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INSIDE

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The Effect of Lifestyle and Diet on Fertility: Fertility-Enhancing Lifestyle Modifications

PART 1 OF A SERIES ON FERTILITY

By Susan T. Marcolina, MD, FACP

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More than 7% of married couples (2.1 million) in the United States are infertile.[1] Defined as the failure to conceive after one year of regular unprotected sexual intercourse, infertility is a chronic health problem for young adults. According to the American Society for Reproductive Medicine, clinical evaluation is recommended after the one-year benchmark because by this time 85% of couples have successfully achieved a pregnancy. Since both male and female infertility require evaluation to identify the probable cause(s), most couples require an initial work-up, which includes semen analysis; an assessment of ovulatory function, such as mid-luteal phase serum progesterone levels and urinary luteinizing hormone (LH) determinations; uterine morphology assessment with a sonohysterogram or hysterosalpingogram (HSG); and fallopian tube patency with either a HSG or laparoscopy.[2]

Follow-up treatments often require accurate determinations of optimal ovulatory intervals during each menstrual cycle with ovulatory test kits for timed intercourse. Judicious use of these ovulation predictor kits makes it easier for patients to identify optimal fertility days within their cycle and time intercourse accordingly.[3] Such intense evaluation and treatment, however, can be ongoing for months or years and involves a significant investment of time, energy, thought, and monetary expense, which can result in disappointment with recurrent failed attempts, and marital stress.

Among infertile couples, problems with ovulation are identified in 18-30% of cases.[4,5] Although treatment options are available for ovulatory dysfunction including in vitro fertilization (IVF), the cost

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($9,500 per cycle in the United States) and complexity of treatment make it available to less than 10% of couples. In addition, it is associated with potentially adverse effects such as multiple pregnancies; ovarian hyperstimulation syndrome; premature deliveries, which can occur with singleton and multiple births; spontaneous abortions; and premature menopause. It is important to identify potentially modifiable risk factors that can augment fertility and be readily available to all patients.[6]

Primary care physicians can recommend initial lifestyle and dietary measures to couples planning a pregnancy that might increase their chances for successful conception within the initial year of attempt. Chavarro et al have identified several "fertility-friendly" dietary and lifestyle interventions *(see Table, page 123)*.[7] Such factors aim to reduce infertility due to ovulation disorders, but can also improve sperm quality issues.[7] The first part of this series reviews lifestyle measures that have been shown to augment fertility. Since these modifications also result in improved overall health, it is important such changes be incorporated at young ages.

Summary Points

- Infertility is a chronic health problem that affects 7.4% of married couples in the United States.
- Incorporation of general health-promoting behaviors such as weight loss in overweight or obese patients, smoking cessation, environmental smoke avoidance, daily vigorous aerobic physical activity for 30 min/d, and substitution of heart-healthy mono- and polyunsaturated (especially omega-3) fats for *trans* fats in the diet improves fertility in infertile couples.
- Alcohol avoidance is strongly encouraged for women who plan a pregnancy since its teratogenic effects occur within the first few weeks after conception.
- Primary care physicians provide initial preventive treatment of infertility by insuring that young patients develop healthy lifestyle habits.

Age Discrimination in Fertility

Though not strictly a modifiable characteristic, it has been shown in multiple studies that increasing age for both men (> 45 years) and women (> 35 years) adversely affects fertility[8,9] and success with assisted reproductive technologies (ART). Older women were less inducible with ART[10] and, once pregnant, had a lower live birth rate due primarily to spontaneous abortion. In a study of 201 pregnancies from women undergoing ovulation induction, Smith et al found a 2.1% risk of spontaneous abortion for women younger than 35 years compared to a 16.1% risk for women older than 36 years.[11]

Smoking

Smoking has a wide range of adverse effects on fertility for both general and infertile populations. Cigarette smoking distorts sperm morphology, causes DNA damage, and decreases sperm production and motility in men,[12] and alters the ovarian follicular fluid microenvironment and luteal phase hormone levels in women.[13] Components of cigarette smoke (nicotine; cotinine, a stable metabolite of nicotine; and cadmium) have been detected in follicular fluid of female smokers as well as females exposed only to passive environmental smoking. Since cotinine easily crosses the blood-follicle barrier and has a relatively long plasma half-life of 19 hours, levels of cotinine in follicular fluid provide a reliable test of tobacco smoke exposure.[14] Paszkowski et al have shown that cigarette smoking in women undergoing IVF treatment for infertility was associated with an increased intensity of oxidative stress within the ovarian follicle, which resulted in free radical-mediated cytotoxicity for oocytes and granulosa cells. Such cytotoxicity is associated with a statistically significant increase in follicular fluid cotinine concentration and a significantly lower yield of oocytes per cycle in

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Table

Fertility-friendly dietary and lifestyle habits[7]

- Physical activity of at least 30 min/d
- Nonsmoking personal and environmental history
- BMI between 20-24.99 kg/m^2
- Plant-based rather than animal-based dietary protein
- Adequate vitamin and mineral intake (especially folate and iron)
- Substitution of monounsaturated and polyunsaturated fats (especially omega-3 PUFAs) for *trans* fat

smokers compared to nonsmokers. It is important to also note that the onset of menopause occurs 1-4 years earlier in smokers.[15]

Alcohol

Alcohol consumption has been associated with reduced fertility at levels as low as one drink per week.[15] Alcohol directly impairs ovum maturation, blastocyst development, and implantation, as well as sperm development and maturation.[16,17] Most importantly, however, alcohol is a teratogen.[18] Since the most vulnerable time for adverse effects on the fetus is during the first few weeks after conception, women who plan a pregnancy should avoid consuming alcohol.[19]

Caffeine

As one of the most commonly consumed drugs, caffeine is present in common beverages such as coffee, tea, soft drinks, products containing cocoa or chocolate, and in various medications such as Excedrin®. Although the literature is mixed, certain studies are noteworthy. Nawrot et al, in a review of several human studies, concluded that reproductive age women are an "at-risk" population that requires specific medical advice about caffeine intake. They suggest consumption of less than 300 mg/d for this subgroup.[20] On the other hand, Tolstrup noted that caffeine intake of only 75 mg/d prior to pregnancy significantly increased the risk of spontaneous abortion.[21] Combination studies with alcohol suggest that caffeine enhances the negative effects of alcohol on fertility.[16]

Insulin Resistance

Certain factors known to increase insulin resistance, such as increased body weight and decreased physical activity, have been associated with an increased risk of infertility secondary to ovulatory dysfunction.[22] For instance, insulin resistance is strongly implicated in the etiology of polycystic ovarian syndrome (PCOS), the most common form of ovulatory disorder. Approximately one of 16 women is affected and the clinical triad of menstrual dysfunction, hyperandrogenism (hirsutism, acne, and elevated androgens—testosterone, dehydroepiandrosterone, and androstenedione), and infertility are cardinal features. Elevated insulin levels augment basal pituitary LH release, resulting in overstimulation of the theca internal cells of the ovary, which produce the elevated androgen levels. Many PCOS patients develop impaired glucose tolerance or type 2 diabetes mellitus and the metabolic syndrome with its attendant risks of cardiovascular disease.[23]

In vitro and in vivo animal and human studies have identified specific nuclear receptors for fatty acids present throughout the body that regulate glucose and lipid metabolism and impact immune function, and thus play important roles in regulation of insulin sensitivity. Currently, three isoforms of these nuclear receptors have been identified in humans: the peroxisome proliferator-activated receptor gamma (PPAR-G), PPAR alpha, and PPAR delta. All three are expressed in a wide variety of tissues including the ovary, adipose tissue, skeletal muscle, heart, kidney, and liver. As a result, ligands that activate these receptors and potentiate their actions have important ramifications upon folliculogenesis and fertility. Ovarian expression of both PPAR alpha and PPAR delta is relatively stable throughout the ovulatory cycle, whereas the expression of PPAR-G in the ovary is more dynamic with an increase in early folliculogenesis. At the time of the LH surge, PPAR-G expression is downregulated. The highest concentrations of PPAR-G are present in granulosa cells, which are responsible for estradiol production and the regulation of follicular fluid content responsible for the growth and development of oocytes.[24-26]

The thiazolidinediones (TZDs), insulin sensitizers whose actions are mediated via activation of PPAR-G, improve reproductive metabolic profiles and ovulatory function in women with PCOS. However, despite these favorable effects, PPAR-G agonists also downregulate leptin, an adipocyte-selective protein that inhibits feeding behavior and increases lipid catabolism. This effect may explain the weight gain seen in diabetic patients who take synthetic PPAR-G ligands such as TZDs.[27]

Association of Weight with Infertility

Several studies of male infertility have shown statistically significant negative correlations between body mass index (BMI), waist circumference, and waist:hip ratios with testosterone levels, semen volume, and total

sperm count, thus strongly suggesting a link between obesity, hypogonadism, and infertility.[28,29]

After correction for multiple variables including illness, caffeine, alcohol, and cigarette exposure, and abstinence prior to sample collection, Jensen et al found sperm concentration and total sperm count to be decreased 26% and 24%, respectively among a group of 1,558 Danish men with a BMI greater than 25 kg/m^2 compared to a reference group with BMIs between 20-25 kg/m^2.[30]

Rich-Edwards et al observed a U-shaped association between BMI and relative risk of infertility secondary to ovulatory dysfunction in 20,417 American nurses from the Nurses' Health Study II, a cohort of married female nurses ages 24-42 followed prospectively for eight years.[22] In comparison to women with a BMI of 21-24 kg/m^2, women with BMIs below 20 kg/m^2 or above 24 kg/m^2 exhibited increasing age-adjusted relative risks of ovulatory infertility.

Exercise

Regular exercise improves general medical health and well-being and provides protection from chronic diseases such as hypertension, cardiovascular disease, diabetes, osteoporosis, and depression. Rich-Edwards et al also found that exercise, specifically vigorous exercise, was associated with a reduced risk of ovulatory infertility. Although this improvement in ovulatory fertility can partly be attributed to diminished weight, it was also noted that even after adjustment for BMI, each hour of vigorous exercise per week produced a relative risk reduction of 5%, suggesting that such regular physical activity protects ovarian function through a mechanism independent of BMI, such as increased insulin sensitivity. Interestingly, nulliparous women benefitted most in terms of improved fertility from this activity, with each hour of vigorous exercise per week resulting in an 8% relative infertility risk reduction, even after multivariable adjustments for smoking, caffeine, alcohol intake, and prior oral contraceptive use. When specific vigorous activities were separately examined, the largest reductions in estimated relative risk were for running (one mile in less than 10 minutes; 34% risk reduction), jogging (one mile in more than 10 minutes; 22% risk reduction), and smaller estimated risk reductions observed for racquet sports (12%), lap swimming (5%), aerobics/calisthenics (5%), and biking (5%).[21] Furthermore, vigorous activity had the strongest protective effect among women in the normal weight range (BMI 20-25 kg/m^2).[22]

For men, it is clear that risk factors for cardiovascular disease such as smoking, hypertension, and type 2 diabetes mellitus have strong links epidemiologically to erectile dysfunction.[31] Esposito et al showed that a treatment group of 55 obese men without chronic disease (ages 35-55) who received ongoing, detailed advice about a 10% body weight reduction through caloric restriction and increased physical activity to 195 minutes per week experienced a statistically significant higher rate of weight loss, improvement in erectile dysfunction, and decrease in C-reactive protein levels compared to a control group.[32]

Conclusion

Implementation of fertility-friendly and overall healthy lifestyle changes, including those listed below, results in improved fertility outcomes for male and female partners. Since these lifestyle interventions also improve general health, it is important to implement them prior to initiation of more complex, expensive and invasive assisted reproductive technologies.

1. Avoidance of active or passive exposure to cigarette smoking;
2. Avoidance of alcohol for women attempting to conceive;
3. Loss of 10-15% of excess weight in overweight/obese infertile couples;
4. Regular vigorous daily aerobic exercise, including running, swimming, cycling; and
5. Avoidance of caffeine ingestion from common foods and beverages.

Recommendations: Primary Care

Primary care physicians can support fertility-friendly lifestyles by:

1. Identifying at-risk patients with measurements of height, weight, waist circumference, and BMI calculation;[33]
2. Screening for the presence of medical illnesses such as sleep apnea,[34] depression,[35] endocrine disorders such as hypothyroidism, PCOS, diabetes, etc., followed by treatment and referral as clinically needed;
3. Avoiding the use of medications that might cause weight gain and substitute alternatives that are weight-neutral;[36]
4. Providing guidance or dietitian referral regarding appropriate dietary caloric restrictions to promote realistic weight-loss goals tailored to patient needs;[37]
5. Emphasizing the importance of smoking cessation;[38]
6. Recommending patients incorporate physical exercise into their daily life with documentation of caloric intake and exercise in daily food and activity diaries;[39] and
7. Monitoring and reviewing progress with sequential

measurements and diet, medication, and activity log reviews during office visits. ❖

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Aristolochic Acid and Renal Toxicity

By Dónal P. O'Mathúna

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EARLY IN 1992, TWO WOMEN IN THEIR 40S WERE TREATED for renal failure in a hospital in Brussels, Belgium. Both had been healthy and not recently taking any medications, although one had previously used a beta-agonist asthma inhaler for 8 years.[1] They had both taken an herbal slimming remedy during 1990 and 1991 while attending the same medical clinic. A survey of all the Brussels dialysis units revealed seven additional young women with chronic interstitial nephritis who had used the same slimming regimen. While this situation was widely reported at the time, a 2008 report claims that the situation has developed into "a worldwide problem," with the culprit herbs still available for sale, especially on the internet.[2] Clinicians with patients who have rapidly deteriorating renal function of unknown origin should be alert to the possibility of aristolochic acid nephropathy. Such patients should be asked about any herbal remedies they may have ingested in the previous couple of years, especially those of Chinese origin.

Background

The medical clinic at the center of the Belgian tragedy had changed the formula of its slimming aid in May 1990.[1] The new remedy was to contain cascara powder, acetazolamide, belladonna extract, and two Chinese herbs, *Stephania tetrandra* and *Magnolia officinalis*. The latter were imported directly from China, and were not subject to quality control at that time in Belgium.[1] Thus, the renal condition was initially called Chinese herb nephropathy. It is now believed that what was originally supplied as *Stephania tetrandra* was actually *Aristolochia fangchi*.[3] This herb contains aristolochic acid, known to be nephrotoxic and carcinogenic in animals. For this reason, the clinical condition is now called aristolochic acid nephropathy (AAN).[2]

By 1998, more than 100 similar cases of rapidly progressive renal failure were diagnosed in Belgium and traced to the same clinic.[3] This represents about 5% of those exposed to the slimming remedy. Why the toxins affect people so differently is one of the questions remaining unanswered about this tragedy. The 2008 report identified cases of AAN in several countries *(see Table, page 127)*.[2] However, the true extent of the problem remains unknown, especially in China and India where herbs containing aristolochic acid are frequently used and interchanged with other botanicals.

In 2000, it was reported that those with AAN were facing additional problems. Examination of renal tissue

Summary Points

- Chinese herbs containing the nephrotoxic and carcinogenic compound aristolochic acid remain available, especially on the Internet.
- Clinicians caring for patients with renal failure of unexplained origin should inquire about consumption of herbal remedies, especially Chinese herbs.
- The unspecified nature of the traditional system for Chinese herbs easily leads to misidentification of plant material.

taken from the first two women with AAN who had received kidney transplants revealed urothelial carcinoma. Subsequently, 39 patients agreed to undergo prophylactic kidney transplantation. Among these, 18 cases of urothelial carcinoma were found (46%).[4] All of the tissue samples removed from patients contained aristolochic acid adducts bound to human DNA, confirming that aristolochic acid was directly involved in the toxicity.

Availability

In response to the Belgian AAN outbreak, many countries banned the importation or sale of *Aristolochia* species. In 2000 and 2001, the FDA issued warnings to various stakeholders and an import alert on herbal products containing aristolochic acid.[5] The FDA has also published a list of various scientific and Chinese names of herbs and products that may contain aristolochic acid.[6]

However, such regulatory actions have not removed the toxins from the market. In 2003, researchers at the University of California, Berkeley examined U.S. web sites and identified, among the items for sale, 19 products containing aristolochic acid and 95 products suspected of containing aristolochic acid.[7] For a study published in 2004, other researchers purchased 25 aristolochia or asarum products from the web sites of U.S. merchants.[8] The Asarum genus is closely related to aristolochia and contains aristolochic acid. Analyses revealed that six products contained aristolochic acid.

In the Netherlands, herbal products are prohibited from containing aristolochic acid. Dutch researchers purchased 68 herbal products with names associated with *Aristolochia* species or other species commonly replaced by *Aristolochia* species.[9] Analyses found that 25 of the products (37%) contained aristolochic acid. All *Aristolochia* species have been banned in the United Kingdom since 2001.[10] However, testing of herbal products available in the United Kingdom and labeled with Chinese names connected with aristolochia found that 40% of the samples contained aristolochic acid.[11] Many products containing aristolochic acid remain on the market.

Table

Reported cases of aristolochic acid nephropathy

Country	Number of Reported Cases
Belgium	128
China	116
France	4
Germany	1
India	*
Japan	6
Korea	1
Spain	1
Taiwan	33
United Kingdom	4
United States	2

* The authors assume there have been cases of aristolochic acid nephropathy in India given the widespread use of herbs there, but found no documentation to substantiate their assumption.

For more detail see: Debelle FD, et al. Aristolochic acid nephropathy: A worldwide problem. *Kidney Int* 2008; 74:158-169.

Naming Problems

As noted earlier, the original outbreak of AAN in Belgium was traced to the replacement of *Stephania tetrandra* by *Aristolochia fangchi*, and other problems in the naming of Chinese herbs.[2] Both plants are known by the same common names in Pin Yin, the phonetic representation of Chinese characters.[9] In addition, the two species are used interchangeably in traditional Chinese medicine.[2]

Lack of naming specificity is commonplace in traditional Chinese medicine. Several plant species can share the same Chinese common name, and some plants have more than one common name.[11] Mistakes happen regularly. A case of AAN was reported in Hong Kong after a man consumed *Aristolochia mollissima*.[12] This plant is known by two common names, Xun Gu Feng and Bai Mao Teng. However, Bai Mao Teng is also the common name for *Solanum lyratum* (also called Bai Ying). The Hong Kong man believed he had purchased *Solanum lyratum*, but was sold the poisonous *Aristolochia mollissima* material instead. A systematic study of Chinese herbs has revealed that this type of confusion occurs repeatedly because the Chinese naming system is not standardized and plant material is not authenticated at source.[12]

Mechanism of Action

Aristolochia species belong to the family Aristolochiaceae, several of which have been used in herbal remedies as anti-inflammatory agents.[11] The toxic compounds in these species are a group of aristolochic acids, with the most abundant being named aristolochic acid I and aristolochic acid II. These compounds are found throughout the plant and have not been found

outside the Aristolochiaceae family.[11] Animal and human studies have found that aristolochic acids are nephrotoxic, carcinogenic, and mutagenic. Nephrotoxicity occurs in humans at μg/kg doses.[11] The aristolochic acids are activated by metabolic enzymes within cells to give a highly reactive intermediate which forms covalent bonds with DNA.[2] These adducts have been shown to cause mutations in animals and humans which probably trigger the growth of cancer. How aristolochic acid leads to renal damage remains unknown.[2]

A Related Condition

From the earliest reports of Belgian AAN, similarities were noted with another type of devastating renal disease. Balkan endemic nephropathy (BEN) affects thousands of men and women living in farming villages along the Danube river basin.[13] Most cases occur in Bosnia, Bulgaria, Croatia, Romania, and Serbia. In contrast to AAN, this disease develops slowly, but leads to chronic renal failure with a strong association with urothelial cancer. The incidence is geographically restricted, and the disease is not inherited. Numerous environmental toxins have been proposed over the 50 years since the condition was first described, but none have satisfactorily explained the disease.[2]

The clinical and histological similarities between BEN and AAN have led to much research in this area. *Aristolochia clematitis* is a weed native to this Balkan area and grows among the wheat used to prepare local bread. Over several years, residents ingest similar amounts of aristolochic acid as those who took the Belgian slimming remedy. Tissue samples taken from BEN patients contain the same aristolochic acid adducts found in AAN patients. The same type of mutation has also been found in the cancer cells of patients with AAN or BEN. A connection between BEN and aristolochia was first noted by Serbian researchers in 1967, but appears to have been overlooked for decades.[13] It has taken the recent Belgian tragedy to redirect research, leading to increasing confidence that the cause of BEN has been identified. The disease will hopefully be eradicated as efforts progress to eliminate *Aristolochia clematitis* from the area.

Conclusion

Efforts to eradicate aristolochia from herbal markets have not been successful. Outside of the original Belgian reports, many cases of AAN were reported after countries had banned the importation or sale of *Aristolochia* species.[2] Regulatory efforts must continue to remove such products from the market.

Recommendation

Clinicians should remain alert to the possibility that rapidly progressing renal problems of unexplained origin may be related to consumption of herbal products. Chinese herbs are particularly prone to including *Aristolochia* species, and to the substitution of other species by *Aristolochia* species. The tragic example of aristolochia provides another reason why patients should be regularly asked about their consumption of herbal remedies and dietary supplements. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Slow is Good? Tai Chi and CAD

Source: Lan C, et al. Effect of T'ai Chi Chuan training on cardiovascular risk factors in dyslipidemic patients. *J Altern Complement Med* 2008;14:813-819.

Goal: To assess the effect of Tai Chi Chuan (TCC) training on risk factors for coronary artery disease (CAD) in people with dyslipidemia.

Study design: One-year, case-controlled trial in a community setting (Taiwan).

Subjects: People < 65 years old (n = 70, data evaluable on 53 subjects, including 29 women) referred from a tertiary hospital center's dyslipidemia clinic who were sedentary and who had been treated for at least 6 months (medication and diet therapy).

Methods: When, at study entry, participants were asked about their interest in engaging in a regular program of exercise, 34 replied "no" and were placed into a "usual care" group that did not participate in any structured exercise over the ensuing year. The remaining 36 subjects received TCC training three times a week that included 24 minutes of TCC (108 postures) sandwiched between 20 minutes of stretching and range of motion exercise, and a 10-minute cool-down period. It was estimated that exercise intensity during TCC training was at 70-80% of peak heart rate. Exercise testing was completed at baseline and at the end of one year's time, and blood tests were obtained at the same time periods for markers of inflammation, fasting glucose and insulin levels, and lipids. Subjects were asked not to change their dietary patterns during the study.

Results: Members of the usual care group showed no significant improvement in markers for cardiovascular risk, in fact exhibiting a diminution in aerobic capacity. Those in the TCC group experienced a slight reduction in blood pressure, and blood tests revealed lower levels of LDL-C (11.9%), total cholesterol (7.3%), triglycerides (26.3%), fasting insulin, and high-sensitivity C-reactive protein. The TCC group also showed improved aerobic capacity by trial's end.

Conclusion: One year of TCC may improve overall cardiovascular risk profile in people with dyslipidemia.

Study strengths: Monthly follow-up; number of parameters examined.

Study weaknesses: Non-randomized protocol; 24% dropout rate; no mention of how exercise intensity was assessed; no monitoring of subjects' diet.

Of note: TCC is sometimes called "moving meditation," reflecting the graceful, slow movements that characterize this traditional martial art; to some eyes TCC would not be classified as exercise, but prior data suggest TCC can improve aerobic capacity as well as balance, perhaps lessening the risk of falls; early research also suggests a beneficial effect on blood pressure and cholesterol levels from regular TCC practice; compliance with TCC attendance in this trial was 77%; reasons for

dropping out of the study included lack of time and loss of interest.

We knew that: Economic growth in Asia has spurred dramatic lifestyle changes, and adjusted mortality rates from cardiovascular disease have increased markedly; data suggest that mean cholesterol levels of people living in Beijing increased by > 45 mg/dL over a 15-year period that ended at the turn of the century; physical activity appears to have a beneficial effect on lipid profiles.

Comments: A number of trials have examined the effects of TCC on physical fitness, the majority suggesting both physical and emotional benefits. The authors of the current trial attempted to build upon earlier data to look at potential reductions in CAD with regular TCC practice, but the flaws of the trial are so significant as to minimize the authors' findings. Thankfully, few practitioners would consider the treatment of a sedentary, dyslipidemic individual solely with medications and diet "usual care." Exercise is a core constituent of any CAD risk-reduction program, and making no intervention in this regard for at-risk patients would be imprudent at best. Another problem is the lack of randomization. Study groups were developed based on subject interest, introducing a major confounding factor. Taken together with the lack of dietary monitoring and a significant dropout rate, reflecting some of the challenges associated with any exercise recommendations, and it appears the authors have undue confidence in their conclusions.

Prior data suggest that TCC may offer aerobic benefits to those unable to participate in more active forms of physical activity, as well as to those who simply enjoy this calming art form. It is reasonable to recommend TCC training to patients at risk for CAD as a gentle form of exercise; however, the

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

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CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

27. Which factor impacts a woman's fertility?
a. Age
b. Smoking history
c. BMI
d. All of the above

28. Infertility is defined as the inability to conceive after 12 months of unprotected intercourse.
a. True
b. False

29. Insulin resistance is strongly implicated in the etiology of polycystic ovarian syndrome, the most common form of ovulatory dysregulation.
a. True
b. False

30. Aristolochic acid has been shown to be:
a. nephrotoxic.
b. carcinogenic.
c. mutagenic.
d. All of the above

31. The naming of Chinese herbs has been found to be:
a. highly variable and unspecific.
b. very specific.
c. scientifically reliable.
d. All of the above

32. Which of the following represents a practical response to the situation with aristolochia?
a. Increase sales of herbal remedies.
b. Ban all herbal remedies in the United States.
c. Clinicians should ask patients about their use of herbal remedies and dietary supplements.
d. Remove slimming remedies from weight-loss clinics.

Answers: 27. d, 28. a, 29. a, 30. d, 31. a, 32. c.

current study does little to further our understanding of TCC's impact on CAD risk, and clinical recommendations should not be made based on this study's conclusions.

What to do with this article: Remember that you read the abstract. ❖

No C for the 'Big C'? Vitamin C and Chemotherapy

Source: Heaney ML, et al. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res* 2008;68:8031-8038.

Goal: To determine the effect of vitamin C on the cytotoxicity of various antineoplastic agents.

Study design: Bench research and animal data.

Subjects: ICR SCID mice.

Methods: Using cell lines (myeloblastic chronic myeloid leukemia cell line K562 and the lymphoma cell line RL), dehydroscorbic acid (DHAA) was employed to increase intracellular vitamin C levels. The cells were then exposed to vincristine, doxorubicin, methotrexate, cisplatin, and imatinib (Gleevec®) in doses corresponding to an IC_{75}, and cellular response was documented. In another part of the study, mice with RL cell xenografts were studied. The animals were divided into cohorts that received vehicle, DHAA, doxorubicin, or DHAA plus doxorubicin through the tail vein. Tumor growth was followed.

Results: Both cell lines accumulated substantial intracellular concentrations of vitamin C. Increased intracellular vitamin C levels not only generated resistance to the therapeutic effects of anticancer drugs that work at least in part through the generation of reactive oxygen species (ROS) within cancer cells, but also negatively impacted the efficacy of antineoplastic drugs that do not rely upon ROS generation for therapeutic effect. Cells with higher intracellular vitamin C levels were more resistant to cytotoxicity, suggesting a dose-dependent effect of vitamin C, but high intracellular vitamin C levels had no effect on cells not exposed to antineoplastics. Vitamin C pretreatment decreased apoptosis with all tested agents, and its effects did not appear to be related to its antioxidant capacity. In the mouse phase of the study, treatment with DHAA alone did not affect tumor growth; however, mice pretreated with DHAA that then received doxorubicin had markedly increased tumor growth compared to those mice receiving doxorubicin alone. Further studies showed that vitamin C did not affect tumor cell uptake of doxorubicin, suggesting that vitamin C might interfere with the intracellular working of the antineoplastic agents. Mitochondrial membrane potential was preserved with vitamin C pretreatment, suggesting a mitochondrial site of action.

Conclusion: Vitamin C may attenuate the cytotoxicity of antineoplastic agents, regardless of mechanism of action.

Study strengths: Use of multiple forms of chemotherapy with varied mechanisms of action; measurement of intracellular vitamin C levels; comparison with another potent antioxidant, N-acetyl cysteine.

Study weakness: Bench and animal data yet to be corroborated in humans.

Of note: Antineoplastic agents like cisplatin and doxorubicin create increases in intracellular ROS that may be important to therapeutic effect; some reports suggest a benefit of vitamin C when combined with chemotherapy, specifically in the setting of arsenic trioxide use, where vitamin C may modulate extracellular production of hydrogen peroxide.

We knew that: Vitamin C is a potent antioxidant that donates electrons to at least eight different important enzymes and helps mitigate the effects of ROS, especially in the mitochondria; ascorbic acid (AA) and DHAA are the main physiologic forms of vitamin C (DHAA has a much wider distribution via facilitated intracellular transport utilizing glucose transporters, after which it is converted into AA); the effects of vitamin C on cancer and its treatment are unclear and a source of significant controversy.

Comments: The results of this study are scary. True, there are reports of vitamin C being an effective aid in the treatment of some cancers, but the supportive data have not been as complete and did not drill down to potential intracellular effects as thoroughly as the authors of the current trial have done.

These results must give practitioners who care for people undergoing cancer treatment pause. In the past, many have left the decision regarding antioxidant supplementation to the oncologists, some of whom are well-versed in this arena but many of whom are not, and the result was often a blanket statement: "Don't use supplements during your treatment." Those days are long past, as it is clear that people are acting on their own to supplement their treatment regimens, and seeking out information from a range of sources that runs the gamut from the lay press to neighbors' folk remedies to the 17-year-old health food store clerk to reputable web sites. In this regard, one of our roles is to provide credible guidance, and caution where appropriate.

This article alone will not end the debate over antioxidant therapy during treatment for cancer. Existing data regarding other antioxidants, such as CoQ10, suggest promise in certain situations where chemotherapy is employed. Clearly the need for further study remains, especially human trials, but for now there is significant reason to consider foregoing the use of high-dose vitamin C supplementation during chemotherapy until greater clarity is achieved. This caution does not appear to apply to the eating of foods high in vitamin C, however.

What to do with this article: Make copies to hand out to your peers. ❖

Enrollment Halted in Trial Studying Chelation Therapy for Treatment of CAD

Enrollment into the Trial to Assess Chelation Therapy (TACT), a five-year, $30-million National Institutes of Health-funded clinical study, has been stopped, according to Heartwire, a professional news service of WebMD.

"The investigators and institutions performing the trial, in conjunction with their institutional review boards, have temporarily and voluntarily suspended enrollment of new participants in the study," Susan Dambrauskas, a media officer at the National Heart, Lung, and Blood Institute, a cosponsor of the study, wrote in an e-mail to the news service.

TACT is a randomized, double-blind, placebo-controlled study evaluating the efficacy of ethylene-diamine-tetra-acetic acid (EDTA) chelation therapy in the treatment of coronary artery disease (CAD). The primary endpoint of the trial is a composite of all-cause mortality, MI, stroke, hospitalization for angina, and hospitalization for congestive heart failure. Enrollment was estimated at around 2,000 patients, and the trial was to be completed in July 2009.

Chelation therapy has been used since 1955 for the treatment of CAD. Agents such as EDTA, which bind metals and are approved by the FDA to treat heavy-metal poisoning, are given intravenously to decalcify atherosclerotic plaque, Heartwire says. While TACT was designed to answer questions about the potential benefit of using chelation to treat CAD, critics have called this trial dangerous, unethical, and a waste of public funds.

The National Center for Complementary and Alternative Medicine is also a study sponsor. ❖

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