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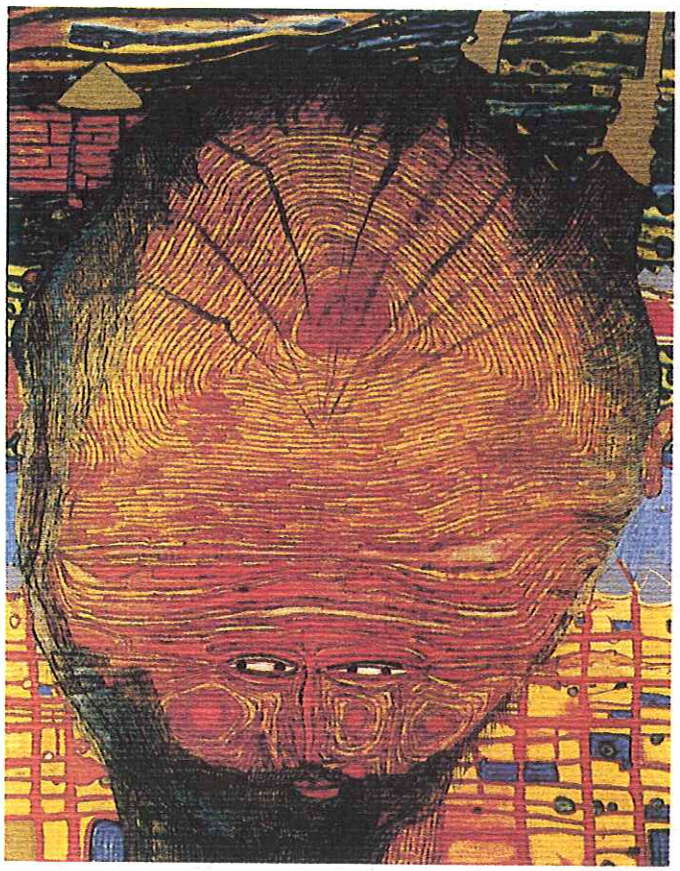

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Double-blind, placebo-controlled study of FertilityBlend®: a nutritional supplement for improving fertility in women

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Summary

Purpose: To determine the impact of nutritional supplementation on female fertility.

Methods: A double blind, placebo-controlled study of the effects of FertilityBlend® for Women, a proprietary nutritional supplement containing chasteberry, green tea, L-arginine, vitamins (including folate) and minerals, on progesterone level, basal body temperature, menstrual cycle length, pregnancy rate and side-effects.

Results: Ninety-three (93) women, aged 24-42 years, who had tried unsuccessfully to conceive for six to 36 months, completed the study. After three months, the FertilityBlend® (FB) group (N = 53) demonstrated a trend toward increased mean mid-luteal progesterone (P_{mL}), but among women with basal pretreatment $P_{mL} < 9$ ng/ml, the increase in progesterone was highly significant. The average number of days with luteal-phase basal temperatures over 98°F increased significantly in the FB group. Both short and long cycles (< 27 days or > 32 days pretreatment) were normalized in the FB group. The placebo group (N = 40) did not show any significant changes in these parameters. After three months, 14 of the 53 women in the FB group were pregnant (26%) compared to four of the 40 women in the placebo group (10%; p = 0.01). Three additional women conceived after six months on FB (32%). No significant side-effects were noted.

Conclusion: Nutritional supplements could provide an alternative or adjunct to conventional fertility therapies.

Key words: Fertility; Infertility; Herbal; Nutritional; Supplements; Chasteberry; L-arginine; Progesterone.

Introduction

The use of complementary and alternative medicine (CAM) therapies has been steadily increasing in the United States [1]. Herbs have been used for the treatment of infertility since at least 200 A.D. Herbal products have the potential to add to existing treatment options. Using nutritional supplements as a first step in treatment could improve key physiological factors essential to fertility. The challenge for physicians and patients has been lack of evidence regarding which herbs and nutrients are most effective, what levels and combinations are safe, and whether product quality is consistent. Vitamins, minerals, and specific co-factors play a major role in fertility function. If infertility is "unexplained", it may be due to subtle hormonal imbalances, aging reproductive systems, or nutritional deficiencies. In many of these cases, natural remedies may be an important first step. If "unexplained" infertility does not respond to natural interventions, the success of subsequent interventions may be improved by optimization of nutrition, reproductive system health, female hormone balance and male sperm parameters prior to more aggressive treatments.

Vitex agnus-castus (chasteberry) is an herb that has been used for gynecologic disorders for centuries. It has weak dopamine agonist activity and can decrease prolactin levels. Luteinizing hormone (LH) levels are increased and better development of the corpus luteum results. Clinical studies in Europe [2-4] show Vitex tincture increased progesterone levels and improved fertility. Loch, *et al.* [5] noted an increase in the pregnancy rate of women taking Vitex in a study of its effects on premenstrual syndrome (PMS) symptoms; no serious side effects were noted in this study of 1,634 patients. Vitex has been shown to reduce PMS symptoms and menstrual cycle irregularities [5-7].

Antioxidants have proven to be helpful in reducing free radical damage to ova, sperm and reproductive organs. Vitamins C, E and selenium are usually used for this purpose, but green tea may perform the same function. Khalsa [8] states that certain green tea catechins are approximately 100 times more potent than vitamin C and 25 times more potent than vitamin E. Antioxidants are also believed to work better in combinations than alone because they protect each other from oxidation [9]. Antioxidant combinations also preclude the need for large doses of a single nutrient, which may be harmful. In studying the presumed negative effects of caffeine on conception, Caan *et al.* [10] found that drinking tea (as opposed to other caffeinated beverages) increased the chance of conception per cycle by 2-fold.

Vitamin B6 [11], vitamin B12 [12], vitamin E [13], folate with multivitamins [14], magnesium with selenium [15], iron [16], and zinc with copper and selenium [17] have been shown to improve female fertility in controlled studies. Folate supplementation also appears to help reduce the incidence of neural tube birth defects [18], and good vitamin B6 and B12 status may reduce the risk of preterm birth [19].

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L-arginine, an essential amino acid, helps improve circulation to the reproductive organs [20], which may enhance oocyte development and embryo implantation. Battaglia, *et al.* [21] monitored uterine and follicular Doppler flow in response to L-arginine treatment during in-vitro fertilization treatment cycles of poor responder patients. The L-arginine-treated group demonstrated improved Doppler flow rates, a lower cancellation rate, and an increased number of oocytes collected and embryos transferred. Of the 17 women in the L-arginine supplementation group, three became pregnant, compared to none of 17 in the non-supplemented group.

As a result of both the documented and proposed mechanisms of these natural products, we postulated that a systematically designed blend of nutrients, herbs and L-arginine (FertilityBlend®) might positively support female reproductive health. A pilot study [22] on the effects of FertilityBlend® demonstrated improved pregnancy rates and other parameters indicative of increased fertility. Based on these positive results, the study was continued and additional patients were enrolled for further evaluation of the benefit of this supplement. Since this supplement is available over-the-counter, women using it may not have had any infertility testing. Therefore, the study was open to a diverse group of patients and included women who did not want other testing.

Materials and Methods

Ninety-three (93) women, aged 24-42 years, who had tried unsuccessfully to conceive for six to 36 months were enrolled in the study, and completed the 3-month trial. None of the participants received any pharmacological treatments for infertility during the course of the study, or for at least two months prior to start of taking the study product. Of the 93 women who completed the study, 40 received placebo (P) and 53 received FertilityBlend® (FB), administered in a randomized, double blind, placebo-controlled fashion. Institutional review board approval was obtained for the study. Statistical analyses were conducted using the Student's t-test, and Bayesian analysis of binomial data.

FertilityBlend® is a proprietary nutritional supplement containing standardized chasteberry (0.5% agnusides) and green tea extracts (50% phenols), the amino acid, L-arginine, vitamins E, B6, B12 and folate, iron, magnesium, zinc and selenium. A thorough literature review of all ingredients demonstrates a long history of safe use for women with a variety of gynecological disorders, as well as for potentially pregnant women. The AHPA Botanical Safety Handbook [23] states that traditional use of chasteberry includes prevention of miscarriage during the first trimester of pregnancy in cases of progesterone insufficiency. The highest level of quality assurance and GMP procedures were used in the manufacture of all ingredients and finished product.

Supplements were taken daily, three capsules per day, for three menstrual cycles after initial baseline measurement of mid-luteal phase progesterone (taken between day 18-22 of cycle). Changes in basal body temperature (BBT), length of menstrual cycle, pregnancy rate and incidence of side-effects were monitored for four months, starting two weeks before taking the supplement. Mid-luteal serum progesterone levels (P_{ml}) were evaluated via immunoassay, specifically using the Immulite 2000 Hormone Analyzer, at baseline (day 18-22 of first cycle) and after three months of nutritional supplementation (day 18-22 of fourth cycle). All subjects received an additional three months of open-label FertilityBlend® after successful completion of the study, with monitoring only of pregnancy status and side-effects.

Results

Mean age, weight and number of months attempting to conceive prior to the study were not statistically different between the women in the FB and P groups (Table 1). Mean ages for the supplement and the placebo groups were 35.4 and 34.8 years, average weights were 148.5 and 153.7 pounds, and average time attempting to conceive prior to the study was 19.6 and 20.7 months, respectively.

After three months, the FB supplement group (N = 53; 40 in P group) demonstrated a strong trend toward an increase in mean mid-luteal phase progesterone (P_{ml} from 8.2 to 10.4 ng/ml, p = 0.06; Table 2). Among women with low initial levels of P_{ml} (< 9 ng/ml, N = 20 in FB and 18 in P group), however, the increase in the FB group with low progesterone was highly significant after three months (3.2 to 8.1 ng/ml; p = 0.016; Figure 1).

The FB group also showed an increase in the average number of days in cycle with BBTs over 37°C (98.6°F)

Table 1. — *Patient characteristics and pregnancy rates in the supplement and placebo groups.*

	FertilityBlend[a] (No. = 53)	Placebo (No. = 40)	p value
Mean age (yrs)	35.4	34.8	0.225[c]
Mean weight (lbs)	148.5	153.7	0.262[c]
Mean months trying[a]	19.6	20.7	0.285[c]
No. of nulligravida (%)	23 (43%)	14 (38%)	0.211[d]
No. with no prior assessment (%)	12 (23%)	9 (20%)	0.503[d]
No. with endometriosis (%)	3 (6%)	3 (8%)	0.652[d]
No. with ovulatory dysfunction (%)	12 (23%)	8 (20%)	0.392[d]
No. with unexplained/other infertility (%)	27 (51%)	19 (50%)	0.373[d]
Clinical pregnancies after 3 mos. (%)	14[e] (26%)	4 (10%)	0.012[e]
Clinical pregnancies after 6 mos. (%)[b]	17 (32%)	[f]	
No. of miscarriages	3/17 (18%)	1/4 (25%)	0.709[d]

[a]) Months of actively trying to conceive before study participation; [b]) After an additional 3 months in which both groups, including placebo, were on open-label FB product; [c]) not significant at p = 0.05 level by Student's t-test; [d]) not significant at p = 0.05 level by Bayesian binomial analysis; [e]) Significantly higher than placebo group at p = 0.01, Bayesian binomial analysis; [f]) Four women (10%) in the placebo group became pregnant during the 3 months on open-label FB product.

Table 2. — *Mid-luteal phase serum progesterone levels in the supplement and placebo groups.*

	FertilityBlend[a]	Placebo	p value
P_{ml}[a] (whole group)	*(No. = 53)*	*(No. = 40)*	
Initial progesterone (ng/ml)	8.2	9.6	0.164
End progesterone (ng/ml)	10.4	10.0	0.399
p[b] @ 0 vs 3 months	0.061	0.389	
P_{ml}[a] < 9 ng/ml	*(No. = 20)*	*(No. = 18)*	
Initial progesterone (ng/ml)	3.2	2.9	0.236
End progesterone (ng/ml)	8.1	4.7	0.339
p[b] @ 0 vs 3 months	0.016	0.101	

[a]P_{ml} = mid-luteal phase progesterone for whole group and groups starting at < 9 ng/ml; [b]p = probability level determined by one-tailed t test.

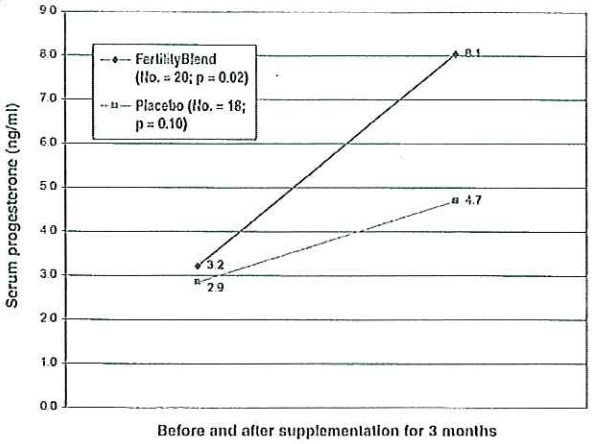

Figure 1. — Women with progesterone level < 9 ng/ml at start of study.

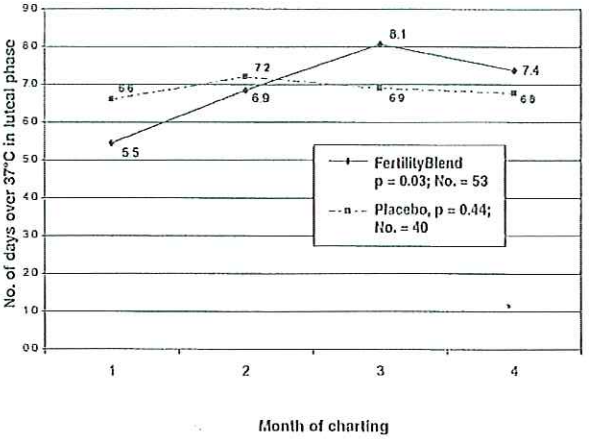

Figure 2. — Number of days over 98°F (37°C) on basal temperature chart.

during the luteal phase (from 5.5 at month 1 to 7.4 days at month 4, p = 0.029; Table 3, Figure 2). No such increase was observed in the P group (p = 0.436).

Table 3. — *Comparison of days over 37°C (98°F) on basal temperature chart after ovulation, and menstrual cycle lengths between supplement (FB) and placebo (P) groups.*

	FertilityBlend[a]	Placebo	p[c]-FB vs P
Days over 37°C on BBT[b]	*(No. = 53)*	*(No. = 40)*	
Month 1	5.5	6.7	NS
Month 2	6.9	7.1	NS
Month 3	8.1	6.8	NS
Month 4	7.4	6.9	NS
p[c] - 1 vs 4 months	0.029	0.436	
Cycle length < 27 days[b]	*(No. = 15)*	*(No. = 9)*	
Month 1	24.2	25.6	< 0.01
Month 2	27.5	27.4	NS
Month 3	27.1	28.0	NS
Month 4	27.6	26.1	NS
p[c] - 1 vs 4 months	0.001	0.268	
Cycle length > 32 days[b]	*(No. = 11)*	*(No. = 6)*	
Cycle length- mo. 1	41.6	35.3	NS
Cycle length- mo. 2	42.2	34.0	NS
Cycle length- mo. 3	35.4	32.6	NS
Cycle length- mo. 4	31.7	29.3	NS
p[c] - 1 vs 4 months	0.017	0.082	

[b]) Number of days in cycle with basal temperature (BBT) readings during luteal phase over 37°C (98°F) during luteal phase; [a]) Women who started the study with menstrual cycle lengths < 27 days or > 32 days; [c]) p = probability level determined by one-tailed t test; NS = p > 0.05 determined by one-tailed t test.

Table 4. — *Side-effects noted in the supplement and placebo groups.*

	FertilityBlend® (No. = 53)	Placebo (No. = 40)
Nausea	3	1
Spotting	2	0
Headache	2	0
Ovarian pain	2	1
Improved mood/PMS	2	1
More moody/PMS	2	1
Weight gain	1	1
Constipation	1	0
Breast tenderness	1	0
Total	16	5
Percent	30%	13%

Among women starting with short cycles (< 27 days, N = 15 in FB and N = 9 in P group), mean cycle length increased significantly in the FB group (from 24.2 to 27.6 days; p < 0.001, Table 3). Among women with longer cycles (> 32 days, N = 11 in FB and 6 in P group), cycles became significantly shorter in the FB group (from 41.6 to 31.7; p = 0.017, Table 3). While both long and short cycles were normalized in the FB group, cycle length did not change significantly in the corresponding P groups.

By the end of the third month of the study, 14 of the 53 women in the FB group were pregnant (26%), compared to four of the 40 women in the P group (10.0%, p = 0.012, Table 1). Three additional FB subjects became pregnant during the three months on an open-label product after the study (total N = 17, 32%). Four of the 40 women who were in the P group during the first three months conceived while on the additional three months of the open-label FB product given after the study (10%). Not all of the women in the study continued on the open-label product, which may explain why the percentage of 10% in the P group while on the open-label product (second 3 months) was much lower than the 26% pregnancy rate for women in the FB group during the first three months.

The 21 women who became pregnant during the first three months ranged in age from 24 to 41 years (mean age of 34.3 years), and had been attempting to conceive for six to 36 months (mean of 18.2 months). Eleven of the 21 had low progesterone levels initially (< 9 ng/ml). Thirteen of the 14 that got pregnant in the FB group demonstrated an increase in the number of days with luteal phase basal temperatures over 37°C (98°F) on their BBT charts. Four of the 14 pregnant in the FB group had started with < 4 days over 37°C at the beginning of the study, and all four increased to ≥ 10 days over 37°C on BBT charts. Only one of the four pregnant women in the P group showed a slight increase in the number of days over 37°C.

Four miscarriages occurred among the 21 pregnancies reported (Table 1). Three of these (18%) were in the FB

group. One of those was due to implantation on a fibroid (verified by ultrasound). One of the miscarriages (25%) was in the P group. These miscarriage rates were within the expected range for this patient population. One other pregnancy, in a 41-year old woman, was terminated due to Down's syndrome.

No serious side-effects were noted in the study. Three women in the FB group (one in the P group) complained of slight nausea when taking the supplement on an empty stomach, which was corrected by taking FB with food. Two women each in the FB group reported either spotting or headache, and one woman each noted either constipation or breast tenderness not reported by anyone in the P group. Other miscellaneous symptoms were mentioned in both groups (Table 4). Menstrual cycle improvements were noted as "side-effects" more frequently in the FB group, but were considered expected effects, as measured by the data above.

Discussion

In the current study, nutritional supplementation significantly improved mean mid-luteal phase progesterone levels, increased the average number of days in cycle with basal temperatures over 37°C (98°F) during the luteal phase, normalized cycle lengths, and resulted in a significantly increased pregnancy rate in the treatment group, compared to the placebo group. Increased fecundity with such nutritional supplementation may help change the paradigm of how unexplained infertility or ovulatory dysfunction is treated. Nutritional supplementation is an easy, well-tolerated option for improving fertility in some women.

The impact of these study results, including the safety and efficacy of this nutritional combination, suggests that using specifically formulated supplementation as a first step in treatment, prior to more invasive therapies or procedures, can improve key physiological factors essential to fertility. The role of nutritional supplementation in fertility health is an extremely important area of research for women attempting to conceive.

Conclusions

Nutritional supplementation may play an important role in optimizing fertility health, leading to improved conception rates, and could provide an effective alternative or adjunct to conventional fertility therapies, particularly in cases of menstrual irregularity or unexplained infertility. Without significant side-effects, Fertility-Blend® is an attractive option for use in the management and optimization of reproductive health in women. Good nutrition is a prerequisite for fertility and childbearing, and is especially important for those deciding to become pregnant at a more advanced age.

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