception involved in endometriosis-associated pain.

Ray K, Fahrmann J, Mitchell B, Paul D, King H, Crain C, Cook C, Golovko M, Brose S, Golovko S, Santanam N.

Endometriosis is a disease characterized by the growth of endometrial tissue outside the uterus and is associated with chronic pelvic pain. Peritoneal fluid (PF) of women with endometriosis is a dynamic milieu and is rich in inflammatory markers, pain-inducing prostaglandins prostaglandin E2 and prostaglandin F2a, and lipid peroxides; and the endometriotic tissue is innervated with nociceptors. Our clinical study showed that the abundance of oxidatively modified lipoproteins in the PF of women with endometriosis and the ability of antioxidant supplementation to alleviate endometriosis-associated pain. We hypothesized that oxidatively modified lipoproteins present in the PF are the major source of nociceptive molecules that play a key role in endometriosis-associated pain. In this study, PF obtained from women with endometriosis or control women were used for (1) the detection of lipoprotein-derived oxidation-sensitive pain molecules, (2) the ability of such molecules to induce nociception, and (3) the ability of antioxidants to suppress this nociception. LC-MS/MS showed the generation of eicosanoids by oxidized-lipoproteins to be similar to that seen in the PF. Oxidatively modified lipoproteins induced hypothermia (intracerebroventricular) in CD-1 mice and nociception in the Hargreaves paw withdrawal latency assay in Sprague-Dawley rats. Antioxidants, vitamin E and N-acetylcysteine, and the nonsteroidal anti-inflammatory drug indomethacin suppressed the pain-inducing ability of oxidatively modified lipoproteins. Treatment of human endometrial cells with oxidatively modified lipoproteins or PF from women with endometriosis showed upregulation of similar genes belonging to opioid and inflammatory pathways. Our finding that oxidatively modified lipoproteins can induce nociception has a broader impact not only on the treatment of endometriosis-associated pain but also on other diseases associated with chronic pain.

Pain. 2015 Mar;156(3):528-39. doi: 10.1097/01.j.pain.0000460321.72396.88

The Effect of Micronutrients on Pain Management of Primary Dysmenorrhea: A Systematic Review and Meta-Analysis

Marzieh Saei Ghare Naz, Zahra Kiani, Farzaneh Rashidi Fakari, Vida Ghasemi, Masoumeh Abed, Giti Ozgoli

Introduction: Primary dysmenorrhea is considered as one of the main problems in women. This review study aimed to characterize the effect of micronutrients on primary dysmenorrhea. Methods: In this systematic and meta-analysis study, the articles were searched at Cochrane library, PubMed, Scopus, Web of Science databases. The searching process was conducted with the key terms related to dysmenorrhea and micronutrients. Risk of bias assessment was performed, using Rev Man 5.3 software. In view of the heterogeneity of some of the studies, they were analyzed, using a qualitative method (n=10), and only 6 studies were included in Meta analyze. STATA statistical software version 11 was used for the analy-

sis. Results: In this study, finally 16 clinical trials were investigated. Most micronutrients studied in the relevant articles had anti-inflammatory and analgesic properties with a desirable effect on dysmenorrhea pain relief. Vitamins (K, D, B1, and E) and calcium, magnesium, zinc sulfate and boron contributed effectively to dysmenorrhea pain management. Two months after the intervention, there was a significant mean decrease in the pain score for the vitamin D intervention group (SMD: -1.02, 95% CI: -1.9 to - 0.14, P =0.024) , as well as in the vitamin E intervention group compared to placebo group (SMD: -0.47,95% CI:-0.74 to - 0.2, P = 0.001). Conclusion: Despite the paucity of related research, the studies indicated the potential effects of micronutrients on reducing the pain severity in primary dysmenorrhea. But more studies are needed to confirm the safety and effectiveness of various types of micronutrients on primary dysmenorrhea.

J Caring Sci. 2020 Mar 1;9(1):47-56.

Polyunsaturated fatty acids and endometriosis

Serum Polyunsaturated Fatty Acids and Endometriosis.

Hopeman MM, Riley JK, Frolova AI, Jiang H, Jungheim ES.

Polyunsaturated fatty acids (PUFAs) are fatty acids containing 2 or more double bonds, and they are classified by the location of the last double bond. Omega 3 (n-3) and omega 6 (n-6) PUFAs are obtained through food sources including fatty fish and seed/vegetable oils, respectively, and they are important to a number of physiologic processes including inflammation. Previous work demonstrates suppressive effects of n-3 PUFAs on endometriotic lesions in animal models and decreased risk of endometriosis among women with high n-3 PUFA intake. Thus, we sought to determine the relationship between circulating levels of PUFAs and endometriosis in women. To do this, we performed a cross-sectional study of serum PUFAs and clinical data from 205 women undergoing in vitro fertilization (IVF). Serum PUFAs were measured using liquid chromatography coupled to tandem mass spectroscopy and included n-3 PUFAs such as a-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid and n-6 PUFAs such as linoleic acid and arachidonic acid. Multivariable logistic regression was used to determine relationships between specific and total serum PUFAs and patient history of endometriosis. Women with high serumEPA levels were 82% less likely to have endometriosis compared to women with low EPA levels (odds ratio = 0.18, 95% confidence interval 0.04-0.78).

Reprod Sci. 2015 Sep;22(9):1083-7. doi: 10.1177/1933719114565030. Epub 2014 Dec 23.

The anti-inflammatory impact of omega-3 polyunsaturated Fatty acids during the establishment of endometriosis-like lesions.

Attaman JA, Stanic AK, Kim M, Lynch MP, Rueda BR, Styer AK.

PROBLEM:
The anti-inflammatory impact of three polyunsaturated fatty acids (3-PUFA) in endometriosis is incompletely understood. The effect of 3-PUFA on endometriosis-like lesions is evaluated as a potential anti-inflammatory treatment target.

METHOD OF STUDY:
Wild Type (WT) and transgenic Fat-1 mice (high levels of endogenous 3-PUFA) were utilized in a uterine tissue transplant endometriosis model. Experimental donor×host pairs included: WT×WT (WW), WT×Fat-1 (WF), and Fat-1×Fat-1 (FF). Cytokine content (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-17A, IFN-γ, TNF-γ, MCP-1 and RANTES) and immunocellular composition in lesions was determined.

RESULTS:
Intralesion IL-6 in WF hosts was 99-fold lower than WW hosts (P=0.03). Compared to WW host lesions, Cox-2 levels were decreased in WF [1.5-fold (P=0.02)] and FF [1.2-fold (P=0.01)] host lesions, respectively, and intralesion VEGF expression was increased [1.8-fold; P=0.02 (WF) and 1.5-fold; P=0.01 (FF)]. Lesions in FF hosts demonstrated reduced phosphohistone 3 expression (70%; P=0.03) compared to WW control hosts.

CONCLUSIONS:
Systemic host 3-PUFA levels influence immune, angiogenic, and proliferative factors implicated in the early establishment of endometriosis.

Am J Reprod Immunol. 2014 Oct;72(4):392-402. doi: 10.1111/aji.12276. Epub 2014 Jun 5.

Efficacies of vitamin D and omega-3 polyunsaturated fatty acids on experimental endometriosis.

Akyol A, Şimşek M, İlhan R, Can B, Baspinar M, Akyol H, Gül HF, Gürsu F, Kavak B, Akın M.

OBJECTIVE:
The aim of this study was to investigate the effects of 1,25-dihydroxyvitamin-D3 (vitamin D) and omega-3polyunsaturated fatty acids (omega-3 PUFA) on experimentally induced endometriosis in a rat model.

MATERIALS AND METHODS:
A prospective, single-blind, randomized, controlled experimental study was performed on 30 Wistar female rats. Endometriosis was surgically induced by implanting endometrial tissue on the abdominal peritoneum. Four weeks later, a second laparotomy was performed to assess pre-treatment implant volumes and cytokine levels. The rats were randomized into three groups: vitamin D group (42 µg/kg/day), omega-3 PUFA group (450 mg/kg/day), and control group (saline 0.1 mL/rat/day). These treatments were administered for 4 weeks. At the end of treatment, a third laparotomy was performed for the assessment of cytokine levels, implant volumes (post-treatment) and implants were totally excised for histopathologic examination. Pre- and post-treatment volumes, cytokine levels within the groups, as well as stromal and glandular tissues between the groups were compared.

RESULTS:
The mean post-treatment volume was statistically significantly reduced in the omega-3 PUFA group (p=0.02) and the level of the interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a),

vascular endothelial growth factor (VEGF) in the peritoneal fluid were significantly decreased at the end of treatment in the omega-3 PUFA group (p=0.02, p=0.03, and p=0.03, respectively). In the vitamin D group, only IL-6 levels were significantly decreased. In the histopathologic examination, the glandular tissue and stromal tissue scores of the implants were significant lower in the omega-3 PUFA group (p=0.03 and p=0.02).

CONCLUSION:
Omega-3 PUFA caused significant regression of endometriotic implants. Vitamin D has not been as effective as omega-3 PUFA on endometriosis.

Taiwan J Obstet Gynecol. 2016 Dec;55(6):835-839. doi: 10.1016/j.tjog.2015.06.018.

Homocysteine Level in the Blood and Follicular Fluid is Higher in Infertile Women with Endometriosis

Muharam Natadisastra

OBJECTIVE: To compare and determine the differences in the level of homocysteine in the blood and follicular fluid in infertile women with and without endometriosis, then analyze the effect of homocysteine levels to oocyte quality.

METHODS: This study was cross-sectional study. Fifty-nine subjects following the in-vitro fertilization program are included in the admission criteria were divided into two equal groups, ie groups of endometriosis and without endometriosis consecutively (consecutive sampling). Each subject taken from the blood and follicular fluid then measured the levels of homocystein levels with immuoassay method. The mean of each group was statistically tested with an independent t test.

RESULT: The mean levels of homocysteine in the blood is higher in the endometriosis group than without endometriosis group and it was statistically significance (8.34 ± 2.68 vs 6.71 ± 1.56, p=0.007; 95% CI: 0.02417-0.14657). Similarly, the levels of homocysteine in follicular fluid , the endometriosis group is higher and statistically significance (6.19 ± 1.67 vs 3.46 ± 1.03; p= 0.000; 95% CI: 0.19310-0.32353). All oocytes are in good quality in both groups, maturation grade 3. There is a correlation between the levels of homocysteine in the blood and follicular fluid in the endometriosis group and assessed with Pearson test, and it found significant (p = 0.002) and the correlation value 0.553 (moderate correlation strength) and direction of a positive correlation.

CONCLUSION: The mean levels of homocysteine in the blood and follicular fluid in infertile women with endometriosis is higher than without endometriosis and were statistically significantly different. These homocysteine levels does not affect the quality of oocytes. There is a positive correlation between the levels of homocysteine in the blood and follicular fluid in endometriosis group.

Indones J Obstet Gynecol 2013; 37-2: 92-8

Apoptosis inhibitors as therapeutic targets

The Role of Survivin in the Pathogenesis of Endometriosis

Bianca Bianco, Carolina Filipchiuk, Denise M Christofolini, Caio P Barbosa, Erik Montagna

Introduction: Endometriosis is a common, estrogen-dependent condition, defined as the presence of endometrial-like tissue outside of the uterus, associated with often chronic and inflammatory reaction. The association of endometriosis with cancer is unclear, although endometriosis and cancer present some molecular similarities. Survinin, encoded by the BIRC5 gene, is a protein that controls cell division, inhibits apoptosis and promotes angiogenesis. Here we aimed to summarize and to discuss the main findings of studies that addressed the involvement of survivin in the pathogenesis of endometriosis.

Evidence acquisition: We conducted a comprehensive retrieval from electronic databases, included the MEDLINE, EMBASE, with no restrictions to time span. We used the search terms endometriosis and survivin or BIRC5 and collected all relevant studies to explore the association between endometriosis and surviving expression.

Evidence synthesis: A total of 21 studies included in the systematic review, comprising sample collected from 1263 women with endometriosis. Results showed the involvement of more than 60 genes and proteins evaluated in eutopic, ectopic, endometrial and ovarian endometriosis, as well as in several gynecological conditions compared to healthy controls.

Conclusions: The studies provided the basis for the involvement of survivin in the pathogenesis of the disease by several and independent pathways.

Minerva Med. 2020 Feb;111(1):21-32. doi: 10.23736/S0026-4806.19.06358-4. Epub 2019 Nov 12.

Survivin and VEGF as Novel Biomarkers in Diagnosis of Endometriosis.

Acimovic M, Vidakovic S, Milic N, Jeremic K, Markovic M, Milosevic-Djeric A, Lazovic-Radonjic G.

BACKGROUND:
The aim of this study was to investigate the role of peripheral blood markers as additional diagnostic tools to transvaginal ultrasound (TVU) findings in the diagnosis of endometriosis.

METHODS:
This study included 40 patients undergoing laparoscopy for suspected endometriosis from January to December 2012. Preoperative levels of serum CA125, CA19-9, CEA and mRNA expression levels for survivin and VEGF were obtained. Real-time PCR was used to determine relative gene expression. A new diagnostic score was obtained by deploying the peripheral blood markers to the TVU findings. Statistical methods used were Chi-square, Fisher's, Student's t-test or the Mann - Whitney test.

RESULTS:
There was a statistically significant difference in serum CA125, survivin and VEGF levels in patients with endometriosis and those without endometriosis ($p<0.001$, $p=0.025$ and $p=0.009$, respectively). False negative TVU findings were noted in 3/13 patients (23.1%) with peritoneal endometriosis without ovaries involvement. High sensitivity (93.3%), specificity (90.0%), PPV (96.6%), NPV (81.8%) and accuracy (92.5%) were obtained for a diagnostic score based on TVU and significant peripheral blood markers (CA125, survivin and VEGF).

CONCLUSIONS:
Determination of serum CA125, mRNA expression levels for survivin and VEGF along with TVU can contribute to higher accuracy of the noninvasive diagnostic tools for endometriosis.

J Med Biochem. 2016 Jan;35(1):63-68. doi: 10.1515/jomb-2015-0005. Epub 2015 Dec 30.

Inhibitor of apoptosis proteins (IAPs) may be effective therapeutic targets for treating endometriosis.

Uegaki T, Taniguchi F, Nakamura K, Osaki M, Okada F, Yamamoto O, Harada T.

STUDY QUESTION:
What is the role of the inhibitor of apoptosis proteins (IAPs) in human endometriotic tissues and a mouse model of endometriosis?

SUMMARY ANSWER:
Four IAP proteins were expressed in endometriotic tissue indicating IAPs may be a key factor in the pathogenesis and progression of endometriosis.

WHAT IS KNOWN ALREADY:
Overexpression of IAPs protects against a number of proapoptotic stimuli. IAPs (c-IAP1, c-IAP2, XIAP and Survivin) are expressed in human ectopic endometrial stromal cells (ESCs) from ovarian endometriomas.

STUDY DESIGN, SIZE, DURATION:
Forty-eight women with or without ovarian endometrioma are included in this study. BALB/c mice (n = 24) were used for the mouse endometriosis model. Mice with surgically induced endometriosis were treated with an IAP antagonist (BV6) for 4 weeks.

PARTICIPANTS/MATERIALS, SETTING, METHODS:
Human ectopic endometrial tissues from chocolate cysts and eutopic endometrial tissue were collected. ESCs were enzymatically isolated from these tissues. ESC proliferation was examined by 5-bromo-2'-deoxyuridine-enzyme-linked immunosorbent assay. IAPs expression in tissue derived from eutopic endometria and chocolate cysts was evaluated using real-time RT-PCR and immunohistochemistry. A homologous mouse endometriosis model was established by transplanting donor mouse uterine tissue into the abdominal cavities of recipient mice. After treating the mice with BV6 (i.p. 10 mg/ml), the extent of endometriosis-like lesions in mice was measured and proliferative activity assessed by Ki67 staining. All experiments were repeated a minimum of three times.

MAIN RESULTS AND THE ROLE OF CHANCE:
IAP (c-IAP1, c-IAP2, XIAP and Survivin) mRNA and protein in human ectopic endometrial tissues were expressed at higher levels than in eutopic endometrial tissues ($P < 0.05$). All four

IAPs proteins were expressed in mouse endometriosis-like implants. BV6 inhibited BrdU incorporation of human ESCs ($P < 0.05$ versus control). BV6 also decreased the total number, weight, surface area and Ki67 positive cells in the endometriosis-like lesions in the mice ($P < 0.05$ versus control).

LIMITATIONS, REASONS FOR CAUTION:
Endometriotic lesions were surgically induced in mice by transplanting mouse uterine tissue only, not human pathological endometriotic tissue. Furthermore, the effects of BV6 on human ESCs and mouse endometriosis-like lesions may differ between the species.

WIDER IMPLICATIONS OF THE FINDINGS:
Our data support the hypothesis that IAPs are involved in the development of endometriosis, and therefore an inhibitor of IAPs has potential as a novel treatment for endometriosis.

STUDY FUNDING/COMPETING INTERESTS:
This work was supported by KAKENHI (Japan Society for the Promotion of Science, Grant-in-Aid: to F.T.; 21592098 and to T.H.; 24659731) and Yamaguchi Endocrine Research Foundation. The authors have no conflicts of interest to disclose.

Hum Reprod. 2015 Jan;30(1):149-58. doi: 10.1093/humrep/deu288. Epub 2014 Nov 5.

Inhibitors of apoptosis proteins in experimental benign prostatic hyperplasia: effects of serenoa repens, selenium and lycopene.

Minutoli L, Altavilla D, Marini H, Rinaldi M, Irrera N, Pizzino G, Bitto A, Arena S, Cimino S, Squadrito F, Russo GI1, Morgia G.

BACKGROUND:
The apoptosis machinery is a promising target against benign prostatic hyperplasia (BPH). Inhibitors of apoptosis proteins (IAPs) modulate apoptosis by direct inhibition of caspases. Serenoa Repens (SeR) may be combined with other natural compounds such as Lycopene (Ly) and Selenium (Se) to maximize its therapeutic activity in BPH. We investigated the effects of SeR, Se and Ly, alone or in association, on the expression of four IAPs, cIAP-1, cIAP-2, NAIP and survivin in rats with experimental testosterone-dependent BPH. Moreover, caspase-3, interleukin-6 (IL-6) and prostate specific membrane antigen (PSMA) have been evaluated.Rats were administered, daily, with testosterone propionate (3 mg/kg/sc) or its vehicle for 14 days. Testosterone injected animals (BPH) were randomized to receive vehicle, SeR (25 mg/kg/sc), Se (3 mg/kg/sc), Ly (1 mg/kg/sc) or the SeR-Se-Ly association for 14 days. Animals were sacrificed and prostate removed for analysis.

RESULTS:
BPH animals treated with vehicle showed unchanged expression of cIAP-1 and cIAP-2 and increased expression of NAIP, survivin, caspase-3, IL-6 and PSMA levels when compared with sham animals. Immunofluorescence studies confirmed the enhanced expression of NAIP and survivin with a characteristic pattern of cellular localization. SeR-Se-Ly association showed the highest efficacy in reawakening apoptosis; additionally, this therapeutic cocktail significantly reduced IL-6 and PSMA levels. The administration of SeR, Se and Ly significantly blunted prostate overweight and growth; moreover, the SeR-Se-Ly association was most effective in reducing prostate enlargement and growth by 43.3% in treated animals.

CONCLUSIONS:
The results indicate that IAPs may represent interesting targets for drug therapy of BPH.

J Biomed Sci. 2014 Mar 10;21:19. doi: 10.1186/1423-0127-21-19.

Survivin and NAIP in Human Benign Prostatic Hyperplasia: Protective Role of the Association of Serenoa repens, Lycopene and Selenium from the Randomized Clinical Study.

Morgia G, Micali A, Rinaldi M, Irrera N, Marini H, Puzzolo D, Pisani A, Privitera S, Russo GI, Cimino S, Ieni A, Trichilo V, Altavilla D, Squadrito F, Minutoli L.

Benign prostatic hyperplasia (BPH) treatment includes the apoptosis machinery modulation through the direct inhibition of caspase cascade. We previously demonstrated that Serenoa repens (Ser) with lycopene (Ly) and selenium (Se) reawakened apoptosis by reducing survivin and neuronal apoptosis inhibitory protein (NAIP) levels in rats. The aim of this study was to evaluate the effectiveness of Ser-Se-Ly association on survivin and NAIP expression in BPH patients. Ninety patients with lower urinary tract symptoms (LUTS) due to clinical BPH were included in this randomized, double-blind, placebo-controlled trial. Participants were randomly assigned to receive placebo (Group BPH + placebo, n = 45) or Ser-Se-Ly association (Group BPH + Ser-Se-Ly; n = 45) for 3 months. At time 0, all patients underwent prostatic biopsies. After 3 months of treatment, they underwent prostatic re-biopsy and specimens were collected for molecular, morphological, and immunohistochemical analysis. After 3 months, survivin and NAIP were significantly decreased, while caspase-3 was significantly increased in BPH patients treated with Ser-Se-Ly when compared with the other group. In BPH patients treated with Ser-Se-Ly for 3 months, the glandular epithelium was formed by a single layer of cuboidal cells. PSA showed high immunoexpression in all BPH patients and a focal positivity in Ser-Se-Ly treated patients after 3 months. Evident prostate specific membrane antigen (PSMA) immunoexpression was shown in all BPH patients, while no positivity was present after Ser-Se-Ly administration. Ser-Se-Ly proved to be effective in promoting apoptosis in BPH patients.

Int J Mol Sci. 2017 Mar 22;18(3). pii: E680. doi: 10.3390/ijms18030680.

Vitamin E succinate inhibits survivin and induces apoptosis in pancreatic cancer cells.

Patacsil D, Osayi S, Tran AT, Saenz F, Yimer L, Shajahan AN, Gokhale PC, Verma M, Clarke R, Chauhan SC, Kumar D.

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. Identifying novel chemotherapeutic and chemopreventive approaches is critical in the prevention and treatment of cancers such as pancreatic cancer. Vitamin E succinate (VES) is a redox-silent analog of the fat-soluble vitamin alpha-tocopherol. In the pre-

sent study, we explored the antiproliferative action of VES and its effects on inhibitor of apoptosis proteins in pancreatic cancer cells. We show that VES inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. Further, we demonstrate that VES downregulates the expression of survivin and X-linked inhibitor of apoptosis proteins. The apoptosis induced by VES was augmented by siRNA-mediated inhibition of survivin in PANC-1 cells. In summary, our results suggest that VES targets survivin signaling and induces apoptosis in pancreatic cancer cells.

Genes Nutr. 2012 Jan;7(1):83-9. doi: 10.1007/s12263-011-0242-x. Epub 2011 Aug 13.

RRR-α-tocopheryl succinate induces apoptosis in human gastric cancer cells via the NF-κB signaling pathway.

Sun Y, Zhao Y, Hou L, Zhang X, Zhang Z, Wu K.

To investigate the effects of the nuclear factor (NF)-κB signaling pathway on the induction of apoptosis by vitamin E succinate (RRR-α-tocopheryl succinate; VES) in human gastric carcinoma cells. Human gastric carcinoma SGC-7901 cells were treated with temperate concentrations of VES and pyrrolidine dithiocarbamate (PDTC), an inhibitor of NF-κB. Cell viability and apoptosis were respectively estimated by methylthiazol tetrazolium (MTT) assay and the Annexin V-FITC method. Western blot analysis was used to evaluate the protein expressions of NF-κBp65 and Bcl-2 family members Bcl-2, Bax and cleavage of caspase-3, caspase-9, and poly (ADP-ribose) polymerase (PARP). The DNA-binding activity of NF-κBp65 was measured by electrophoretic mobility shift assay (EMSA). Reverse transcription and polymerase chain reaction (RT-PCR) was implemented to evaluate the transcription of inhibitor of apoptosis (IAP) genes. Apoptosis assessment showed that VES induces apoptotic cell death in human gastric carcinoma cells. In the following experiments, PDTC (100 μM) was used in cell treatment 2 h before VES. The decreased ratio of the nuclear and cytosolic NF-κBp65 protein level was induced by VES and PDTC reinforced this trend. PDTC treatment significantly enhanced the decrease of NF-κB-DNA binding activity induced by VES in human gastric SGC-7901. The decrease in protein expression of Bcl-2 as well as the increase in the protein expression of Bax were induced by VES treatment. The cleavage of caspase-9, caspase-3 and PARP was induced. There was no effect on the gene transcription of c-IAP-1, c-IAP-2, and x-linked IAP (XIAP) compared with the control group, whereas mRNA levels of survivin and the neuronal apoptosis inhibitory protein (NAIP) markedly decreased. Notably, pretreatment with PDTC reinforced all the above VES-induced effects. In conclusion, VES-induced apoptosis in SGC-7901 cells is accompanied by the inhibition of the NF-κB signaling pathway, including changes in Bcl-2 family members, cleavage of caspases and gene transcription of survivin and NAIP.

Oncol Rep. 2014 Sep;32(3):1243-8. doi: 10.3892/or.2014.3282. Epub 2014 Jun 23.

Vitamin D Intake and its Protective Role in Multiple Sclerosis: The Checkmate to Survivin?

Raffaella Mormile

Vitamin D has long been speculated to reduce the risk of multiple sclerosis (MS). However, its role in development and modulating the course of MS has yet to be clarified. To date, there is no scientific evidence for the use of vitamin D as monotherapy for MS in clinical practice and perplexities still exist on potential disadvantages of Vitamin D intake. MS is one of the most common disabling neurological disorders of the Central Nervous System (CNS) in young and middle-aged adults. The pathogenesis of MS has long been thought to be an immune mediated disorder of the CNS. It has been verified that failure of autoreactive T cells to undergo apoptosis may contribute to the pathogenesis of MS. Studies of lymphocytes from patients with active relapsing-remitting MS have suggested a potential role for survivin in MS pathology. Survivin is the smallest member of the inhibitor of apoptosis protein family. Abnormal up-regulation of survivin has been involved in the inability to remove autoreactive lymphocytes in MS. Over-expression of survivin in mitogen stimulated T lymphocytes from patients with active MS has been correlated with cellular resistance to apoptosis and with features of disease activity, such as disease duration and the number of enhanced lesions on cranial magnetic resonance. Survivin is widely expressed in fetal tissue and over-expressed in cancer cells where it is described as a biomarker predictive of aggressive cancer. Vitamin D has been found to suppress cell proliferation and induce apoptosis in a variety of cancer cell models such as human colon carcinoma, breast cancer, prostate cancer andKaposi sarcoma. A large body of data indicates that Vitamin D promotes inhibition of cancer cell proliferation by suppression of survivin. Although survivin level is considered as an unfavourable risk factor for cancer and MS, it plays an important anti-apoptosis role in vascular cell responses to injuries. Even if survivin is scarcely detectable in normal adult tissues, its expression can be reactivated by a number of pro-survival stimuli such as ischemia and hypoxia. Upregulation of survivin seems to have valuable effects on heart and brain ischemia-reperfusion injury limiting tissue damage and improving functional outcome. Survivin myocardial expression after acute myocardial infarction (AMI) has been linked to survival of at risk myocardium and favorable remodeling after AMI. Furthermore, survivin has been shown to be a key determinant in enhancing neural cell survival after a traumatic brain injury and in response to hypoxia/ ischemia conditions such as stroke. Reendothelialization represents an important therapeutic strategy for repairing injured blood vessels. Survivin has been reported to control the proliferation of endothelial progenitor cells (EPC) that are implicated in the prevention of restenosis after vascular injury. EPC are the major source of cells related to endothelium repair and re-endothelialization. The DNA binding 1 (Id1)/ PI3K/Akt/nuclear factor kappa B (NFκB)/survivin signaling pathway has been described as a critical player in EPC proliferation after vascular injury. Of note, patients affected by MS have been supposed to be at high risk for cardiovascular diseases (CVDs) and a careful surveillance and CVD preventive health measures are recommended. All these contentions led us to hypothesize that vitamin D may be effective against MS inhibiting survivin gene expression and thereby affecting the development and progression of the disease. However, decreased levels of survivin may lead to worse outcomes during the acute phase of cardiovascular conditions such as AMI and stroke taking into account the highest risk status of patients with MS. Thus, vitamin D should be administered to patients with MS after excluding potential associated risk factors for CVD and defining

threshold Vitamin D levels above which supplementations might negatively influence recovery from AMI and stroke.

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Survivin is associated with cell proliferation and has a role in 1a,25-dihydroxyvitamin D3 induced cell growth inhibition in prostate cancer.

Koike H, Morikawa Y, Sekine Y, Matsui H, Shibata Y, Suzuki K.

PURPOSE:

Prostate cancer cell proliferation is inhibited by 1a,25-dihydroxyvitamin D(3). Survivin is a member of the inhibitors of apoptosis protein family. Several studies indicate that survivin down-regulation sensitizes human tumor cells of different histological origins to conventional chemotherapeutic drugs. We assessed the effect of survivin gene expression on the proliferation of prostate cancer cells in vitro and in vivo. We also examined the antitumor sensitization effect of survivin inhibition in 1a,25-dihydroxyvitamin D(3) treatment for prostate cancer cells.

MATERIALS AND METHODS:

We knocked down gene expression levels of survivin using siRNA against survivin in vitro and in vivo. We then assessed survivin expression in 1a,25-dihydroxyvitamin D(3) treatment and examined the antitumor sensitization effect of survivin inhibition using siRNA in 1a,25-dihydroxyvitamin D(3) treatment of hormone resistant prostate cancer cells.

RESULTS:

In vitro and in vivo siRNA against survivin significantly inhibited cell and tumor growth compared with control siRNA. In LNCaP and PC3 cells 1a,25-dihydroxyvitamin D(3) decreased survivin gene expression and inhibited cell proliferation. However, survivin gene expression and cell proliferation were not inhibited in DU145 cells but after siRNA transfection against survivin DU145 cell proliferation was inhibited by 1a,25-dihydroxyvitamin D(3).

CONCLUSIONS:

Findings suggest that survivin has a significant association with prostate cancer cell proliferation and an essential role in 1a,25-dihydroxyvitamin D(3) induced prostate cancer cell growth inhibition. It seems that the eliminating survivinin 1a,25-dihydroxyvitamin D(3) therapy for hormone refractory prostate cancer is a potential therapeutic option.

J Urol. 2011 Apr;185(4):1497-503. doi: 10.1016/j.juro.2010.12.005. Epub 2011 Feb 22.

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Based on the current literature, we have developed a food for special medical purposes taking into account the needs of women with endometriosis wishing to conceive. Given the fact that endometriosis affects fertility on a wide variety of levels, a suitable supplementation needs to address a wide variety of aspects, too, thus multiplying the effects of single ingredients. The patent-protected formula presents as an advancement to all the preparations that have been developed so far.

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-

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Austrian-based Gonadosan Distribution GmbH is dedicated to the development and ongoing research of state-of-the-art nutraceuticals meeting the specific nutritional needs of men and women planning for pregnancy. The Fertilovit® range of supplements is based on the latest scientific data, tested in cooperation with big European ART centers and has been proven to support fertility treatment effectively. A variety of patent-protected preparations offer highly specific solutions for different male and female fertility patients, ranging from mature patients to patients with thyroid autoimmunity, endometriosis, PCOS, and idiopathic OAT.

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