Volume 27, Number 5, October–December, 2001

ISSN: 0092-623X

R. Taylor Segraves, M.D., Ph.D.

JOURNAL OF SEX & MARITAL THERAPY

Journal of Sex & Marital Therapy, 27:541–549, 2001

0092-623X/01 $12.00 + .00

A Double-Blind Placebo-Controlled Study of ArginMax, a Nutritional Supplement for Enhancement of Female Sexual Function

THOMAS Y. ITO
University of Hawaii, School of Medicine, Honolulu, Hawaii, USA
AILEEN S. TRANT
Daily Wellness Company, Mountain View, California, USA
MARY LAKE POLAN
Department of Gynecology/Obstetrics, Stanford University School of Medicine, Stanford, California, USA

This study was open to women over the age of 21 years with an interest in improving their sexual function. Of the 77 participants, 34 received ArginMax and 43 received a placebo. ArginMax for Women is a proprietary nutritional supplement consisting of extracts of ginseng, ginkgo, and damiana, L-arginine, multivitamins, and minerals. After 4 weeks, 73.5% of the ArginMax group improved in satisfaction with their overall sex life, compared with 37.2% of the placebo group ($p < 0.01$). Notable improvements were also observed in sexual desire, reduction of vaginal dryness, frequency of sexual intercourse and orgasm, and clitoral sensation. No significant side effects were noted.

INTRODUCTION

A recent survey (Laumann, Paik, & Rosen, 1999) found that the incidence of sexual dysfunction in the United States was greater in women (43%) than in men (31%). Responses varied with certain demographic characteristics, including age, marital status, and level of education. In general, the prevalence of sexual problems tends to decrease with age in women, except for those who report vaginal dryness, which increases with age. Nonmarried women are roughly 1½ times more likely to have orgasmic dysfunction and sexual

Address correspondence to Mary Lake Polan, M.D., Ph.D., Department of Gynecology/Obstetrics, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA.

anxiety than are married women. High educational attainment is inversely related to sexual problems for both sexes. Fully recognizing the complex and multidimensional nature of female sexual dysfunction, this study focuses on evaluating one important dimension—the role of nutritional supplementation in female sexual health.

Nitric oxide (NO) has been well established as the key mediator for the up-regulation of cyclic guarosine monophosphate (cGMP) which in turn mediates circulation and sexual function (Burnett, 1995). L-arginine is a precursor of NO. The conversion of L-arginine to NO is mediated by nitric oxide synthase (NOS). Increasing tissue L-arginine levels result in the increase of NO and cGMP (Jung et al., 1997; Kimura et al., 1993). Supplementation with L-arginine has been shown to play a role in restoring endothelial-derived NO production in many disorders which reduce or impair this production, including diabetes (Pieper & Dondlinger, 1997), hypercholesterolemia (Creager et al., 1992; Hutchison, et al., 1999), and mechanisms related to hypertension (Noguchi, Sasaki, Seki, Giddings, & Yamamoto, 1999). Studies also point to the role of L-arginine in reducing cell-mediated breakdown of NO (Wascher et al., 1997).

In female sexual function, neurotransmitter-mediated vascular smooth muscle relaxation, the first phase of response, results in increased vaginal lubrication, vaginal wall engorgement, and vaginal luminal diameter expansion, as well as increased clitoral length and diameter (Goldstein & Berman, 1998). Atherosclerotic vascular disease can interfere with these functions, resulting in conditions such as insufficient vaginal engorgement and clitoral erectile syndromes. NO is involved in this response, and during menopause vaginal atrophy and declining sexual function may be NO-dependent (Berman, McCarthy, & Kyprianou, 1998). Estrogen withdrawal appears to play a role in the regulation of vaginal NOS expression and apoptosis in nerves, smooth muscle, vascular endothelium, and epithelium of the vagina, implying an NO-related mechanism in female sexual function. L-arginine, as an NO precursor, has been shown to be essential to sexual maturation in the female rat (Pau & Milner, 1982).

The efficacy of Korean ginseng (*Panax ginseng*) in treating sexual dysfunction was recently demonstrated in a randomized controlled clinical trial involving a total of 90 male patients studied over 3 months, 30 each receiving a placebo, trazadone, or ginseng (Choi, Seong & Rha, 1995). Ginseng was the most efficacious treatment with improvements measured in erectile parameters such as girth, libido, and patient satisfaction. Frequency of intercourse, ejaculations, and erections did not differ among groups. In a controlled study, Ginseng was demonstrated to increase spermatozoa count and motility in 66 patients with fertility problems (Salvati et al., 1996). Ginsenosides, the primary active component of ginseng, have been shown to increase NO production in endothelial cells (Chen, 1996; Han & Kim, 1996). One observed mechanism for the increase in NO production was the up-regulation of NOS activity by ginsenosides (Chen & Lee, 1995). The effects of ginsenosides

on NO production has implications for improved sexual function, and may partly account for the aphrodisiac effect of *Panax ginseng* used in traditional Chinese medicine.

Ginkgo biloba is well established to facilitate microvascular circulation that may physiologically lead to improvement in sexual function (Auguet, Delaflotte, Hellegouarch, & Clostre, 1986; Welt, Weiss, Koch, & Fitzl, 1999). In addition to its ability to facilitate microvascular circulation, there is evidence that Ginkgo biloba extract may directly elucidate smooth muscle relaxation, likely via effects on the NO pathway (Paick & Lee, 1996; Chen, Salwinski, & Lee, 1997). Ginkgo bilboa also appears efficacious in the treatment of antidepressant-induced sexual dysfunction, particularly in women (Cohen & Bartlik, 1998).

Damiana (*Turnera diffusa*) has been traditionally used as a tonic for the central nervous and hormonal system, and as an aphrodisiac in Latin American lore (Foster, 1991). Sexually impaired rats treated with Damiana increased their rates of copulatory performance (Arletti, Benelli, Cavazzuti, Scarpetta, & Bertolini, 1999). Damiana has been shown to have receptor activity as a phyto-progestin, although no progestin activity was demonstrated on induction of alkaline phosphatase (Zava, Dollbaum, & Blen, 1998).

B-complex vitamins are important for the activity of hundreds of enzymes and energy metabolism. Low levels of circulating folate and vitamin B_6 create an increased risk of peripheral vascular disease, leading to potential reduction of sexual function (Robinson et al., 1998). Vitamin B_{12} injections have increased sperm counts in men (Sandler & Faragher, 1984; Kumamoto et al., 1988). Multivitamin supplementation has been shown to enhance fertility in women (Czeizel, Metneki, & Dudas, 1996). Vitamin E supplementation has been shown to increase fertility in both men and women (Bayer, 1960).

Calcium supplementation over a 3-month treatment period has been shown to reduce premenstrual symptoms by 48% from baseline scores, as compared with 30% reduction in a placebo group (Thys-Jacobs, Starkey, Bernstein, & Tian, 1998). Iron is known to help reduce fatigue in cases of chronic iron insufficiency common in women due to monthly blood loss. Zinc is a fundamental mineral in the maintenance of human reproductive function. Low levels of serum zinc have been shown to cause sexual dysfunction, and are associated with infertility in males (Mohan et al., 1997).

Previous clinical studies have been conducted on men with erectile dysfunction to preliminarily evaluate the role of a similar combination nutritional product in optimizing NO production and enhancing sexual function. In the pilot study, twenty-five men were consecutively enrolled through a urology clinic, with participation open to all individuals diagnosed with mild to moderate erectile dysfunction of varying etiology. The study instrument was the International Index of Erectile Function (IIEF; Rosen et al., 1997). Following the completion of the study, 88.9% of the subjects experienced improvement in ability to maintain an erection during intercourse, and 75.0%

experienced improvement in satisfaction with their overall sex life (Ito, Kawahara, & Das, 1998). In the ensuing double-blind, placebo-controlled study of 52 men with erectile dysfunction, 84% reported improvement in their ability to maintain an erection, compared with 24% in the placebo group. In addition, 80% rated improvement in satisfaction with their overall sex life compared with 20% in the placebo group ($p < 0.001$; Ito, Kawahara, & Das, 1999). Given the critical role of circulation in the physiology of vaginal lubrication, clitoral engorgement, and sexual arousal, a double-blind, placebo-controlled study was designed to evaluate the role of the nutritional supplement, ArginMax for Women, in the enhancement of female sexual function.

MATERIALS AND METHODS

All participants were enrolled based on their expressed interest in improving their current sexual function. Of the 77 participants (ages 22 to 71 years), who successfully followed and completed the study protocol, 6 had been previously treated for sexual dysfunction. The survey instrument was the Female Sexual Function Index (FSFI), a validated questionnaire with multidimensional scales for assessment of sexual function that was used in the evaluation of sildenafil citrate (Viagra) in women (Kaplan et al., 1999). Medical histories, FSFI scores, and blood pressure measurements were collected at 0 and 4 weeks. Upon enrollment, subjects were randomly assigned ArginMax or avplacebo in a double-blind fashion. Of the 77 subjects, 34 were on ArginMax and 43 were on a placebo. The age distributions were similar, with the ArginMax group ranging from 24 to 71 years (44.5±11.6) and the placebo group ranging from 22 to 68 years (41.0±11.7).

ArginMax for women is a proprietary nutritional supplement that incorporates a standardized combination of the following ingredients: Korean ginseng (*Panax ginseng*- 30% ginsenosides), Ginkgo biloba (24% flavone glycosides, 6% terpene lactones), Damiana leaf (*Turnera aphrodisiaca*), and L-arginine (precursor to NO), along with vitamins B_6, B_{12}, biotin, folate, niacin, pantothenic acid, riboflavin, and thiamin; antioxidant Vitamins, A, C, and E, and minerals calcium, iron and zinc.

RESULTS

In the ArginMax group, 70.6% reported improvement in their level of sexual desire (vs. 41.9% in the placebo group; $p < 0.01$) (Table 1), and 73.5% improved in satisfaction of their overall sex life (vs. 37.2% in the placebo group; $p < 0.01$). Frequency of intercourse increased in 64.7% of the supplement group (vs. 25.6% in the placebo group; $p < 0.01$), and 61.8% improved in the

TABLE 1. ArginMax Versus Placebo Group Female Sexual Function Index (FSFI) Scores

	ArginMax Group (n = 34)								
FSFI question	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]
Mean score, 0 weeks	3.412	2.941	3.000	2.206	1.794	2.000	2.412	2.824	2.794
Mean score, 4 weeks	4.147	3.912	3.735	3.059	2.882	3.206	3.500	3.471	3.412
Improvement (%)	38.2	52.9	64.7	61.8	70.6	73.5	61.8	47.1	52.9

	Placebo Group (n = 43)								
FSFI question	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]
Mean score, 9 weeks	3.512	2.837	3.233	2.000	1.791	2.209	2.442	2.419	2.512
mean score, 4 weeks	3.442	2.860	3.302	2.233	2.116	2.512	2.860	2.674	2.744
Improvement (%)	18.6	25.6	25.6	34.9	41.9	37.2	34.9	30.2	34.9

[a]1. Over the past 4 weeks how often did you experience **discomfort** during sexual intercourse? (1=Almost always, 2=Most times, 3=Sometimes, 4=A few times, 5=Almost never)

[b]2. Over the past 4 weeks how often did you experience **dryness** during sexual intercourse? (1=Almost always, 2=Most times, 3=Sometimes, 4=A few times, 5=Almost never)

[c]3. Over the past 4 weeks how often did you **attempt sexual intercourse**? (1=0, 2=1–2, 3=3–4, 4=5–6, 5=7–10, 6=11+)

[d]4. Over the past 4 weeks how often have you **felt sexual desire**? (1=Almost never, 2=A few times, 3=Sometimes, 4=Most times, 5=Almost always)

[e]5. Over the past 4 weeks how would you rate your **level of sexual desire**? (1=Very low, 2=Low, 3=Moderate, 4=High, 5=Very high)

[f]6. Over the past 4 weeks how satisfied have you been with your **overall sex life**? (1=Very dissatisfied, 3=About equally satisfied and dissatisfied, 5=Very satisfied)

[g]7. Over the past 4 weeks how satisfied have you been with your **sexual relationship** with your partner? (1=Very dissatisfied, 3=About equally satisfied and dissatisfied, 5=Very satisfied)

[h]8. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you have the **feeling of orgasm**? (1=Almost never, 2=A few times, 3=Sometimes, 4=Most times, 5=Almost always)

[i]9. Over the past 4 weeks, when you had sexual stimulation or intercourse, how would you rate your **degree of clitoral sensation**? (1=Very low, 2=Low, 3=Moderate, 4=High, 5=Very high)

sexual relationship with the partner (vs. 31.9% in the placebo group; $p < 0.01$). Intensity of clitoral sensation was rated higher by 52.9% of subjects in the ArginMax group (vs. 34.9% in the placebo group; $p < 0.06$), 52.9% experienced less dryness during intercourse (vs. 25.6% in the placebo group; $p < 0.01$), and 47.1% increased in frequency of orgasm (vs. 30.2% in the placebo group; $p < 0.07$). Although relatively few women experienced discomfort during intercourse, the ArginMax group reported a greater decrease in discomfort (38.2%) than the placebo group (18.6%; $p < 0.03$). No headaches, nausea, vomiting, visual disturbance, blood pressure alterations, dizziness, hypersensitivity, or other significant side effects were noted in either group.

DISCUSSION

Despite the prevalent nature of sexual dysfunction in women, no efficacious pharmaceutical therapies are currently available. For example, administration of sildenafil citrate (Viagra) in 30 postmenopausal women did not significantly improve sexual function, although there was some increase in vaginal lubrication and clitoral sensitivity (Kaplan et al., 1999). Clitoral discomfort and "hypersensitivity" occurred in 7 women (21%). Treatment with testosterone, on the other hand, may result in the undesirable androgen-mediated side effects of hirsutism and acne.

Although female sexual function is a complex result of psychological and physiological factors, nutritional supplementation appears to play a role in improvement of a number of key female sexual health parameters. The proposed mechanism is through enhancement of the NO pathway. NO derived from L-arginine is central to smooth muscle relaxation, vascular dilatation, and the regulation of circulation. In this study population, the treatment group experienced an increase in lubrication, clitoral sensitivity, frequency of orgasm, and an accompanying increase in sexual desire.

Although infrequently discussed, the management of sexual health is an extremely important topic, particularly for women. Even though more women than men experience sexual dysfunction, the majority of research has been conducted on men. As consumers develop an ever-increasing interest in a wellness-oriented approach towards healthcare, the role of nutritional supplementation in sexual function will become more important. For women, in particular, research into potentially useful treatment methodologies is very much needed. This clinical area will be further evaluated through expansion of the current double-blind, placebo-controlled study to a large-scale multicenter clinical study of ArginMax for Women in which the role of age and menopause will be examined.

REFERENCES

Arletti, R., Benelli, A., Cavazzuti, E., Scarpetta, G., & Bertolini, A. (1999). Stimulating properties of Turnera diffusa and Pfaffia paniculata extracts on the sexual behavior of male rats. *Psychopharmacology, 1,* 15–19.

Auguet, M., Delaflotte, S., Hellegouarch, A., & Clostre, F. (1986). Pharmacological bases of the vascular impact of Ginkgo biloba extract. *La Presse Medicule, 15,* 1524–1528.

Bayer, R. (1960). Treatment of infertility with vitamin E. *International Journal of Fertility, 5,* 70-78.

Berman, J. R., McCarthy, M. M., & Kyprianou, N. (1998). Effect of estrogen withdrawal on nitric oxide synthase expression and apoptosis in the rat vagina. *Urology, 51,* 650-656.

Burnett, A. L. (1995). Nitric oxide control of lower genitourinary tract functions: A review. *Urology, 45,* 1071–1083.

Chen, X. (1996). Cardiovascular protection by ginsenosides and their nitric oxide releasing action. *Clinical & Experimental Pharmacology & Physiology, 23,* 728–732.

Chen, X., & Lee, T. J. (1995). Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. *British Journal of Pharmacology, 115,* 15–18.

Chen, X., Salwinski, S., & Lee, T. J. (1997). Extracts of Ginkgo biloba and ginsenosides exert cerebral vasorelaxation via a nitric oxide pathway. *Clinical & Experimental Pharmacology & Physiology, 24,* 958–959.

Choi, H. K., Seong, D.H., & Rha, K.H. (1995). Clinical efficacy of Korean red ginseng for erectile dysfunction. *International Journal of Impotence Research, 7,* 181–186.

Cohen, A. J., & Bartlik, B. (1998). Ginkgo biloba for antidepressant-induced sexual dysfunction. *Journal of Sex & Marital Therapy, 24,* 139–143.

Creager, M. A., Gallagher, S. J., Girerd, X. J., Coleman, S. M., Dzau, V. J., & Cooke, J. P. (1992). L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. *Journal of Clinical Investigation, 90,* 1248–1253.

Czeizel, A. E. Metneki, J. & Dudas, I. (1996). The effect of preconceptional multivitamin supplementation on fertility. *International Journal of Vitamin & Nutrition Research, 66,* 55–58.

Foster, S. (1991). Herbs and sex: Separating fact from fantasy. *Health Foods Business, 74,* 30–33.

Goldstein, I., & Berman, J. R. (1998). Vasculogenic female sexual dysfunction: Vaginal engorgement and clitoral erectile insufficiency syndromes. *International Journal of Impotence Research, 10,* S84–S90.

Han, S. W., & Kim, H. (1996). Ginsenosides stimulate endogenous production of nitric oxide in rat kidney. *International Journal of Biochemical & Cell Biology, 28,* 573–580.

Hutchison, S. J., Sudhir, K., Sievers, R. E., Zhu, B. Q., Sun, Y. P., & Chou, T. M. (1999). Effects of L-arginine on atherogenesis and endothelial dysfunction due to secondhand smoke. *Hypertension, 34,* 44–50.

Ito, T., Kawahara, K., Das, A. (1998). The effects of ArginMax, a natural dietary supplement for enhancement of male sexual function. *Hawaii Medical Journal, 57,* 741–744.

Ito, T., Kawahara, K., Das, A. (1999). A double-blind placebo-controlled clinical study on the effects of ArginMax, a natural dietary supplement for enhancement of male sexual function. Paper presentation at the meeting of the American Urological Association Western Section Meeting, Monterey, CA.

Jung, H. C., Mun, K. H., Park, T. C., Huh, K., Seong, D. H., & Suh, J. K. (1997). Role of nitric oxide in penile erection. *Yonsei Medical Journal, 38,* 261–269.

Kaplan, S. A., Reis, R. B., Kohn, I. J., Ikeguchi, E. F., Laor, E., & Te, A. E. (1999). Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. *Urology, 53,* 481–486.

Kimura, K., Takahashi, M., Naroda, T., Iriguchi, H., Miyamoto, T., & Kawanishi, Y. (1993). The relaxation of human corpus cavernosum caused by nitric oxide. *Nippon Hinyokika Gakkai Zasshi, 84,* 1660–1664.

Kumamoto, Y., Maruta, H., Ishigami, J., Kamidono, S., Orikasa, S., & Kimura, M. (1988). Clinical efficacy of mecobalamin in treatment of oligozoospermia. *Acta Urology Japan, 34,* 1109–1132.

Laumann, E. O., Paik, A., & Rosen, R. C. (1999). Sexual dysfunction in the United States. *JAMA, 281,* 537–544.

Mohan, H., Verma, J., Singh, I., Mohan, P., Marwah, S., & Singh, P. (1997). Interrelationship of zinc levels in serum and semen in oligospermic infertile patients and fertile males. *Indian Journal of Pathology & Microbiology, 40,* 451-455.

Noguchi, T., Sasaki, Y., Seki, J., Giddings, J. C., & Yamamoto, J. (1999). Effects of voluntary exercise and L-arginine on thrombogenesis and microcirculation in stroke-prone spontaneously hypertensive rats. *Clinical & Experimental Pharmacology & Physiology 26,* 330–335.

Paick, J. S., & Lee, J. H. (1996). An experimental study of the effect of ginkgo biloba extract on the human and rabbit corpus cavernosum tissue. *Journal of Urology, 156,* 1876–1880.

Pau, M. Y., & Milner, J.A. (1982). Dietary arginine and sexual maturation of the female rat. *Jounal of Nutrition, 112,* 1834–1842.

Pieper, G. M., & Dondlinger, L. A. (1997). Plasma and vascular tissue arginine are decreased in diabetes: Acute arginine supplementation restores endothelium-dependent relaxation by augmenting cGMP production. *Journal of Pharmacology & Experimental Therapeutics, 283,* 684–691.

Robinson, K., Arheart, K., Refsum, H., Brattstrom, L., Boers, G., & Ueland, P. (1998). Low circulating folate and vitamin B6 concentrations: Risk factors for stroke, peripheral vascular disease, and coronary artery disease. *Circulation, 10,* 437–443.

Rosen, R. C., Riley, A., Wagner, G., Osterloh, I. H., Kirkpatrick, J., & Mishra, A. (1997). The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology, 49,* 822–830.

Salvati, G., Genovesi, G., Marcellini, L., Paolini, P., De Nuccio, I., Pepe, M., & Re, M. (1996). Effects of Panax ginseng C.A. Meyer saponins on male fertility. *Panminerva Medica, 38,* 249–254.

Sandler, B., & Faragher, B. (1984). Treatment of oligospermia with vitamin B12. *Infertility, 7,* 133–138.

Thys-Jacobs, S., Starkey, P., Bernstein, D., & Tian, J. (1998). Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms. Premenstrual syndrome study group. *American Journal of Obstetrics & Gynecology, 179,* 444–452.

Wascher, T. C., Posch, K., Wallner, S., Hermetter, A., Kostner, G. M., & Graier, W. F. (1997). Vascular effects of L-arginine: Anything beyond a substrate for the NO-synthase? *Biochemical & Biophysical Research Communications, 234,* 35–38.

Welt, K., Weiss. J., Koch, S., & Fitzl, G. (1999). Protective effects of Ginkgo biloba extract Egb 761 on the myocardium of experimentally diabetic rats. II. Ultrastructural and immunohistochemical investigation on microvessels and interstitium. *Experimental & Toxicologic Pathology, 51,* 213–222.

Zava, D. T., Dollbaum, C. M., Blen, M. (1998). Estrogen and progestin bioactivity of foods, herbs, and spices. *Proceedings of the Society for Experimental Biology & Medicine, 217,* 369–378.