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The Effects of Thiamine Supplementation on General Health and Infertility Treatment Outcomes in Women with Polycystic Ovary Syndrome: A Triple-Blinded Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: The aim of this study was to evaluate the effects of thiamine (vitamin B1) on general health and infertility treatment outcomes in women with polycystic ovary syndrome (PCOS).

Materials and Methods: The study is a triple-blinded, randomized, placebo-controlled clinical trial performed on 64 infertile women with PCOS referred to Sarem Hospital in Tehran, Iran. The primary outcomes of the study were general health and infertility treatment outcomes. Eligible women were randomly assigned to the vitamin B1 group (n=32, vitamin B1 tablet at a dose of 300 mg/day for 4 weeks) or the placebo group (n=32, placebo tablet daily for 4 weeks). A general health questionnaire was completed before and after the intervention by both groups, and treatment success was evaluated at the end of the study. Data were analyzed using SPSS software ver.16 $P<0.05$ was considered statistically significant.

Results: The mean age of participants in the vitamin B1 (VB1) group was 30.4 ± 3.27 years and in the placebo (Pl) group was 29.1 ± 2.66 years with the mean duration of marriage 12.7 ± 3.01 and 13.2 ± 2.97 years respectively. Our results showed that there were significant differences between the two groups in overall score ($P<0.001$) and scores for all domains of the general health questionnaire including somatic symptoms ($P<0.001$), anxiety and insomnia ($P<0.001$), social dysfunction ($P=0.028$), and severe depression ($P<0.001$) after the intervention. Four weeks consumption of vitamin B1 also resulted in higher numbers of positive pregnancy tests ($P=0.006$), although the number of fetuses was not significantly different between the two groups after the intervention.

Conclusion: The results of the current study support a possible favourable effect of vitamin B1 on improving general health, infertility treatment outcome, and retrieved follicle count without changing the number of fetuses in women with polycystic ovary syndrome (registration number: IRCT201510266917N3).

Keywords: Depression, Fetus, Polycystic Ovary Syndrome, Thiamine, Vitamin B1

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Introduction

Infertility is very important for couples (1) as it affects about 15% of couples of reproductive ages worldwide. Globally 48.5 million couples have trouble conceiving (2). In Iran, the prevalence of infertility has been reported to be between 10.3 and 24.9% (3, 4). Women's infertility is due to a variety of causes such as ovarian disorders, endometriosis, and uterus anomalies (5).

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among reproductive-age

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women with an overall prevalence of 4-20%, and is a frequent cause of infertility (6). It is estimated that 46% of women with PCOS are infertile (7).

While infertility per se commonly causes distress, depression, anxiety, sexual dysfunction, and social discord, women with PCOS are more concerned about their fertility than other women. Indeed, women with PCOS face various socio-cultural and psychological pressures that lead to lower well-being and quality of life. These issues are due to adverse physical manifestations and endocrine disorders such as reproductive problems (irregular menstruation, infertility, hyperandrogenism), metabolic disorders (obesity, insulin resistance, cardiovascular diseases) and psychological changes (stress, depression, anxiety) (8, 9). Almeshari et al. (8), reported depressive and anxiety symptoms among women with PCOS to be 49 and 40% respectively. Other studies have also reported higher levels of general and psychiatric morbidity in women with PCOS (10).

Interventions in lifestyle, such as dietary modification, may improve fertility and reduce adverse effects of PCOS on mood and psychological well-being (11). Recent studies have shown that nutrition-associated signaling pathways are important in the regulation of ovarian function, meaning that nutritional modification with supplements may contribute to diminishing PCOS complications (12). There is some evidence that thiamine (vitamin B1) is associated with fertility function (12, 13). Vitamin B1 is a water-soluble vitamin associated with cellular energy metabolism. It seems that severe vitamin B1 deficiency can increase the number of abnormal oocytes (13) due to a reversible inhibition of the meiotic maturation of oocytes (14). DNA synthesis, which is the main stage of oocyte development in the reproductive cycle, is influenced by B vitamins (15). Studies also indicate that vitamin B1 plays an important role in the nervous system, can improve quality of life and decrease depression, fatigue, and anxiety (15, 16).

Although some studies of the effects of vitamin B1 on women's reproductive problems have shown positive results, surprisingly, to the best of our knowledge, there is insufficient evidence about the effects of vitamin B1 on infertility treatment outcomes and the general health of infertile women with PCOS. Despite an increase in the use of complementary treatments in infertility, little research on this has been done in Iran. For these reasons we conducted this study to determine whether oral vitamin B1, used as a complementary vitamin therapy in the infertility treatment process, would improve general health and infertility treatment outcomes in women with PCOS.

Materials and Methods

The present study was a triple-blinded randomized placebo-controlled clinical trial undertaken to investigate effects of vitamin B1 on mental health as the primary and infertility treatment outcomes as the secondary in infertile women with PCOS undergoing infertility treatment.

The study was conducted between September 2016 and July 2017, in Sarem Hospital, Tehran, Iran. Seventy infertile women (18-40 years) with PCOS referred to the Sarem infertility clinic for infertility treatment by *in vitro* fertilization (IVF) were randomly assigned to the intervention or control group (Fig.1).

The research protocol was approved by the Iran University of Medical Sciences Ethical Committee (IR.IUMS.REC.1394.26840). All participants were thoroughly informed about the study goals and methods and then signed an informed consent form. The trial protocol was registered in the Iran Registry of Clinical Trials (IRCT201510266917N3). The inclusion criteria for participation in this study were PCOS infertile women without any diagnosed psychological disorders. PCOS was diagnosed by a gynecologist based on the Rotterdam criteria (the presence of two out of three of the following: oligo-anovulation, hyperandrogenism and polycystic ovaries on sonography) (17). Eexclusion criteria included smoking, alcohol consumption, use of corticosteroids or psychological drugs, vitamin B1 or other vitamin consumption during the past month, chronic systematic disease (such as hypertension, diabetes, thyroid dysfunctions, autoimmune disease, inflammatory bowel disease), infertility treatment withdrawal for any reason, and vitamin B1 allergic reactions (such as fatigue, headache, dizziness, visual problems, nausea, and vomiting).

The sample size was determined using the appropriate formula for a two-mean comparison, according to the researcher's estimate and based on the general health as primary outcome. To achieve a study power of 80% with a 95% confidence interval, and accounting for at least a 10% sample loss due to follow-up or study dropouts, a sample size of 70 women (35 in each group) was determined. After women eligible for the study had been identified, they were randomly assigned to two study groups using a simple randomization method: the vitamin B1 group (VB1, n=35) given a tablet of vitamin B1 [1 tablet 300 mg/day (18), manufactured by Hakim Pharmaceutical Co., Tehran, Iran] and the placebo group (Pl, n=35) given placebo pills (1 tablet daily contains mannitol, magnesium stearate, and polyvinylpyrrolidone manufactured by Hakim Pharmaceutical Co., Tehran, Iran) for 4 consecutive weeks.

The intervention was started 4 weeks before the scheduled time of egg transfer. Simple randomization was performed by a person not involved in the research process. The vitamin and placebo pills were identical in appearance and packed in similar boxes named A or B by a person who was not affiliated to the research team. Accordingly, participants, researchers, and statisticians were blind to the groups (triple-blinded). The main outcomes were general health and infertility treatment outcomes including the number of retrieved follicles, fetuses, and a positive pregnancy [blood beta-human chorionic gonadotropin (β-hCG)] test.

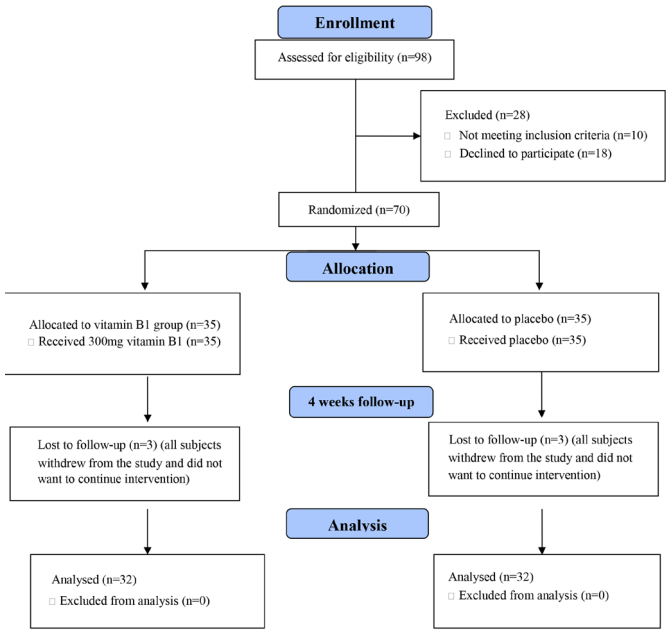

Fig.1: The CONSORT flow diagram.

After being assigned to the two groups the participants completed self-reported questionnaires. Data collection tools included: demographic information, the general health questionnaire 28 (GHQ-28), and the treatment success checklist. The GHQ-28 was introduced by Goldberg and Hillier (19) and is a suitable questionnaire for assessing the general health of infertile women. The questionnaire has four sub-scales, each consisting of 7 items as follows: physical symptoms (1-7), anxiety and insomnia (8-14), social function (14-20), and symptoms of depression (21-27). A likert scale of 0-3 is used for scoring each question making the score range for each domain and the total 0-21 and 0-84, respectively. Lower scores signify better general health (20, 21). Psychometric evaluation of the GHQ-28 has confirmed the questionnaire's reliability and validity in numerous studies (22). Shayan et al. (20) reported a 0.90 reliability coefficient. Scores higher than 23 for the total score and higher than 6 for each of the sub-scales were considered abnormal. The GHQ-28 was completed again by participants in the two study groups again after the intervention. The treatment success checklist, including data for the number of retrieved follicles and fetuses and the pregnancy test (blood β-hCG), was completed by researchers from hospital records two weeks after egg transfer. Finally, 64 women (32 women in each group) completed the study protocol and entered to data analysis (Fig.1). The quantitative data for the two groups were compared using independent and paired t-tests. Dichotomous variables were compared using the chi-square or Fisher's exact test. SPSS ver. 16 16 (Chicago, SPSS Inc; 2007) was used to perform the statistical analyses and$P<0.05$ was considered statistically significant.

Results

Mean age of participants in the vitamin B1 (VB1, n=32) group was 30.4 ± 3.27 years and in the placebo (Pl, n=32) group was 29.1 ± 2.66 years. Mean marriage duration in the VB1 group was 12.5 ± 3.01 years and in the Pl group was 13.2 ± 2.9 years. Infertility duration was 9.7 ± 3.00 years in VB1 group and 10.2 ± 2.97 years in the Pl group. Table 1 shows there were no statistically significant differences between the two groups regarding demographic and other characteristics.

Table 1: Characteristics of participants

Groups/Variables	Vitamin B1	Placebo	P value
Age (Y)			0.091**
≤25	2 (6.2)	5 (15.6)	
26-30	11 (34.4)	17 (53.1)	
≥30	19 (59.4)	10 (31.3)	
Husband age (Y)			0.051**
≤35	5 (15.6)	6 (18.7)	
35-39	20 (62.5)	24 (75)	
≥40	7 (21.9)	2 (6.3)	
Marital duration (Y)			0.533**
<10	4 (12.5)	4 (12.5)	
10-14	19 (59.4)	16 (50)	
15-19	9 (28.1)	12 (37.5)	
Educational duration (Y)			0.609*
≤12	8 (25)	5 (15.7)	
>12	24 (75)	27 (84.3)	
Employed			0.599**
No	10 (31.2)	12 (37.5)	
Yes	22 (68.8)	20 (62.5)	
Economic status			0.432**
Poor	5 (15.6)	2 (6.2)	
Relatively good	25 (78.1)	26 (81.3)	
Good	2 (6.3)	4 (12.5)	
Infertility duration (Y)			0.533**
5-7	8 (25)	6 (18.8)	
8-10	14 (43.8)	12 (37.4)	
>10	10 (31.2)	14 (43.8)	

Data are presented as n (%). *; Fisher's exact test and **; Chi-square test.

Results from the GHQ-28 and its domains are shown in Table 2. According to this table, the two groups did not show any significant differences in GHQ-28 total score or in scores for the body symptoms, anxiety and insomnia, social dysfunction, and severe depression domains before the intervention. After 4 weeks of intervention, the mean of GHQ-28 total score in the VB1 group was significantly lower than in the Pl group ($P<0.001$). Also, after the intervention, the mean scores for somaticsymptoms ($P<0.001$), anxiety and insomnia ($P<0.001$), social dysfunction ($P=0.028$), and severe depression ($P<0.001$) were significantly lower statistically in the VB1 groups compared with the Pl group.

Table 2: Comparison of genneral health status between the study groups before and after the intervention

General health		Vitamin B1 n (%)	Placebo n (%)	P value
Total score		Before intervention		
	Normal (score<24)	0 (0)	0 (0)	0.596*
	Distressed (score≥24)	32 (100)	32 (100)	
	Total	32 (100)	32 (100)	
	Mean ± SD	47.87 ± 10.43	46.5 ± 10.22	
		After intervention		<0.001*
	Normal (score<24)	9 (28.1)	1 (3.1)	
	Distressed (score≥24)	23 (71.9)	31 (96.9)	
	Total	32 (100)	32 (100)	
	Mean ± SD	30.68 ± 10.66	47.75 ± 10.09	
	Test result	P<0.001**	P=0.639**	
Somatic symptoms		Before intervention		0.574*
	Normal (score<6)	0 (0)	0 (0)	
	Distressed (score≥6)	32 (100)	32 (100)	
	Total	32 (100)	32 (100)	
	Mean ± SD	12.43 ± 3.93	11.91 ± 3.56	
		After intervention		<0.001*
	Normal (score<6)	10 (31.3)	0 (0)	
	Distressed (score≥6)	22 (68.7)	32 (100)	
	Total	32 (100)	32 (100)	
	Mean ± SD	7.25 ± 2.84	11.91 ± 3.96	
	Test result	P<0.001**	1.000**	
Anxiety and insomnia		Before intervention		0.722*
	Normal (score<6)	6 (18.8)	6 (18.8)	
	Distressed (score≥6)	26 (81.2)	26 (81.2)	
	Total	32 (100)	32 (100)	
	Mean ± SD	11.34 ± 5.05	10.91 ± 4.74	
		After intervention		<0.001*
	Normal (score<6)	20 (62.5)	3 (9.4)	
	Distressed (score≥6)	12 (37.5)	29 (90.6)	
	Total	32 (100)	32 (100)	
	Mean ± SD	6.09 ± 3.60	11.56 ± 5.07	
	Test result	P<0.001**	P=0.622**	
Social dysfunction		Before intervention		0.764*
	Normal (score<6)	13 (40.6)	11 (34.4)	
	Distressed (score≥6)	19 (59.4)	21 (65.6)	
	Total	32 (100)	32 (100)	
	Mean ± SD	7.62 ± 2.88	7.84 ± 2.93	
		After intervention		0.028*
	Normal (score<6)	10 (31.3)	11 (34.4)	
	Distressed (score≥6)	22 (68.7)	21 (65.6)	
	Total	32 (100)	32 (100)	
	Mean ± SD	6.78 ± 1.66	8.03 ± 2.66	
	Test result	P=0.176**	P=0.762**	

Table 2: Continued

Severe depression		Before intervention		0.637*
	Normal (score<6)	2 (6.3)	4 (12.5)	
	Distressed (score≥6)	30 (93.7)	28 (87.5)	
	Total	32 (100)	32 (100)	
	Mean ± SD	16.46 ± 4.98	15.84 ± 5.53	
		After intervention		<0.001*
	Normal (score<6)	6 (19.4)	2 (6.3)	
	Distressed (score≥6)	26 (80.6)	30 (93.7)	
	Total	32 (100)	32 (100)	
	Mean ± SD	10.96 ± 4.93	16.25 ± 4.87	
	Test result	P<0.001**	P=0.755**	

*; Independent t test and **; Paired t test.

Results for the infertility treatment outcomes (Table 3) showed that 4-weeks of vitamin B1 consumption was associated with a statistically significant increase in the number of retrieved follicles in the intervention group compared with the placebo group (P<0.001). There was also a significantly greater number of positive pregnancy tests (P=0.006) in the intervention group, despite no statistically significant differences between the two groups in the number of fetuses. No important harms or unintended effects were reported in VB1 group.

Table 3: Comparison of infertility treatment outcomes between the study groups after the intervention

Groups/Variable	Placebo	Vitamin B1	Test result
Number of retrieved follicles	7.15 ± 2.17	11.93 ± 2.13	P<0.001*
Number of fetuses	4.62 ± 0.97	4.65 ± 0.90	P=0.895*
β-hCG			P =0.006**
Positive	9 (28.1)	20 (62.5)	
Negative	23 (71.9)	12 (37.5)	
Total	32 (100)	32 (100)	

Data are presented as mean ± SD or n (%). β-hCG; Beta-human chorionic gonadotropin, *; Independent t test, and **; Chi-squared test.

Discussion

Our triple-blinded randomized placebo-controlled clinical trial showed that in infertile PCOS women undergoing infertility treatment a 4-week intake of vitamin B1 was associated with a statistically significant improvement in general health parameters measured using the GHQ-28. This improvement was seen in the total score and all its domains including body symptoms, anxiety and insomnia, social dysfunction, and severe depression. Vitamin B1 has been shown to have psychological effects in other studies. For example, Ghaleiha et al. (15) showed that in patients with major depressive disorder vitamin B1 alleviated symptoms of depression faster than placebo. Zhang et al. (16) showed an association between lower thiamine levels and symptoms of depression. Other research has shown the effects of thiamine on anxiety disorders, chronic fatigue, insomnia, aggression, diaphoresis, and headache (23). Regardless of the underlying cause of thiamine deficiency, it can have severe adverse effects on the nervous system (24) and positive changes have been shown to occur in energy, appetite, sleep patterns, and fatigue after thiamine supplementation (25). Vitamin B1 appears to be an essential micronutrient for neuronal cell function through its effect on oxidative metabolism and several coenzyme activities, and glucose utilization by nerve tissue (26). Vitamin B1 can also modulate cognitive performance and help people to fulfill work activities. However, Young et al. (27) noted that daily supplementation with B group vitamins reduced stress, but failed to reduce depressive symptoms and anxiety.

Other findings from the present study showed that 300 mg of oral vitamin B1 daily for 4 weeks could improve infertility treatment outcomes in PCOS women undergoing infertility treatment. It increased the number of retrieved oocytes and positive pregnancy tests (blood β-hCG) but had no effect on the number of fetuses. Tsuji et al. showed that there is a relationship between vitamin B1 nutrition and mice oocyte maturation (28). As the ART process does not occur under natural fertilization conditions, the development of reactive oxygen species (ROS) can adversely affect gamete or embryo development (29). In contrast, in the natural fertilization process, there is a physiological antioxidant system to protect gametes and embryos or repair free radical damage. This antioxidant system does not exist *in vitro* (30). Antioxidants can normally enhance oocyte maturation, fertilization, and embryo development by mitochondrial function enhancement, possibly improving ART outcomes (31). In women with PCOS, the conditions of follicular maturity are unfavorable because ROS can promote completion of the first meiotic division in the follicles rendering them immature (32). Consistent with our study, there is sufficient evidence that antioxidant supplementation significantly affects oocyte quality and pregnancy rate in women with PCOS (33, 34). Thiamine interacts with ROS, has desirable antioxidant properties, and can scavenge free radicals with high efficiency (35). Szczuko et al. (36) showed that women with PCOS have lower levels of thiamine in their serum. However this deficiency did not remain after lifestyle and dietary

changes Szczuko et al. (37).

We want to highlight our study limitations, which should be considered in interpreting our results. First, since our participants were in the treatment period, we could not continue our intervention for more than 4 weeks. Second, we did not measure our participants' vitamin B1 levels before the study started.

Conclusion

Results of the current intervention study in infertile women with polycystic ovaries support a possible favorable effect of thiamine (vitamin B1) on mental health, retrieved follicle count, and a positive pregnancy test after infertility treatment, despite no effect on the number of fetuses. We suggest future studies with larger sample sizes and longer study duration are required to clarify the potential effects of thiamine on mental health and pregnancy outcomes of infertile women with PCOS undergoing infertility treatment.

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Authors' Contributions

L.A.; Conceptualization., Methodology, Writing original draft, and Supervision. M.M.; Conceptualization, Methodology, and Sampling. H.H., M.R.N.; Formal analysis. H.H., M.R.N., M.M.; Writing-review and editing. All authors have read and agreed to the published this version of manuscript.

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