

A comparison between the efficacy of dydrogesterone and calcium plus vitamin D in improving women's general health

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Abstract

Objective: The aim of this randomized, double-blind, placebo-controlled clinical trial was to evaluate the effect of dydrogesterone and calcium plus vitamin D on young women's general health. **Method:** One hundred and eighty students studying at Shiraz University were recruited. Students completed the General Health Questionnaires (GHQ-28) prior to participation. They were then randomly assigned to take a tablet containing either 5 mg of dydrogesterone, 500 mg of calcium plus 200 mg of vitamin D, or a placebo twice daily from the 15th to the 24th day of their menstrual cycle for 2 consecutive cycles, and to complete the same questionnaires during both the intervention cycles. **Results:** The effects of dydrogesterone and calcium plus vitamin D on general health scores were similar during the first month of intervention (11.41 ± 4.28 , 12.23 ± 3.76 , respectively) ($p > 0.05$) and both of them were more effective than placebo (16.69 ± 3.28) ($p < 0.05$). However, dydrogesterone was more effective than calcium plus vitamin D and placebo during the second month of intervention (4.33 ± 2.69 , 6.2 ± 3.55 , 14.39 ± 3.45 , respectively) ($p < 0.05$). No significant differences between groups regarding drugs' side effects ($p > 0.05$) were found. **Conclusion:** Both dydrogesterone and calcium D were more effective than placebo in promoting women's general health. Dydrogesterone was, however, more efficient than calcium plus vitamin D.

Key words: Dydrogesterone; Calcium plus vitamin D; General health; Women

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Introduction

Mental health refers to a broad array of activities directly or indirectly related to the mental well-being component included in the WHO's definition of health: "A state of complete physical, mental and social well-being, and not merely the absence of disease".¹ It can be conceptualized as a state in which the individual realizes his or her own abilities, can cope with the normal stresses of life, work productively, and is able to contribute to his or her community. Mental health and physical health are integrally linked.²

A variety of diverse conditions affect psychological well-being, and, consequently, general and mental health, in both men and women. Females experience certain mental and affective disorders at higher rates than males, partially due to sex hormone changes during menstrual cycles. Most of these disabling situations occur during the luteal phase of the menstrual cycle (7-10 days prior to the onset of menstrual bleeding and at the time of declining plasma progesterone levels).³

The neuroactive steroids (e.g. progesterone) pass across membranes easily (due to their lipophilic nature), thus the changes in brain levels of these steroids parallel those in the plasma. It has been documented that these substances modulate depression-related behavior.⁴ Progesterone also exerts a rapid, non-genomic action via its metabolite allopregnanolone (ALLO) which acts at membrane-bound receptors to potentiate neuronal

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responses to Gamma Amino Butyric Acid (GABA). GABA alleviates psychotic stimulation and exerts anti depressive effects in the neural system.⁵ As a result of this, it has been demonstrated that there is a link between the plasma level of progesterone and mood changes. In addition, it is acknowledged that female reproductive hormones mediate the functions of neurotransmitters, such as serotonin, dopamine, norepinephrine, and gamma amino butyric acid (GABA), and that hormone shifts indirectly result in psychological distress.⁶ Animal models of anxiety-related behaviors have consistently shown an increase in anxiety during progesterone withdrawal.^{7,8}

Dydrogesterone is an active progesterone, available as an oral preparation. This pharmaceutical product is free from some of the side effects that other synthetic progestins might have (i.e. oestrogenic, androgenic, anabolic, and corticoid effects). These properties make this pharmaceutical preparation superior to other synthetic progesterones.^{9,10}

Because of the current interest in using alternative medicine for treating different kinds of diseases, dietary supplements are being evaluated in various trials. Investigations have shown that blood levels of calcium and vitamin D fluctuate during the menstrual cycle and this might influence a woman's affective state resulting in premenstrual psychological problems. Additional data provide support for a biological relationship between calcium and symptoms such as depression, anxiety, and fatigue. It is believed that the releasing and reabsorbing of serotonin in the neural system is under the influence of calcium.^{11,12,13}

Furthermore, vitamin D, an essential factor for both promoting calcium absorption in the gut and maintaining calcium homeostasis and bone health¹⁴, appears to be crucial for brain development and function.¹⁵ Recent data demonstrating the neuroprotective role of vitamin D has attracted interest.¹⁶ It's most active metabolite, 1,25-dihydroxy-vitamin D, is a hormone with multiple roles. Vitamin D is mainly synthesized in the skin by the ultra-violet component of sunlight and partly obtained in food, particularly fatty fish (salmon, eel, cod) and fortified milk or margarine.¹⁷ A decline in the serum level of vitamin D has been associated with reduced cognitive function, anxiety, and depression.¹ Based on a study of 1283 community-based elderly residents, Hoogendijk et al. reported that vitamin D levels were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder compared with levels in 1087 control individuals. Depression severity was significantly associated with decreased serum vitamin D levels and increased serum PTH levels.¹⁹

Based on the aforementioned data, we hypothesized that both dydrogesterone and calcium plus vitamin D might have a positive effect on individuals' general and mental health. To our knowledge, there are no studies in which the effect of dydrogesterone and calcium plus vitamin D on general health has been assessed. To evaluate this hypothesis, we conducted a double-blind, randomized, placebo-controlled study.

Method

Questionnaire/sample selection

A total of 750 full-time undergraduate female students studying at Shiraz University of Medical Sciences

participated in this study during the year 2008. The sample was non-clinical. Participants were studied for three months. Their demographic characteristics were gathered before intervention commenced. Psychological assessment was conducted by means of the General Health Questionnaires (GHQ).²⁰ The short version of GHQ-28 has been widely used for the screening of psychiatric problems in the general population.^{21,22} The GHQ-28 contains 28 items divided into four sub-scales evaluating somatic symptoms, anxiety, social dysfunction, and depression. All the items have a 4-point scoring system, with descriptors of "better/healthier than normal", "same as usual", "worse/more than usual" and "much worse/more than usual".

The Likert scoring method was used in the current study (scoring ranges: 0-1-2-3). The cutoff point for GHQ-28 scoring was 23. Higher scores indicate greater severity of problems. Reliability and validity of the questionnaire have been reported before.^{21,22}

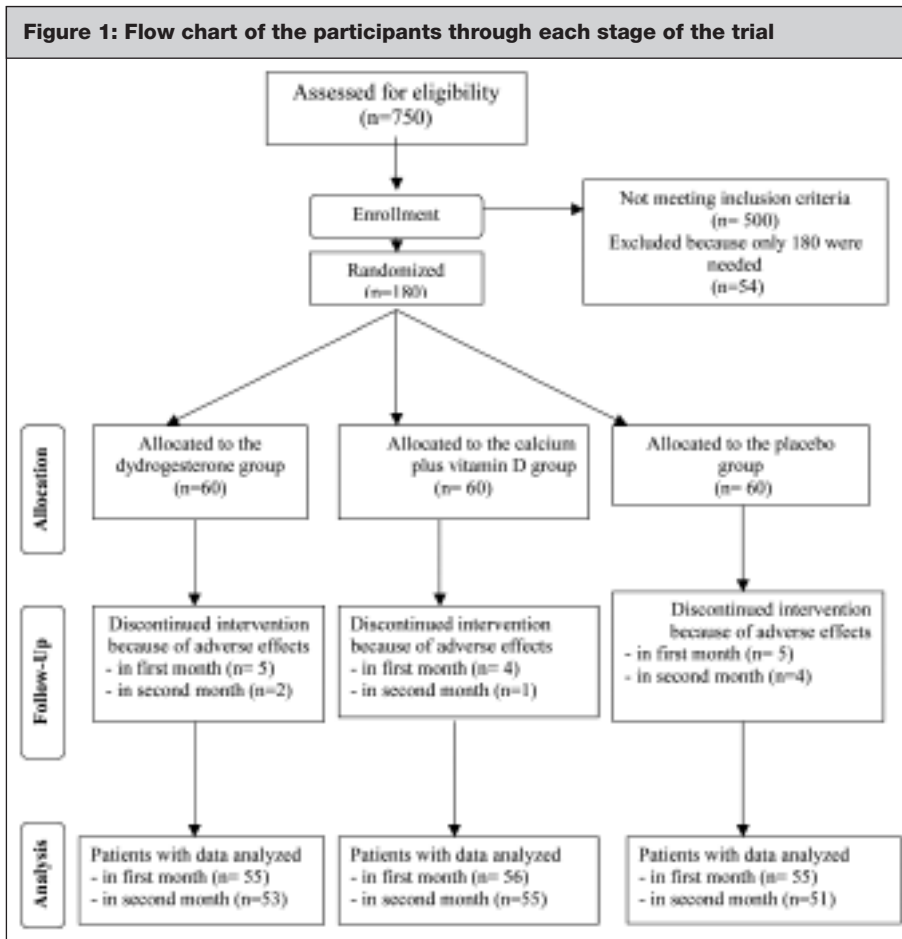
Questionnaires were completed after the first menstrual cycle. The participants who acquired a score of more than 23 were referred to psychologists for further assessment. The data of the participants with scores of 23 or less were analyzed. Two hundred and fifty individuals met inclusion criteria.

Inclusion criteria: (1) regular menstrual cycles (3-8 days of menstruation with intervals of 22-35 days); (2) absence of any medication such as hormonal contraceptives, antipsychotics, vitamins; (3) lack of contraindication for taking dydrogesterone or calcium and/or vitamin D; (4) psychological problems not explained by a psychiatric disorder such as major depressive disorder, panic disorder, or epilepsy (5) being resident in the dormitory; and (6) self-reported diet lacking in a large quantity of calcium and/or vitamin D. Exclusion criteria: (1) acquiring GHQ scores more than 23; (2) the presence of any psychiatric disorders; (3) taking any kind of antidepressants, tranquilizers, and psychotropic drugs. Those who did not meet inclusion criteria were excluded from the study.

Randomization

Of these, 180 patients were randomly allocated to one of the 3 study groups in the following way: we first assigned a number to each blank questionnaire, and then chose 3 numbers randomly from those assigned numbers to designate the first persons to join each of the groups. After that, we divided the 177 remaining participants into 59 groups consisting of 3 persons. Next, each of these 3 participants was randomly assigned to one of the 3 study groups. We thus had 3 groups of 60 participants. One group (60 participants) received dydrogesterone tablets (Dydrogesterone, Aburaihan Pharmaceutical Mfg. Co. Tehra-Iran) 5 mg twice daily; another group of 60 participants received Calcium plus vitamin D tablets twice daily (Calcium-D, Darou Paksh Pharmaceutical Mfg. Co. Tehra-Iran; the reason for using calcium D in our study was its efficacy, safety, and low cost; each tablet contained 500 mg calcium & 200 mg vitamin D) and the third group of 60 women received placebo tablets twice daily (Figure 1)

Figure 1: Flow chart of the participants through each stage of the trial



Procedure

All participants took tablets from day 15 to 24 of their menstrual cycle for two consecutive menstrual cycles. Placebo and active treatments were identical in appearance and the packaging of capsules was labeled with code numbers. Moreover, the authors were blind to the drug codes during the trial and statistical analysis. As a result of this, neither »participants« nor »researcher« could have identified the intervention received. A courier delivered the study medication to the participants to reduce the potential for bias. Participants completed General Health Questionnaires during two intervention cycles and all possible adverse effects were reported. After two cycles, questionnaires were collected and data was analyzed.

Statistical analysis

By calculation, a total of 60 students in each treatment group with 39 completing the study were deemed necessary for 80% power to detect a 56% difference in general health scores at the statistical significance level of $p < 0.05$.

The Independent t-test was used to compare the mean scores of general health before and after intervention in each study group ($\alpha = 0.05$, confidence interval=95%). The ANOVA was used to compare differences in mean scores of general health between groups. Tukey's Post-hoc was used for pair comparison. Descriptive Statistics were used in order to summarize demographic data and adverse events. Effects were considered statistically significant when $p < 0.05$.

Ethics

The Medical Research Ethics Committee of Shiraz University of Medical Sciences approved the study and permission was obtained from the Dean of Faculty, the Deputy of Educational Affairs, and the Educational Affairs Administration of Shiraz University to conduct the study. The participants gave written informed consent before enrollment. They were assured of the confidentiality and anonymity of the study.

Results

There were fourteen drop-outs during the first month of intervention (5 on placebo, 4 on calcium D, 5 on dydrogesteron) and 7 during the second month (4 on placebo, 1 on calcium D, 2 on dydrogesteron). The evaluation was thus based on 166 patients during the first month and 159 during the second month of study. Socio-demographic and psychometric status were not statistically different among those who finished the study and those who did not.

The mean age of those who completed the study was 20.84 ± 1.64 years (range 18–26).

The total scores of GHQ-28 did not differ between the three groups before intervention ($p = 0.651$) (Table I). In addition, the mean scores for each domain of

Table I: Comparison of the mean total general health scores among the three study groups before interventions, first month, and second month of interventions a

		dydrogesterone	Calcium plus vitamin D	Placebo	Significance
General health scores	Before intervention	19.6±3.97	18.93±4.73	19.41±3.37	F 2,177)=0.431 P=0.651
	1st month of intervention	11.41±4.28	12.23±3.76	16.69±3.28	(2,163)=30.77, P<0.001
	2nd month of intervention	4.33±2.69	6.2±3.55	14.39±3.45	2,156)=139.76, P<0.001

a= values are given as mean ± standard deviation. *= Tuckey's Post hoc comparison showed that the differences between the dydrogesterone & placebo groups ($p < 0.001$); and the calcium plus vitamin D & placebo groups ($p < 0.001$) were statistically significant. There was no statistically significant difference between the dydrogesterone & calcium plus vitamin D groups ($p > 0.05$). Tuckey's post hoc comparison showed that the differences between the dydrogesterone & placebo groups ($p < 0.001$); the calcium plus vitamin D & placebo groups ($p < 0.001$); and the dydrogesterone & calcium plus vitamin D groups ($p < 0.001$) were statistically significant.

Table II: The mean scores of the four domains of general health before intervention in the three study groups

GHQ domains								Group
Depression		Social dysfunction		Anxiety		Somatic		
SD	M	SD	M	SD	M	SD	M	
.97	3.88	1.88	5.93	1.98	4.75	1.23	5.03	Dydrogesterone Calcium plus vitamin D Placebo
.83	3.08	1.97	5.2	1.41	4.98	1.46	5.66	
.99	3.3	1.21	5.48	1.71	4.96	1.85	5.66	
P=0.109 F(2,177)=2.24		P=0.139 F(2,177)=1.99		P=0.786 F(2,177)=0.24		P=0.193 F(2,177)=1.66		Significance
M=mean SD=standard deviation								

Table III: Mean scores for the four domains of general health after taking one month of the medications in the three study groups

GHQ domains								Group
Depression		Social dysfunction		Anxiety		Somatic		
SD	M	SD	M	SD	M	SD	M	
1.75	2.12	1.72	3.63	.99	2.83	1.84	2.81	Dydrogesterone Calcium plus vitamin D Placebo
1.7	2.82	1.6	4.01	1.08	3.28	1.06	3.09	
1.87	2.58	1.09	4.7	1.03	4.3	1.73	4.09	
P=0.08 F(2,163)=2.56		P=0.001 F(2,163)=7.40		P<0.001 F(2,163)=9.59		P<0.001 F(2,163)=20.02		Significance*
M= mean SD= standard deviation *= Tuckey's post hoc comparison showed that the difference between the dydrogesterone & placebo groups (p<0.001); the calcium plus vitamin D & placebo groups (p<0.001); the dydrogesterone & calcium plus vitamin D groups (p<0.001) were statistically significant in the somatic domain. In addition, the difference between the dydrogesterone & placebo groups (p<0.001); the calcium plus vitamin D & placebo groups (p<0.001) were statistically significant in the anxiety and social dysfunction domains.								

Table IV: Mean scores for the four domains of general health after taking medications for two months in the three study groups.

GHQ domains								Group
Depression		Social dysfunction		Anxiety		Somatic		
SD	M	SD	M	SD	M	SD	M	
0.06	0.71	.69	1.41	.54	1.13	.72	1.07	Dydrogesterone Calcium plus vitamin D Placebo
.58	1.07	1.01	3.09	1.07	2.65	.69	2.25	
1.01	2.11	1.5	3.07	1.93	3.06	.98	3.52	
P<0.001 F(2,156)=19.22		P<0.001 F(2,156)=45.98		P<0.001 F(2,156)=36.03		P<0.001 F(2,156)=63.78		Significance*
M: mean SD: standard deviation *=Tuckey's post hoc comparison showed that the difference between the dydrogesterone & placebo (p<0.001); the calcium plus vitamin D & placebo (p<0.001); and the dydrogesterone & calcium plus vitamin D (p<0.001) groups were statistically significant in the somatic domain. In addition, the difference between the dydrogesterone & placebo (p<0.001); and the calcium plus vitamin D & placebo (p<0.001) groups were statistically significant in the anxiety, social dysfunction and depression domains.								

GHQ-28 in all three groups were similar prior to intervention and there were not any statistically significant differences between groups ($p>0.05$) (Table II).

General health improved after the intervention and the amelioration of symptoms in four domains was noticeable in all three study groups. There were statistically significant differences between groups when comparing scores from before the intervention to after the first month of intervention ($p<0.001$). Dydrogesterone and calcium plus vitamin D had the same effects and there was no statistically significant difference between these two groups after the first month of intervention ($p=0.06$). However, both of these drugs were more effective than placebo ($p<0.05$) (Table III & I).

The general health status of participants changed considerably more during the second month for those who completed the dydrogesterone treatment. There was a significant difference between the first and second months of the intervention. There was also a significant difference in GHQ-28 scores comparing baseline to the end of the second month ($P<0.05$, within group).

Likewise, scores decreased in patients who completed the calcium plus vitamin D treatment ($P<0.05$, within group) and the placebo group ($P<0.05$, within group). A treatment comparison between the 3 groups showed that dydrogesterone was significantly more effective than the two other treatments in decreasing the GHQ-28 scores of participants ($P<0.05$) (Table IV & I).

Sixteen patients reported adverse events during the first month of treatment and 18 participants during the second month. Nausea and constipation were the most prevalent reported side effects during treatment (Table V).

Table V: Adverse events recorded at any time in the 3 groups during the intervention a

Side effect	Groups					
	Dydrogesterone		Calcium plus vitamin D		Placebo	
	1st month	2nd month	1st month	2nd month	1st month	2nd month
Nausea	2 (33.32)	1 (16.67)	1 (20)	2 (33.33)	2 (40)	1 (16.67)
Constipation	1 (16.67)	1 (16.67)	1 (20)	1 (16.67)	2 (40)	1 (16.67)
Breast tenderness	1 (16.67)	1 (16.67)	1 (20)	0	0	1 (16.67)
vertigo	1 (16.67)	1 (16.67)	2 (40)	2 (33.33)	0	1 (16.67)
Headache	1 (16.67)	2 (33.32)	0	1 (16.67)	1 (20)	2 (33.32)
Total	6(100)	6(100)	5(100)	6(100)	5(100)	6(100)

a: Values are given as number (percentage).

Discussion

To our knowledge, this is the first study focusing on the effect of dydrogesterone and calcium plus vitamin D on women's general health. There is a connection between the menstrual cycle and psychiatric complaints in some women; therefore, the relationship between the menstrual cycle and presenting complaints should be considered in the evaluation of female patients during their reproductive years. However, complaint patterns could vary from woman to woman. We showed that both of the active preparations improved the general health of women when compared to placebo; however, dydrogesterone was more effective than calcium plus vitamin D.

After ovulation, at midcycle, serum levels of progesterone increase. If there is no fertilization, the hormone level decreases. Most women feel physical or mood changes during the days before menstruation, at the time of the decline in progesterone. The most frequently reported symptoms include irritability, fatigue, anxiety, nervous tension, mood swings, depression, feeling overwhelmed or out of control and physical symptoms. These changes affect a woman's daily life, her general health and could induce psychological distress.²³ Furthermore, the greater the increase in plasma levels of progesterone during the luteal phase, the more intensive the psychological symptoms created by its diminution before bleeding commences. We hypothesized that prescribing dydrogesterone might stabilize psychological status. The sexual hormones can be prescribed in accordance with their regular fluctuations during the menstrual cycle, so participants were given dydrogesterone, at a dose of 10mg daily, from day 15 to 24 of their menstrual cycle.

In an attempt to minimize confounding variables, we selected participants among students living in the same setting, omitted those consuming a diet containing a great deal of calcium and vitamin D, conducted a randomized, placebo-controlled, double-blind study and used a courier to deliver the study drugs. However, we had to rely on participants' remarks and their reports of medication adherence.

Despite this, we believe it fair to conclude that our

results warrant future studies in this area. As can be seen in Tables III and IV, statistically significant differences were shown in all four domains of the GHQ-28 in each group after intervention. Active preparations were more effective during the second month of intervention and the differences between the first and second month of intervention were statistically significant within groups.

When comparing the mean scores of individual domains within groups before and at the end of the intervention, it was noted that the diminution in scores of the social dysfunction and somatic symptoms scales (difference of means: -4.52, -3.96, respectively) were more significant than those of anxiety and depression. Participants receiving calcium plus vitamin D improved the most (difference of means: -3.41, -2.37, respectively) in the domains of somatic symptoms and depression. Individuals who took placebo showed the greatest change in social dysfunction and somatic symptoms (difference of means: -2.37, -2.14, respectively). Overall, the somatic domain of the GHQ-28 showed the most improvement across all three groups.

Comparing the active preparations, during the first month of intervention dydrogesterone and calcium plus vitamin D were similar in terms of efficacy. However, dydrogesterone was more effective in the second month of treatment and improved the scores on the GHQ-28 to a greater degree than the two other preparations ($p < 0.05$). It can consequently be inferred that the longer the treatment period, the more effective drugs can be.

Clinical and preclinical studies have suggested that fluctuations in the peripheral and brain concentrations of progesterone and its metabolites, 3α -hydroxy- 5α -pregnan-20-one (allopregnanolone) and $3\alpha,21$ -dihydroxy- 5α -pregnan-20-one (THDOC), might play an important role in certain pathological conditions characterized by emotional or affective disturbances. These include major depression, anxiety disorders, and schizophrenia in people of all ages.²⁴ Bitzer stated that progesterone and progestogens could have an important potential role in the maintenance or improvement of psychosomatic health in climacteric women.²⁵ Klein reported that the irritability, nervousness, and anxiety of a 46-year-old woman were alleviated by using very low dose transdermal estrogen

combined with natural progesterone.²⁴ Brinton et al. asserted that progesterone would have multiple non-reproductive functions in the central nervous system to regulate cognition, and mood.²⁶ Furthermore, Hellberg et al. showed that medroxyprogesterone acetate relieved depression, tension, sadness, anxiety, and aggression in 21-46 year old women.²⁷

Calcium, too, is an integral factor in health maintenance. Many studies concentrating on this subject have indicated that a balanced diet is crucial not only in maintaining physical health, but also in promoting emotional well-being and psychosocial functioning.²⁸

Furthermore, vitamin D3 (calciferol) is a fat-soluble vitamin, with a large number of effects. It acts through vitamin D receptors which are widely distributed, particularly in the developing and adult brain.²⁹ It has been proposed that vitamin D deficiency during pregnancy is a risk factor for schizophrenia and psychosis in the offspring, and that this deficiency during adulthood is associated with psychotic episodes.³⁰ In addition, there is growing evidence that low prenatal levels of 1,25(OH)₂D can influence critical components of early brain development.³¹ Berk et al. also found an association between vitamin D insufficiency and psychiatric illness.³² In our study, we hypothesized that vitamin D could alleviate participants' depression and stabilize their mood. Most of the women responded positively to treatment with calcium plus vitamin D with an improved mental status. There is a growing body of evidence linking hypovitaminosis D and depression. Wilkins et al. declared that vitamin D deficiency was associated with the presence of an active mood disorder.³³ It has been suggested that fluctuating levels of vitamin D3 leads to changes in brain serotonin and causes mood problems.³⁴ Other mechanisms by which vitamin D affects adult cerebral functions remain unknown. However, possible positive effects could be direct, as suggested by the observation that 1,25(OH)₂D treatment increases choline acetyltransferase activity in rat brain nuclei³⁵ or could operate via a neuroprotective pathway, as demonstrated by the stimulation of neurotrophin production³⁶ and modulation of neuronal Ca²⁺ homeostasis by vitamin D.³⁷ Further investigations are needed before firm conclusions can be drawn in this regard.

Side effects occur with the use of all drugs to varying degrees. In our study, some participants recorded side effects even in the placebo group. The rate of adverse effects that occurred with both dydrogesterone and calcium D could be attributed to both real drug side effects and personal resistance to drug usage. These factors may have amplified the severity of adverse events in these two study groups.

The present study indicated that a high score on the GHQ-28, is associated with a reduced serum level of progesterone, calcium and vitamin D in women.

Conclusion

In the present study, both dydrogesterone and calcium D were more effective than placebo in promoting women's well being and were able to improve the mean scores of general health; however the positive effect of dydrogesterone was more noticeable and it was more

effective than calcium plus vitamin D and placebo. Future studies with a larger sample size and among different study populations should be performed in order to strengthen the value of the findings.

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