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Standardized Management of Preconception Hypertension: Postprint

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Date: 2022-12-20T00:00:00+00:00

Abstract

In recent years, due to increasing life stressors, a growing number of men and women of reproductive age in China have developed hypertension; consequently, the standardized management of hypertension during the preconception period has emerged as a current focus. This article elaborates that the management of hypertension in women during the preconception period should prioritize maternal and fetal safety, with pharmacological selection strictly guided by anti-hypertensive indications. Currently recognized relatively safe medications both domestically and internationally include methyldopa, labetalol, and nifedipine, while ACEI and ARB drugs are contraindicated, and the use of diuretics remains controversial. For male hypertensive patients during preconception, both the efficacy of antihypertensive agents and their adverse effects on sexual function and sperm quality, motility, and concentration must be considered. Currently recommended antihypertensive options for male hypertensive patients during the preconception period include nebivolol, as well as ACEI and CCB drugs. With a view to improving maternal and fetal outcomes, achieving healthy childbearing and child-rearing, and ultimately reducing national healthcare expenditure through standardized management of hypertension during the preconception period.

Full Text

Standardized Management of Hypertension During the Preparation for Pregnancy

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Funding: Gansu Provincial Natural Science Foundation (20JR10RA716); Gansu Provincial Youth Science and Technology Fund Program (20JR10RA762); Lanzhou University Education Development Fund; Lanzhou University Second Hospital Cuiying Science and Technology Innovation Plan (CY2020-MS09)

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Abstract

In recent years, increasing life stress has led to a growing number of men and women of childbearing age suffering from hypertension in China. Consequently, the standardized management of hypertension during preconception has become a critical focus. This article outlines that management of hypertension in women preparing for pregnancy must prioritize maternal and fetal safety, with antihypertensive agents selected strictly according to indications. Currently recognized relatively safe medications worldwide include methyldopa, labetalol, and nifedipine. ACEI and ARB drugs are contraindicated, while diuretic use remains controversial. For hypertensive men preparing for pregnancy, both drug efficacy and adverse effects on sexual function, sperm quality, motility, and concentration must be considered. Currently recommended antihypertensive agents for men during preconception include nebivolol, ACEI, and CCB drugs. Through standardized management of preconception hypertension, we can improve outcomes for pregnant women and fetuses, achieve optimal perinatal care, and ultimately reduce national healthcare expenditures.

Keywords: Preparation for pregnancy; Hypertension; Standardized management; Pre-pregnancy monitoring; Reproductive function

Introduction

Hypertension is increasingly affecting younger populations, with 1.4 billion people worldwide suffering from this condition, and up to 10% of pregnancy-related deaths attributed to hypertensive disorders [1]. While most pregnancy-related hypertension manifests as gestational hypertension (onset after 20 weeks of gestation, resolving within 12 weeks postpartum), approximately 5% of women of childbearing age have pre-existing hypertension before conception [2-3], which significantly increases the risk of severe gestational hypertension or pre-eclampsia, compromising both maternal and fetal health [4]. Additionally, hypertension adversely affects reproductive function in men of childbearing age, as elevated blood pressure can cause erectile dysfunction, and certain antihypertensive medications may impair sexual function and sperm quality [5-6]. Without standardized blood pressure management in hypertensive men and women of reproductive age, serious complications may arise during future pregnancies. This issue has become particularly pressing under China's three-child policy, representing a shared concern among couples, obstetricians, hypertension specialists, and the broader community. While current guidelines and consensus statements primarily emphasize the diagnosis and management of gestational hypertension, standardized protocols for managing preconception

hypertension remain lacking. This review summarizes the standardized management of hypertension during preconception for both sexes to guide hypertensive patients in preparing for pregnancy.

Methods

We searched the literature using keywords including “备孕期” (preparation for pregnancy), “育龄期” (childbearing age), “妊娠期” (gestational period), “高血压” (hypertension), and their English equivalents “during the preparation for pregnancy,” “childbearing age,” “gestation period,” and “hypertension” in the CNKI, Wanfang, VIP, PubMed, and Web of Science databases from inception to August 2022. Inclusion criteria comprised full-text articles closely related to the topic, while exclusion criteria included irrelevant studies, those with insufficient information, and unavailable full-text data.

Management of Hypertension in Women During Preconception

Blood Pressure Monitoring and Assessment

Enhanced monitoring and assessment of blood pressure during preconception are crucial for preventing gestational hypertensive disorders and related complications. Compared with normotensive women, those with preconception hypertension face significantly higher risks of maternal and perinatal complications, including pre-eclampsia, eclampsia, placental abruption, cesarean delivery, preterm birth (<37 weeks), and low birth weight infants (<2500 g) [7-8]. Furthermore, research has demonstrated a linear association between maternal preconception hypertension and anemia risk in offspring [9]. However, detection rates of hypertension before and during early pregnancy remain low, with most women not identified until the third trimester. This underdetection stems from multiple factors: many women are unaware of their blood pressure status, some pregnancies are unplanned without preconception blood pressure measurement, and normal hemodynamic changes during pregnancy (systemic vasodilation, increased cardiac output, and decreased total peripheral resistance) cause a modest blood pressure decline in the second trimester that may mask underlying chronic hypertension [1,8]. Therefore, comprehensive assessment of preconception women should include detailed history of hypertension and gestational hypertensive disorders, evaluation for target organ damage, and screening for secondary hypertension when indicated [10]. International guidelines and consensus statements unanimously recommend preconception blood pressure monitoring through multiple modalities, including ambulatory blood pressure monitoring (ABPM), office blood pressure measurement, and home self-monitoring [1,11-12]. ABPM is emphasized as more accurate than office or home measurements, enabling early detection of masked hypertension while avoiding overtreatment of white-coat hypertension [11,13]. Preconception counseling is also strongly advocated as highly beneficial for preventing pregnancy-related

complications. Guidelines stress that pregnancy potential must be considered when managing hypertension in reproductive-age women, and that preconception counseling should be offered to all hypertensive women planning pregnancy. Such counseling provides health education on chronic conditions like hypertension, assesses risks for pre-eclampsia and preterm birth, and offers interventions to reduce pre-eclampsia risk [12].

Antihypertensive Therapy Indications and Target Blood Pressure

Selecting appropriate indications and target blood pressure for chronic hypertensive patients during preconception is essential. Studies have demonstrated clear benefits of active blood pressure control during pregnancy [14-15], though specific research on preconception blood pressure reduction is limited. The Chinese Expert Consensus on Blood Pressure Management in Gestational Hypertensive Disorders provides comprehensive recommendations: for newly diagnosed preconception hypertension without secondary causes or target organ damage, lifestyle interventions such as weight reduction and salt restriction should be implemented, with pharmacotherapy initiated when necessary. For women with pre-existing hypertension already receiving antihypertensive treatment, contraindicated medications should be discontinued at least six months before conception and replaced with relatively safe alternatives, with pregnancy considered only after blood pressure is controlled below 140/90 mmHg. Women with stage 2 hypertension or higher ($\geq 160/100$ mmHg) and those with target organ damage or secondary causes should receive specialized hypertension management for 3-6 months before re-evaluation for pregnancy [10].

Antihypertensive Drug Selection

General Principles and Contraindicated Medications Chronic hypertensive patients must avoid medications with teratogenic effects or adverse impact on fetal growth during preconception. Currently recognized relatively safe oral antihypertensive agents include α - and β -adrenergic receptor blockers (labetalol), calcium channel blockers (nifedipine), methyldopa, and direct vasodilators (primarily hydralazine), all of which should be administered under specialist supervision. Intravenous labetalol and phentolamine are recommended for emergency blood pressure reduction [1,10,16-18]. Atenolol is specifically not recommended [1], as studies have shown that preconception atenolol use increases the risk of intrauterine growth restriction and low birth weight [19]. Diuretic use remains controversial, as these agents can reduce circulating blood volume, potentially causing oligohydramnios, fetal growth restriction, and hypercoagulable states [10]. The WHO guidelines acknowledge that while diuretics are rarely used during pregnancy due to blood volume contraction, they may benefit patients with fluid retention and recommends that women already on long-term thiazide diuretics may continue these medications during pregnancy [1].

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are contraindicated throughout preconception and all stages

of pregnancy [16-17]. Extensive research demonstrates that first-trimester ACEI/ARB exposure causes fetal cardiovascular malformations and polydactyly, while second- and third-trimester use reduces placental perfusion, causing fetal growth impairment and intrauterine growth restriction [20-21]. These adverse effects result from direct inhibition of the fetal renin-angiotensin system combined with maternal hypotension and reduced placental blood flow [22]. A meta-analysis further reported that ACEI/ARB use before pregnancy recognition increases risks of congenital malformations, cardiovascular defects, and stillbirth [23]. Therefore, antihypertensive regimens should be switched to safer alternatives within two weeks of pregnancy detection. Since over half of pregnancies are unplanned, reproductive-age women with hypertension are generally recommended to use pregnancy-safe antihypertensive agents [24].

Specific Medications **Labetalol** is widely used in gestational hypertensive disorders and holds first-line status in China, applicable throughout preconception and pregnancy. As a mixed α - and β -adrenergic receptor blocker, labetalol crosses the placenta but does not compromise uteroplacental blood flow. It provides effective blood pressure control without adverse effects on fetal heart rate, blood pressure, or oxygen uptake. However, due to potential bronchoconstriction and negative cardiac effects, labetalol is contraindicated in women with asthma, decompensated cardiac function, heart block, or bradycardia [12,25].

Nifedipine, a dihydropyridine calcium channel blocker available in immediate-release and sustained-release formulations (sustained-release tablets in China), selectively inhibits calcium influx in myocardial cell membranes, blocking excitation-contraction coupling, reducing myocardial contractility, and decreasing myocardial energy and oxygen consumption [20]. Sustained-release nifedipine is suitable for all stages of preconception and pregnancy [10], while immediate-release nifedipine is reserved for emergency blood pressure reduction, offering a significant advantage when intravenous agents are unavailable, though sublingual administration and routine use are not recommended [26]. A prospective cohort study found that oral immediate-release nifedipine significantly reduced systolic blood pressure, mean arterial pressure, and cerebral perfusion pressure compared to intravenous labetalol [27]. However, nifedipine may cause reflex tachycardia, headache, and flushing, warranting caution in patients with tachycardia [10,25].

Methyldopa is recommended as first-line therapy in international guidelines and holds a prominent position in clinical management of gestational hypertensive disorders [13]. Its antihypertensive effect is mediated through the active metabolite α -methylnorepinephrine, which stimulates central inhibitory α -adrenergic receptors and acts as a false neurotransmitter, reducing plasma renin activity and arterial blood pressure [13,20]. Although methyldopa crosses the placenta, studies have shown no fetal harm [18,28]. However, methyldopa frequently causes drowsiness and may lead to postpartum depression, resulting in limited clinical use in China [10].

Management of Hypertension in Men During Preconception

Elevated blood pressure in men causes penile cavernous vascular sclerosis, endothelial dysfunction, reduced nitric oxide release, and decreased androgen levels, leading to erectile dysfunction [5]. Erectile function depends on sexual stimulation triggering impulses that activate penile cavernous nerve endings and endothelial cells to release nitric oxide, which relaxes penile vascular smooth muscle and increases blood flow [5,29]. Additionally, certain antihypertensive agents, particularly diuretics and most β -blockers, reduce androgen levels and impair erectile function [17,30]. Network meta-analyses indicate that thiazide diuretics pose the greatest risk to erectile function, followed by β -blockers and CCBs, while ARBs carry the lowest risk, with ACEIs being the second safest option [6]. Therefore, antihypertensive selection for hypertensive men preparing for pregnancy must balance efficacy with potential adverse effects on reproductive function and sperm quality.

Drug-Specific Considerations

β -blockers are associated with decreased libido, erectile dysfunction, and impaired sperm motility [31-33]. Non-selective β -blockers directly affect penile vascular smooth muscle cells, causing vasoconstriction and reduced cavernous blood flow, while agents such as metoprolol, atenolol, and propranolol also impair reproductive function by lowering testosterone levels [31,34]. Third-generation β -blockers (carvedilol, labetalol, nebivolol) possess both receptor selectivity and vasodilatory properties, resulting in minimal impact on male reproductive function. Nebivolol, in particular, stimulates endothelial nitric oxide release, increasing penile nitric oxide content and exerting vasodilatory effects with the least impact on reproductive function [32-33]. Consequently, nebivolol is recommended as the preferred β -blocker for hypertensive men during preconception [34].

Diuretics impair fertility through various mechanisms. Thiazides reduce penile blood flow causing erectile dysfunction, while spironolactone, a weak inhibitor of testosterone synthesis, reduces testosterone production by inhibiting C17 hydroxylation and may cause gynecomastia, decreased sperm motility and concentration, and reduced libido [34-36]. The mechanism by which loop diuretics affect fertility remains unclear.

ACEI/ARB effects on reproductive function are less studied. These agents block angiotensin II, which is synthesized in penile arterial and cavernous endothelial and smooth muscle cells and promotes penile vascular collagen proliferation, narrowing the lumen [30,34]. While captopril may inhibit angiotensin-converting enzyme activity released during capacitation and the acrosome reaction, slowing sperm-egg fusion, it does not significantly alter semen quality or cause male infertility [37].

CCB effects on reproductive function lack definitive evidence. Although animal

studies show that nimodipine, nifedipine, verapamil, and diltiazem may reduce sperm concentration, motility, acrosome reaction, and litter size [38], no adverse effects on fertilization or fertility have been observed in men undergoing assisted reproductive technology [34].

In summary, nebivolol, ACEIs, and CCBs are recommended as preferred agents for hypertensive men preparing for pregnancy. Additionally, smoking, alcohol consumption, obesity, sedentary lifestyle, and substance use contribute to sexual dysfunction and reduced sperm quality [30,39]. Therefore, beyond appropriate medication selection, lifestyle modification including regular exercise, balanced diet, weight reduction, and smoking cessation is essential for hypertensive men during preconception.

Summary and Outlook

Increasing life stress has contributed to the younger onset of hypertension, and China's three-child policy will lead to advanced maternal age trends, both factors elevating pregnancy-related complication risks. To reduce hypertension-related pregnancy complications and achieve optimal perinatal outcomes, enhanced blood pressure monitoring in reproductive-age couples and blood pressure control through lifestyle modification and rational antihypertensive use are imperative. Community health centers should actively provide health education, encourage preconception counseling, and implement ambulatory blood pressure monitoring when feasible, while promoting calibrated home blood pressure measurement devices to enable early screening, diagnosis, and treatment. Cardiovascular specialists should refer women with chronic hypertension to gestational hypertension experts for evidence-based preconception advice. Ultimately, multidisciplinary collaboration will optimize preconception blood pressure management and create optimal conditions for pregnancy.

Author Contributions

Tian Meixiang identified the research content, reviewed the literature, and wrote the initial draft. Zhang Zhengyi established the overall research objectives, revised and finalized the manuscript, and controlled the quality of the article.

Conflict of Interest

This article has no conflict of interest.

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