

Clinical Therapeutic Effect of Liuwei Dihuang Decoction Combined with Methimazole on Gestational Hyperthyroidism with Insomnia

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Abstract

Objective: Hyperthyroidism is one of the common endocrine disorders in pregnant women during pregnancy, often accompanied by insomnia. The current treatment plan has shortcomings such as long treatment time and significant adverse reactions, and our study aimed to detect the clinical therapeutic effect of Liuwei Dihuang Decoction combined with methimazole on gestational hyperthyroidism with insomnia. **Methods:** 46 cases of gestational hyperthyroidism with insomnia, who were treated with Liuwei Dihuang Decoction combined with methimazole, were included as the combination group, and 46 cases treated with methimazole were enrolled as the control group. The clinical efficacy and pregnancy outcome were compared between the two groups, and the serum hormone level and Pittsburgh Sleep Quality Index (PSQI) scores of the two groups were collected. **Results:** The combination group had a higher total effective rate compared to the control group ($p < 0.05$). After treatment, free triiodothyronine (FT₃) level, free thyroxine (FT₄) level and PSQI score in both groups were decreased, which were lower in the combination group than the control group ($p < 0.05$). Thyroid stimulating hormone (TSH) level was elevated in both groups, and was higher in the combination group than the control group ($p < 0.05$). The adverse pregnancy rate in the combination group was lower than that in the control group ($p < 0.05$). No serious adverse reactions occurred in both groups. **Conclusions:** Liuwei Dihuang Decoction combined with methimazole is effective in the treatment of gestational hyperthyroidism with insomnia, which can improve thyroid function, sleep quality and pregnancy outcome, and will not cause serious adverse reactions.



1 Introduction

Hyperthyroidism is an endocrine disease, featuring palpitation, sweating, overeating, visual deterioration and other clinical symptoms [1]. Overproduction of thyroid hormone in pregnancy may promote sympathetic nerve excitation and cause insomnia, easily leading to various preterm delivery, abortion and other adverse pregnancy outcomes [2,3]. Hence, positive clinical responses to the elevation of therapeutic efficacy towards pregnant patients with hyperthyroidism and insomnia can control disease progression and guarantee maternal and infant health.

At present, methimazole, belonging to the thiourea anti-thyroid drugs, is mainly responsible for treating gestational hyperthyroidism with insomnia. It can inhibit the activity of thyroid peroxidases, block the oxidation of iodides in thyroid tissue, repress the synthesis of triiodothyroxine and thyroxine, and lead to a decrease in thyroid hormone secretion, which can to some extent alleviate the symptom of hyperthyroidism-caused insomnia [4,5]. However, methimazole alone has some limitations, such as long treatment time and severe adverse reactions [4,5], so the current clinical treatment is more inclined to the combination of traditional Chinese medicine (TCM) and Western medicine.

In TCM, hyperthyroidism-caused insomnia cannot simply be attributed to deficiency or sufficiency, but is accompanied by dysregulation of liver and stagnation of qi throughout the disease progress. In the late stage, deficiency fire brings about burning body fluid to cause its loss, and deficiency is the main symptom; therefore, hyperthyroidism-caused insomnia combines with deficiency and sufficiency, manifested by vexation, anxiety, difficulty falling asleep, waking up easily after sleep, and night sweating [6,7]. Liuwei Dihuang Decoction is mainly composed of *Rehmanniae Radix Praeparata*, *Dioscoreae Rhizoma*, *Fructus Corni*,

etc. and the components together can tonify liver and kidney, soothe the liver and relieve depression [8]. The role of Liuwei Dihuang Decoction in many diseases has been uncovered, for example, it can treat primary osteoporosis [9], diabetes retinopathy [10] and Parkinson's Disease [11]. It has been documented that Liuwei Dihuang Decoction can be applied to effectively treat hyperthyroidism patients with yin deficiency leading to yang hyperactivity through relieving swelling of anterior neck as well as soreness and weakness of waist and knees and reducing thyroid-related hormone expressions [12]. The modified Liuwei Dihuang Decoction can also effectively mitigate insomnia of elderly diabetic patients [13]. In addition, it has been reported that application of Chaihu-Guizhi-Longgu-Muli decoction combined with Liuwei Dihuang Pills can reduce negative emotions and improve sleep quality of menopausal insomnia patients [14]. In view of these findings, this study explored the therapeutic efficacy of Liuwei Dihuang Decoction combined with methimazole on gestational hyperthyroidism with insomnia, and analyzed its clinical value, with the purpose of providing references to clinical treatment.

2 Information and methods

2.1 General information

46 cases of gestational hyperthyroidism with insomnia, who were treated with Liuwei Dihuang Decoction combined with methimazole in our hospital from June 2020 to December 2022, were included as the combination group, and 46 cases with the same conditions treated with methimazole were enrolled as the control group during the same period. The general information of the two groups had no obvious difference ($p > 0.05$) and was comparable (Table 1). This study was authorized by the Ethics Committee of our hospital and all patients signed the written informed consent.

Table 1 Comparison of general information.

Group	Case	Age (year old)	Primiparity/Multiparity (case)	Gestational weeks
Combination group	46	32.07 ± 1.72 (26-35)	25/21	33.78 ± 1.76 (31-37)
Control group	46	31.57 ± 1.82 (29-36)	28/18	34.11 ± 1.61 (32-37)
	X ² /t	1.354	0.401	0.927
	p	0.179	0.527	0.357

2.2 Diagnosis criteria

(1) Hyperthyroidism meets the diagnostic criteria in *the Chinese Guidelines for the Diagnosis and Treatment of Thyroid Diseases* [15]; (2) Insomnia meets the diagnostic criteria for non-organic insomnia in *the Chinese Guidelines for the Diagnosis and Treatment of Insomnia* [16]; (3) The diagnostic criteria for TCM refer to the syndrome differentiation and classification criteria for gestational hyperthyroidism with insomnia in *the Guiding Principles for Clinical Research on New Drugs of Chinese Medicines* [17].

2.3 Inclusion criteria

(1) Patients are pregnant women; (2) Patients have not received systematic treatment for gestational hyperthyroidism with insomnia before enrollment; (3) Patients meeting the diagnostic criteria.

2.4 Exclusion criteria

(1) Patients with allergic constitution; (2) Patients combined with thyroiditis, high function adenoma, etc. that trigger hyperthyroidism syndrome; (3) Patients combined with other endocrine disorders; (4) Patients combined with autoimmune and hematological diseases; (5) Patients combined with severe infection; (6) Patients with liver and kidney dysfunction; (7) Patients having a history of tumors; (8) Patients having a history of mental illness.

2.5 Treatment methods

In the control group, patients were treated with methimazole (2.5-20 mg, National medicine

permission number (NMPN): H20120405, Merck, Germany) once per day until parturition. In the combination group, patients received methimazole and Liuwei Dihuang Decoction (15 g *Rehmanniae Radix Praeparata*, 15 g *Dioscoreae Rhizoma*, 10 g *Fructus Corni*, 10 g *Poria*, 10 g *Moutan Cortex*, 10 g *Alismatis Rhizoma*) one dose per day. These medicinal materials were decocted twice with water to obtain a total of 300 mL decoction and the warm decoction was taken in the morning and at night. The therapeutic efficacy was evaluated after 8 weeks of treatment between the two groups.

2.6 Study indicators

(1) Clinical efficacy: The clinical efficacy was compared between the two groups. According to *the Guiding Principles for Clinical Research on New Drugs of Chinese Medicines*, cure refers to the disappearance of palpitations, anxiety, restlessness, and tremors, mitigation of thyroid storm and exophthalmos, reduction of thyroid nodule classification by I grade or above, and normal laboratory indicators; significant effectiveness means apparent improvement in symptoms and signs, weight gain to the pre-disease state, reduction of thyroid nodule classification by I grade, and basically normal laboratory indicators; effectiveness signifies improved symptoms and signs, increase of weight to some extent, and reduction of laboratory indicators; ineffectiveness represents failure to meet the above criteria. Total effective rate of treatment = (Cure + Significant effectiveness + Effectiveness) cases/total cases × 100% [18].

(2) Serum hormone level: The serum hormone level was contrasted between the two groups before and after treatment. 4-5 mL fasting peripheral venous blood was collected and centrifuged (3500 r/min, centrifugal radius of 10 cm, BY-320C, Beijing Baiyang Medical Equipment Co., LTD.) for 10 min to acquire supernatant. Next, levels of free triiodothyronine (FT₃), free thyroxine (FT₄), and thyroid stimulating hormone (TSH) were determined through chemiluminescence immunoassay with specific kits (Beckman Coulter, Inc., Brea, CA, USA).

(3) Sleep quality: The sleep quality was compared before and after treatment between two groups. The Pittsburgh Sleep Quality Index (PSQI) was used for evaluation, with a maximum score of 21. The lower score indicates the better sleep condition. The average number of days when patients suffer from insomnia per week was recorded before and after treatment. Insomnia can be defined by the presence of any of the following conditions: a. time to fall asleep > 30 min; b. the total sleep time usually < 6 h; c. wake up at least 2 times throughout the night or wake up early [7].

(4) Adverse reactions: The possible adverse reactions including liver and kidney dysfunction, gastrointestinal reactions, etc. that may occur between two groups of patients during treatment were collected and compared.

(5) Pregnancy outcome: The pregnancy outcomes from two groups of patients were recorded, including abortion, preterm delivery, and full-term delivery.

2.7 Statistical methods

Statistical analysis was conducted using SPSS 20.0, with counting data expressed as examples (%) and χ^2 test for comparison. The counting data were verified using chi square test, and the normality analysis for measurement data was achieved with Kruskal Wallis method. The measurement data conforming to the

normal distribution were described as mean \pm standard deviation. Independent samples t-test was exploited for comparison between two groups, and paired samples t-test for comparison at different time points within the same group. A difference of $p < 0.05$ was considered statistically significant.

3 Results

3.1 Comparison of clinical efficacy between the two groups

The total effective rate was higher in combination group than control group ($p < 0.05$, Table 2).

3.2 Comparison of serum hormone levels between the two groups before and after treatment

Prior to treatment, FT₃, FT₄ and TSH levels were similar in both groups ($p > 0.05$). Owing to treatment, FT₃ and FT₄ levels were decreased while TSH level was increased in both groups ($p < 0.05$), and the changing trends were more apparent in combination group compared to control group ($p < 0.05$, Table 3).

3.3 Comparison of PSQI score between the two groups before and after treatment

PSQI score had no difference between the two groups before treatment ($p > 0.05$). However, the treatment resulted in decreased PSQI score in both groups and the score was lower in combination group than control group ($p < 0.05$, Table 4).

3.4 Comparison of adverse reactions and pregnancy outcomes between the two groups

No serious adverse reactions such as liver and kidney dysfunction or gastrointestinal reactions were found in both groups. In addition, the incidence of adverse pregnancy in the combination group was lower than that in the control group ($p < 0.05$, Table 5).

Table 2 Comparison of clinical efficacy between the two groups (case (%)).

Group	Case	Cure	Significant effectiveness	Effectiveness	Ineffectiveness	Total effective rate
Combination group	46	21 (45.66)	14 (30.43)	8 (17.39)	3 (6.52)	43 (93.48)
Control group	46	14 (30.43)	12 (26.09)	9 (19.57)	11 (23.91)	35 (76.09)
χ^2						5.392
ρ						0.020

Table 3 Comparison of serum hormone levels between the two groups before and after treatment (mean ± standard deviation).

Group	Case	FT ₃ /(pmol/L)		FT ₄ /(pmol/L)		TSH/(mIU/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	46	8.20 ± 0.35	5.52 ± 0.20 *	32.26 ± 3.85	20.48 ± 2.05 *	1.70 ± 0.54	6.76 ± 0.53 *
Control group	46	8.24 ± 0.34	7.45 ± 0.21 *	32.40 ± 3.42	25.53 ± 3.12 *	1.73 ± 0.50	3.75 ± 0.58 *
t		0.556	45.138	0.184	9.175	0.276	25.984
ρ		0.580	0.000	0.855	0.000	0.783	0.000

Note: compared with before treatment in the same group, * $\rho < 0.05$.

Table 4 Comparison of PSQI score between the two groups before and after treatment (mean ± standard deviation).

Group	Case	Before treatment	After treatment
Combination group	46	13.59 ± 2.60	8.11 ± 1.69 *
Control group	46	13.87 ± 2.83	11.26 ± 2.52 *
t		0.499	7.054
ρ		0.619	0.000

Note: compared with before treatment in the same group, * $\rho < 0.05$.

Table 5 Comparison of pregnancy outcomes between the two groups (case (%)).

Group	Case	Abortion	Preterm delivery	Full-term delivery	Adverse pregnancy
Combination group	46	2 (4.35)	1 (2.17)	43 (93.48)	3 (6.52)
Control group	46	9 (19.57)	8 (17.39)	29 (63.04)	17 (36.96)
χ^2					12.522
ρ					0.000

4 Discussion

To improve the clinical efficacy of patients with gestational hyperthyroidism and insomnia, this study assessed the therapeutic effect of Liuwei Dihuang Decoction combined with methimazole, and ultimately confirmed the better efficiency of the combined therapy.

When loads of TSH receptor stimulating antibodies are activated in gestational hyperthyroidism patients, they directly act on the TSH receptors on the thyroid cell membrane and stimulate thyroid cell proliferation via the adenylate cyclase signaling pathway, leading to sympathetic nervous system excitation and promoting the up-regulation of FT₃ and FT₄. Meanwhile, under

the feedback of the thyroid and pituitary axes, TSH level is reduced and thyroid function is affected, which can increase the risk of adverse pregnancy outcomes such as abortion and preterm delivery in pregnant women [18]. This study indicated that Liuwei Dihuang Decoction combined with methimazole increased the TSH level yet suppressed the levels of FT₃ and FT₄ in patients, which proved that this combined treatment can enhance thyroid function and improve the pregnancy outcome of patients with gestational hyperthyroidism and insomnia. In addition, the levels of FT₃ and FT₄ in the combination group were lower than those in the control group, but the combination group presented a higher TSH level when compared with the control group, indicating the efficacy of Liuwei Dihuang Decoction combined with methimazole was better than methimazole alone. Methimazole can regulate the pituitary-thyroid axis function of gestational hyperthyroidism patients, achieve feedback inhibition of FT₃ and FT₄ secretion, and promote TSH generation, contributing to improving thyroid function and strengthening maternal and infant health [19], which was consistent with our results of control group. Liuwei Dihuang Decoction primarily consists of *Rehmanniae Radix Praeparata*, *Dioscoreae Rhizoma*, *Fructus Corni*, *Poria*, *Moutan Cortex*, and *Alismatis Rhizoma*. Among them, the *Rehmanniae Radix Praeparata* can promote liver and kidney meridian affinity, *Dioscoreae Rhizoma* can tonify spleen, lung and kidney, *Fructus Corni* can astringe essence to prevent collapse, *Poria* can strengthen the spleen and calm the mind, *Moutan Cortex* can clear heat and cool blood, and *Alismatis Rhizoma* can transform turbidity and lower lipid, which together can tonify kidney and liver, soothe the liver and regulate qi [8,20]. The modern pharmacology revealed that the *Rehmanniae Radix Praeparata* in Liuwei Dihuang Decoction can mediate abnormal thyroid hormone secretion and pituitary-thyroid axis function, down-regulate FT₃ and FT₄ levels, promote

TSH generation, and enhance thyroid function, thereby improving pregnancy outcomes [21]. *Fructus Corni* elevates serum TSH concentration, restore thyroid function and thus boost the metabolism of thyroid and systemic tissue cells, so as to improve the pregnancy outcome of patients [22]. Compared with previous literature, the innovation of this paper lies in that we discovered Liuwei Dihuang Decoction combined with methimazole can ameliorate thyroid function and pregnancy outcome of patients with gestational hyperthyroidism and insomnia, which is better than methimazole in terms of therapeutic efficacy.

Hyperthyroidism during pregnancy can affect the central nervous system and cause tension, anxiety, irritability, and insomnia in patients, seriously affecting their sleep quality [22]. In this study, the results unveiled that the combined therapy decreased the PSQI score of patients, and the PSQI score in the combination group was lower than that in the control group, evidencing the combined therapy can promote sleep quality of patients with gestational hyperthyroidism and insomnia, with the effects superior to methimazole alone. Methimazole effectively diminishes the levels of thyroid peroxidase antibodies and thyroglobulin antibodies, thereby protecting thyroid follicular cells and improving the central nervous system to elevate the quality of sleep [19]. In line with the modern pharmacology, *Poria* triterpene acid in Liuwei Dihuang Decoction can increase the content of γ -aminobutyric acid (GABA) and has a hypnotic effect; meanwhile, *Poria* polysaccharides can inhibit the central nervous system of pentobarbital, thereby exerting hypnotic and sedative effects [23]. Based on the above efficacy, Liuwei Dihuang Decoction combined with methimazole can enhance the sleep quality of patients with gestational hyperthyroidism and insomnia, which is superior to methimazole alone.

Collectively, Liuwei Dihuang Decoction combined with methimazole can effectively improve thyroid function, sleep quality and pregnancy outcomes without severe adverse reactions in patients with gestational hyperthyroidism and insomnia. However, there are limitations in this study. The current study mainly applies subjective scales as observation indicators, so that subsequent studies require objective indicators such as polysomnography monitoring and laboratory tests.

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Conflicts of Interest

The author declares no conflicts of interests.

Author Contributions

L.M. and Y.J. conceptualized the trial, and participated in creating the study design and the statistical analysis plan. Y.J. made the first draft of the manuscript. All authors reviewed and revised the manuscript critically for important intellectual content, reviewed the final manuscript as submitted, read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was authorized by the Ethics Committee of our hospital and all patients signed the written informed consent.

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Availability of Data and Materials

The original contributions presented in the study are

included in the article, further inquiries can be directed to the corresponding authors.

Supplementary Materials

Not applicable.

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