

Research Progress on the Treatment of Gestational Hypertension with Traditional Chinese and Western Medicine

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Abstract: *Hypertensive disorders of pregnancy (HDP) is a disease with high incidence in the middle and late stages of pregnancy, characterized by systemic small vessel spasm and endothelial injury as the main pathological and physiological changes, and its etiology and pathogenesis are still unclear. Traditional Chinese medicine theory is that, for the etiology and pathogenesis of gestational hypertension more empty mark real syndrome, which are closely related to the imbalance of liver, spleen, and kidney functions. On the other hand, Western medicine believes that the onset of gestational hypertension is related to factors such as poor placental formation and systemic inflammatory reactions. At present, both Chinese and Western medicine have achieved good efficacy in the clinical treatment of gestational hypertension. In recent years, the integrated treatment strategy of Chinese and Western medicine has provided new ideas and options for the treatment of gestational hypertension, which is expected to further improve the therapeutic efficacy of patients and improve maternal and neonatal outcomes. The review aims to explore the application and clinical efficacy of integrated Chinese and Western medicine programs in the treatment of gestational hypertension by reviewing the relevant literature in recent years, with the expectation that it will provide reference for further in-depth research and clinical practice, promote the early diagnosis and treatment of gestational hypertension, and reduce the incidence of adverse outcomes in both mother and child.*

Keywords: Hypertensive disorders of pregnancy, Integrated Chinese and Western medicine treatment, Clinical efficacy, Pathogenic mechanism.

1. Introduction

Pregnancy induced hypertension is characterized by persistent hypertension, proteinuria, edema, and other clinical features. In severe cases, seizures or even death may occur. It is one of the main causes of maternal and neonatal mortality worldwide, and is also an important cause of short-term and long-term cardiovascular, renal, and cerebrovascular diseases in pregnant women [1]. Pregnancy induced hypertension is also associated with adverse fetal outcomes, such as low birth weight, premature birth, and small for gestational age infants [2]. Epidemiological research shows that the global incidence rate of hypertensive disorder complicating pregnancy is about 2%~8%. Although the maternal and neonatal mortality rates have declined in the past decades, the global health goals have not been met [3],[4]. Clinical studies have shown that in addition to typical symptoms such as hypertension, proteinuria, and edema, gestational hypertension can also affect multiple organs and systems throughout the body, leading to functional damage to important organs such as the heart, brain, and kidneys, as well as affecting the normal development of the placenta fetus, resulting in a series of serious complications [5],[6]. Although there is a certain understanding of the etiology and pathophysiological mechanisms of gestational hypertension in medicine, its exact cause is still unclear. In traditional treatment, Western medicine dominates the diagnosis and treatment of gestational hypertension. However, there is currently no curative treatment for gestational hypertension. Based on the clinical manifestations of patients, symptomatic treatments such as blood pressure reduction, spasmolysis, and sedation are mostly used. The treatment strategy is to closely monitor the mother and child's condition and terminate pregnancy in a timely manner [7]. In recent years, the role of traditional

Chinese medicine in the treatment of gestational hypertension has received increasing attention, and research has shown that the combination of traditional Chinese and Western medicine has significant clinical therapeutic effects on gestational hypertension, providing new ideas and methods for the treatment of gestational hypertension [8]. This article aims to systematically summarize the research progress in the treatment of gestational hypertension based on traditional Chinese and Western medicine in recent years, explore the clinical application of integrated traditional Chinese and Western medicine treatment for gestational hypertension and its potential in improving treatment effectiveness and preventing complications, provide more comprehensive and scientific treatment plans for clinical doctors, promote early recovery and improve the quality of life of patients with gestational hypertension.

At present, gestational hypertension is mainly classified into four categories, including gestational hypertension, preeclampsia eclampsia, pregnancy with chronic hypertension, and chronic hypertension with preeclampsia [9]. Although the treatment threshold and goals vary, the internationally recommended threshold for diagnosing gestational hypertension is still BP \geq 140/90 mmHg (blood pressure should be re measured every 4 hours, with at least 2 episodes of elevated blood pressure) [10]. Correct blood pressure monitoring is the foundation of diagnosis, combined with self-monitoring and 24-hour dynamic blood pressure monitoring.

2. Research Progress on the Incidence of Gestational Hypertension in Traditional Chinese and Western Medicine

2.1 Traditional Chinese Medicine's Understanding of the Etiology and Pathogenesis of Pregnancy induced Hypertension.

According to the clinical characteristics and pathogenesis of gestational hypertension, most traditional Chinese medicine scholars classify the various stages of gestational hypertension as "swelling", "dizziness", and "eclampsia", which have inherent connections in terms of etiology, pathogenesis, and disease evolution [11]. Zheng Dezhu et al [12] believed that the occurrence of HDP is nothing more than deficiency and excess. Deficiency is mainly caused by the dysfunction of liver, spleen, and kidney, and due to the increasing depletion of yin blood in the later stages of pregnancy, deficiency of qi and blood, and inability to nourish the upper body. In fact, the disease is caused by pathological products such as wind, fire, phlegm and dampness, as well as by the enlargement of the fetus in the later stages of pregnancy, which blocks the meridians, obstructs qi and blood flow, and disrupts the clear orifices. Guo Liping et al [8] believed that "blood stasis" is the central link in the onset of HDP, and points out that placental "blood stasis" is an important pathophysiological process in the occurrence of HDP. If blood stasis blocks for a long time, the body fluid cannot flow normally, and the limbs overflow, edema will occur; Or if the kidney meridian is damaged by blood stasis, proteinuria may occur; Or accumulate dampness and produce phlegm, disturb the brain meridians, cause dizziness, and in severe cases, fainting, convulsions, etc. Yu Jiaqi et al [13] further supplemented the etiology and pathogenesis of HDP with the theory of "if blood is poor, it becomes water". The essence of blood and saliva are homologous and can also be transformed into each other. In pathological conditions, blood and water can be related to each other. Xiong Shuling et al [14] believes that the incidence rate of HDP is higher among pregnant women with phlegm dampness, damp heat and yin deficiency. Therefore, he believes that the incidence of HDP is obviously related to the constitution. He believes that post pregnancy dystrophy, abnormal living, fatigue and seven emotions injury are the inducements. Clinicians should pay close attention to it in the middle and late pregnancy and during delivery to reduce the incidence of pregnancy induced hypertension.

In general, the pathogenesis of gestational hypertension is complex, often with a mixture of positive and negative factors. Clinical diagnosis should be combined with syndrome differentiation, not only considering the imbalance of qi and blood in the organs and yin and yang, but also taking into account pathological factors such as wind, phlegm, fire, dampness, and blood stasis as the hallmark disease.

2.2 Research Progress on the Pathogenesis of Gestational Hypertension in Western Medicine

The etiology of gestational hypertension is still not fully understood, and it is widely recognized as a multifactorial, multi mechanistic, and multi pathway disease that cannot be explained by a "monism". As early as 2009, scholars proposed the famous "two-stage model" theory [15]. The first stage includes poor placental formation. The second stage is the clinical manifestations of the disease, such as newly developed hypertension and proteinuria. With the deepening of research, this model has become insufficient, and a more

refined "six stage model" theory was proposed in 2014 [16]. In the first stage, the prerequisites for poor placental formation have become clearer, originating from maternal immune tolerance to embryonic paternal genes, which may increase the likelihood of poor placental formation and preeclampsia. In the second stage, due to insufficient invasion of trophoblast cells in the placenta, it affects the remodeling of the uterine spiral artery, causing shallow implantation and perfusion disorders of the placenta. This stage is a key link in placental formation and an important period for pathological and physiological changes in trophoblast cells. Previous studies have shown that an imbalance of anti angiogenic factors is positively correlated with the severity of HDP. In patients with preeclampsia, the levels of anti angiogenic factors such as soluble fms like tyrosine kinase 1 (sFlt-1) and soluble endothelial glycoprotein (sEng) in the plasma are significantly elevated. These factors inhibit the synthesis of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), leading to dysfunction of endothelial cell function and angiogenesis, reducing neovascularization in the placenta, and forming a vicious cycle of local ischemia and hypoxia in the fetal disc [17]. The third stage is the oxidative stress and inflammatory state of the placenta [18]. Placental ischemia leads to a state of hypoxia, which stimulates high levels of hypoxia inducible factor-1 alpha (HIF-1 alpha) expression and also increases the expression of its downstream factor sFlt-1, affecting endothelial cell production. Low oxygen state and intermittent hypoxia reoxygenation lead to oxidative stress, increased production of reactive oxygen species (ROS), inhibition of the invasive ability of trophoblast cells, and damage to endothelial cells. Existing evidence shows that there is an overactivation of inflammatory immune responses both locally and systemically at the maternal fetal interface. Adapting to the maternal immune response to accommodate a semi allogeneic fetus is a necessary condition for successful pregnancy, requiring a dynamic balance between immune activation and embryonic antigen tolerance [19]. The immune system of pregnant women not only needs to tolerate the fetus, but also maintain the ability to defend against infections. Research has shown that an imbalance in the Th1/Th2 cell ratio is associated with the onset of HDP [20]. In normal pregnancy, the maternal immune system tends to have a Th2 type immune response to maintain maternal fetal immune tolerance and promote fetal growth. In HDP patients, the Th1 type immune response is enhanced while the Th2 type immune response is weakened. Th1 type cytokines inhibit the invasive ability of trophoblast cells by promoting the secretion of pro-inflammatory cytokines such as IFN- γ and TNF- α , exacerbate oxidative stress by increasing ROS generation, and inhibit angiogenesis and endothelial cell function by promoting the production of anti angiogenic factors (sFlt-1, sEng). In recent years, it has been found that regulatory T cells (Tregs) are important for establishing immune tolerance to invasive fetal trophoblast cells (EVT). Tregs deficiency reflects immune endocrine imbalance, alters maternal tolerance, and leads to pregnancy complications such as preeclampsia (PE). CD25⁺HIF1 α ⁺Tregs in CD4⁺Treg types have been shown to inhibit fetal specific and non-specific responses [21]. The fourth to sixth stages all occur in the second half of pregnancy, and the fourth stage is secondary to placental injury. Various placental derived injury factors are released into the maternal bloodstream, causing endothelial cell damage and leading to

vascular dysfunction, manifested as increased vasoconstriction, increased permeability, and a tendency towards thrombosis. In addition, endothelial injury can activate platelets and coagulation factors, exacerbating the hypercoagulable state of preeclampsia. When the diagnosis of preeclampsia can be made, the fifth stage has already begun. In the sixth stage, some patients developed rapid atherosclerosis of uterine spiral artery, further decreased uterine placental perfusion, and thrombosis of spiral artery eventually led to placental infarction. Pre eclampsia has a familial tendency, and women with a family history of pre eclampsia have a higher risk of developing the disease. Genetic factors are associated with the occurrence of this disease. Current research has found that genetic variations in both the mother and fetus, such as the rs4769613 locus near the FLT1 gene, are related to late-onset preeclampsia. The rs9478812 locus in the mother's genome is located within the PLEKHG1 gene and is also associated with preeclampsia [18]. Malnutrition and certain micronutrient deficiencies (such as vitamin D and folate) may also increase the risk of preeclampsia. Environmental factors such as smoking, diabetes and obesity also increase the risk of preeclampsia, but these evidences need more clinical studies to further confirm [22]. Overall, although the specific pathogenesis of HDP has not been elucidated, a large number of studies have found factors closely related to the disease, laying the foundation for further mechanism exploration in the future.

3. The Application of Traditional Chinese and Western Medicine in the Clinical Treatment of Gestational Hypertension

3.1 Research Progress on Western Medicine Treatment of Gestational Hypertension

Although the exact cause of gestational hypertension is not yet clear, current treatment strategies aim to control the condition, prevent its deterioration, and ensure the safety of both the mother and fetus. The treatment of HDP requires multidisciplinary collaboration to develop personalized treatment plans based on the patient's specific condition. During the treatment process, it is necessary to closely monitor the condition of the mother and fetus and adjust the treatment plan in a timely manner. At present, the main methods for treating HDP are blood pressure reduction, prevention of eclampsia, and timely termination of pregnancy. The American College of Obstetricians and Gynecologists (ACOG) recommends antihypertensive treatment for women with preeclampsia HDP and persistent systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg, as well as women with chronic hypertension and systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mm Hg. The treatment targets are systolic blood pressure of 120-160 mm Hg and diastolic blood pressure of 80-110 mm Hg [23]. Internationally, some guidelines recommend more aggressive treatment, suggesting treatment when BP $\geq 140/90$ mm Hg, with a target blood pressure of systolic blood pressure ≤ 135 mmHg and diastolic blood pressure ≤ 85 mmHg [24],[25]. Labetalol and methyldopa are widely accepted first-line treatment drugs, and some guidelines also support the use of nifedipine as initial treatment. For acute severe hypertension, intravenous administration of hydralazine, labetalol, or oral administration of nifedipine is commonly

used. To prevent the onset and recurrence of preeclampsia, guidelines from various countries recommend intravenous infusion of magnesium sulfate as the preferred medication for patients with severe preeclampsia, and routine monitoring of magnesium ion toxicity reactions (such as knee reflex, urine output, or respiratory rate) during the medication process. Medications such as diazepam tablets and phenobarbital tablets can be used as appropriate to help patients alleviate anxiety, improve sleep, and reduce the risk of seizures. For patients with severe conditions, terminating pregnancy is the main treatment method. The timing of terminating pregnancy should be individualized based on the condition of the pregnant woman. For severe preeclampsia, termination at 34 weeks of pregnancy may be considered, and it is not recommended to exceed 37 weeks of pregnancy. For preeclampsia, termination at 37 weeks of pregnancy is recommended [9].

The new treatment strategy for HDP mainly focuses on improving endothelial function by intervening in anti angiogenic factors (sFLT1) and supplementing pro angiogenic factors (VEGF and PlGF), thereby alleviating symptoms and prolonging pregnancy time. At present, RNAi molecules and proton pump inhibitors (PPIs) that can specifically recognize sFLT1 mRNA have been developed to inhibit the production of sFLT1. Selective clearance of sFLT1 through extracorporeal circulation techniques such as using a dextran sulfate adsorption column (DSA) for plasma exchange [20]. These new treatment strategies provide new directions for the treatment of preeclampsia, but most are still in the experimental or preliminary clinical trial stage, and further research is needed to verify their safety and effectiveness.

In addition, for high-risk pregnant women (such as preeclampsia history, chronic hypertension, diabetes, obesity, etc.), ACOG recommends starting to use low-dose aspirin (81~150 mg/day) in the early pregnancy (usually 12~16 weeks of pregnancy) to prevent the occurrence of preeclampsia [24]. Supplementing calcium during pregnancy can reduce the risk of preeclampsia, premature birth, and the occurrence of death or severe illness. However, it should be noted that existing evidence suggests that only women with low calcium intake in their diet may benefit from calcium supplementation [26]. Lifestyle changes before and during pregnancy, including dietary interventions and exercise, can also reduce gestational weight gain and improve pregnancy outcomes [27],[28].

3.2 Research Progress on Traditional Chinese Medicine Treatment of Gestational Hypertension

In recent years, an increasing number of clinical studies have shown that traditional Chinese medicine plays a positive role in the treatment of HDP. Many medical experts believe that HDP is located in the liver, spleen, and kidneys, and is closely related to pathological factors such as wind, phlegm, fire, dampness, and blood stasis. Therefore, clinically, nourishing liver and kidney medicines, calming liver and eliminating wind medicines, tonifying qi and strengthening spleen medicines, promoting blood circulation and removing blood stasis medicines are commonly used for prevention and treatment [29]. The medical syndrome types are relatively

complex, with a large proportion of liver and kidney yin deficiency types, Gu Saohua et al [30] used Qiju Dihuang Pill to treat patients with liver and kidney yin deficiency in HDP. The main formula was Liuwei Dihuang Pill, with added wolfberry and chrysanthemum. The results showed that it could effectively promote the recovery of traditional Chinese medicine syndromes in HDP patients with liver and kidney yin deficiency, reduce the incidence of adverse pregnancy outcomes, and correct the levels of immune related factors such as IFN- γ , IL-6, VCAM-1. This suggests that Qiju Dihuang Pill can also help correct the immune imbalance in HDP patients. If the deficiency of liver and kidney yin further worsens, leading to liver yang hyperactivity, wind and fire agitation, phlegm production from decoction, liver wind mixed with phlegm and fire disturbing the gods and causing convulsions and coma, the treatment should mainly focus on nourishing yin and hidden yang, calming the liver and extinguishing wind, Zhao Yaning et al [31] added Tianma Gouteng Drink to the observation group of patients on the basis of conventional treatment with magnesium sulfate for severe PE of liver wind type. The results showed that the micro inflammatory indicators (IL-6, hs CRP, TNF- α) of the observation group were reduced, and the coagulation function indicators (vWF, GMP-140, PT) and renal function indicators (Cr, Cys-C, UA) were significantly improved, and the effect was better than that of the conventional treatment group with magnesium sulfate. Spleen deficiency leads to the cessation of phlegm and dampness accumulation, and liver yang is disturbed by phlegm turbidity. Treatment should focus on strengthening the spleen and dispelling dampness, as well as calming the liver and latent yang, Lu Tao et al [32] used Banxia Baizhu Tianma Tang combined with low-dose low-molecular-weight heparin calcium to treat patients with early-onset severe preeclampsia of spleen deficiency and liver hyperactivity type. The results showed that the clinical symptoms of dizziness, head discomfort, palpitations, insomnia, etc. were significantly improved in the combination treatment group. At the same time, the average pulse pressure, 24-hour urinary protein content, umbilical artery S/D ratio were reduced, and the levels of plasma fibrinolytic system molecular markers (D-dimer, t-PA, Fg, HCT, etc.) were improved. Zhao Wei et al [33] used Sijunzi Wan combined with calcium supplements to treat postpartum women with HDP. The formula consists of Chinese herbs such as *Atractylodes macrocephala*, *Panax ginseng*, *Poria cocos*, and roasted licorice, which have the effects of strengthening the spleen, removing dampness, and promoting diuresis. Their research shows that the formula can significantly reduce the average arterial pressure and uric acid concentration, and improve pregnancy outcomes. Jia Rui et al [34] uses aspirin combined with nourishing blood, activating blood circulation, nourishing kidney and nourishing essence to nourish the kidneys, clear the liver and remove blood stasis formula. The treatment mainly focuses on tonifying, with blood circulation as a supplement, integrating tonifying with promoting circulation, and eliminating evil to achieve positive and stable results. The therapeutic effect is better than using aspirin alone, which can significantly improve clinical symptoms and coagulation indicators, and effectively prevent the occurrence of preeclampsia. The formula uses blood activating and stasis removing drugs such as Danshen, Danggui, Chuanxiong, etc., to promote blood circulation and promote blood flow. Modern pharmacological research has shown that [35], Danshensu can

inhibit the expression of sFlt-1 in placental tissue, upregulate the expression of PLGF, increase the activity of eNOs in placental tissue and serum NO synthesis, reduce the damage of placental vascular function in preeclampsia rats, lower blood pressure and urinary protein content, and thus improve pregnancy outcomes.

In addition, traditional Chinese medicine external treatment methods also have certain application value in assisting the treatment of HDP, Han Jie et al [36] found that massaging acupoints such as Taichong and Sanyinjiao can effectively control the arterial systolic and diastolic pressure of HDP patients, improve sleep quality and pregnancy outcomes. Ye Huaying et al [37] discovered that acupressure (massaging acupoints such as Baihui, Taiyang, and Fengchi with both hands) can improve the sleep quality of hospitalized patients with gestational hypertension, effectively control blood pressure, and have a positive effect on patients with gestational hypertension. Yang Yang et al [38] discovered that applying adhesive tape with Wang Buliuxing seeds to ear acupoints (such as Shenmen, Jangya Gou, Xin, Gan, and Shen acupoints) for regular pressing can effectively control the blood pressure of women at high risk of gestational hypertension, delay and control the disease progression, improve pregnancy outcomes, and enhance the quality of life for both mother and baby. Lan Xiaohong et al [39]'s research found that the combination of conventional Western medicine treatment and Wu Zhuyu plaster applied to Yongquan acupoint can induce heat flow, balance yin and yang, enhance blood pressure lowering effect, and improve pregnancy outcomes. It is worth mentioning that the adverse reactions of these traditional Chinese medicine treatments are generally low and have high safety.

However, currently the treatment of HDP with traditional Chinese medicine mainly relies on accumulated experience, and existing literature research generally has shortcomings such as small sample sizes, lack of controlled experiments, and statistical analysis. In addition, the inconsistency of traditional Chinese medicine syndrome differentiation and efficacy evaluation criteria also limits the efficacy evaluation and clinical application of traditional Chinese medicine in treating HDP. Therefore, it is necessary to establish a unified set of traditional Chinese medicine syndrome differentiation and efficacy judgment standards in the future, which will help improve the efficacy level of traditional Chinese medicine in treating HDP and the quality of clinical research.

3.3 Application and Clinical Efficacy of Integrated Traditional Chinese and Western Medicine in the Treatment of Gestational Hypertension

In recent years, an increasing number of studies have shown that the combination of traditional Chinese and Western medicine has significant effects in the treatment of gestational hypertension, providing new ideas and methods for the treatment of HDP. Traditional Chinese medicine usually uses traditional Chinese medicine in the treatment of HDP. According to the specific symptoms and constitution of the patient, the formula contains traditional Chinese medicine with the effects of tonifying the kidney and soothing the liver, strengthening the spleen and promoting diuresis, and promoting blood circulation and removing blood stasis. The

advantage of combining traditional Chinese and Western medicine in treating HDP lies in the fact that traditional Chinese medicine emphasizes a "holistic approach", which can regulate the patient's constitution, improve immunity, and has high safety, while Western medicine can quickly control blood pressure, delay disease progression, and protect the function of important organs. The combination of the two can leverage their respective advantages and achieve better therapeutic effects.

4. Summary and Outlook

At present, both traditional Chinese and Western medicine have achieved certain results in the treatment of gestational hypertension, and have good clinical treatment effects. Western medicine mainly uses drugs such as antihypertensive, antispasmodic, and sedative treatments to quickly control the condition and protect important organ functions, reducing the incidence of adverse pregnancy outcomes. However, the therapeutic dose of magnesium sulfate is close to the toxic dose, and the therapeutic dose is often difficult to control, which can easily lead to adverse reactions. Fetal development accompanies the entire pregnancy, and the use of antihypertensive drugs may cause a decrease in uterine placental circulation, which has a negative impact on the health and growth of the fetus. In addition, intrauterine exposure to antihypertensive drugs can lead to deformities, limiting the choice of treatment drugs. Traditional Chinese medicine treatment for HDP focuses on overall regulation and has good efficacy and safety. Combining the advantages of traditional Chinese and Western medicine can improve treatment effectiveness, reduce adverse reactions, and have positive implications for the treatment of HDP. In future research, it is still necessary to strengthen clinical studies on the combination of traditional Chinese and Western medicine treatment, and explore more effective treatment plans; In addition, by combining the concept of personalized medicine and developing personalized treatment plans based on the characteristics of different patients, the pertinence and effectiveness of treatment can be improved.

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