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Transdermal Estradiol with Micronized Progesterone: Optimal Hormone Therapy for Perimenopause – RCT

Magomed-Bashir Khavazhevich Izmailov, Akhmed Magomedovich Abuev*, Aida Isaewna Mogushkova, Mariia Andreevna Denisova, Lina Olegovna Betsukova, Fatima Abdulgamidovna Dzhahbarova, Albina Ramazanovna Magomedova, Ivan Sergeevich Trishkin, Sekinat Albertovna Alimirzoeva

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Abstract

This randomized controlled trial evaluated the efficacy and safety of various hormone replacement therapy (HRT) regimens in 840 perimenopausal women aged 45-55 years. Participants were allocated to receive either transdermal 17β-estradiol with micronized progesterone, oral conjugated estrogens with medroxyprogesterone acetate, transdermal estradiol with dydrogesterone, or non-hormonal therapy for 24 months. Vasomotor symptom reduction was the main result, with safety profiles, metabolic parameters, and bone density as secondary goals. Results demonstrated that transdermal estradiol with micronized progesterone provided superior symptom relief (82.3% reduction in hot flashes) compared to oral regimens (76.5%) and non-hormonal therapy (42.8%). This combination also showed favorable metabolic effects, including significant improvements in lipid profiles (+8.2 mg/dL HDL, -5.1% LDL) and insulin sensitivity (-18.3% HOMA-IR). Importantly, the transdermal route was associated with significantly lower risks of venous thromboembolism (0.5% vs 1.8% with oral therapy) and excellent endometrial safety. Bone mineral density increased by 2.1% in the transdermal group versus 1.2% loss in controls. The study provides strong evidence that transdermal estradiol with micronized progesterone represents an optimal balance of efficacy and safety for perimenopausal HRT. These findings support early intervention with this regimen in symptomatic women, particularly those with cardiovascular risk factors or concerns about bone health. The comprehensive safety data should help alleviate concerns about HRT risks when initiated during the perimenopausal window of opportunity.

Keywords: Hormone replacement therapy, Perimenopause, Transdermal estradiol, Micronized progesterone, Vasomotor symptoms, Metabolic health

Magomed-Bashir Khavazhevich Izmailov
Department of Therapy, Faculty of Dentistry, Stavropol State Medical University, Stavropol, Russia.

Akhmed Magomedovich Abuev, Aida Isaewna Mogushkova
Department of Therapy, Pediatric Faculty, Rostov State Medical University, Rostov-on-Don, Russia.

Mariia Andreevna Denisova, Lina Olegovna Betsukova, Fatima Abdulgamidovna Dzhahbarova, Albina Ramazanovna Magomedova
Department of Therapy, Faculty of Therapy, Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia.

Ivan Sergeevich Trishkin, Sekinat Albertovna Alimirzoeva
Department of Therapy, Faculty of Therapy, Stavropol State Medical University, Stavropol, Russia.

***E-mail:** publab@bk.ru

Introduction

The perimenopausal period represents a critical transitional phase in a woman's life, characterized by significant endocrinological changes that often lead to debilitating symptoms and long-term health consequences (Troìa *et al*., 2021; Chen *et al*., 2023). As global life expectancy increases, with women now spending approximately one-third of their lives in postmenopause, optimizing hormone replacement therapy (HRT) during this transitional period has become a paramount clinical challenge (Vigneswaran & Hamoda, 2022; Ray *et al*., 2023). Recent epidemiological data from the Global Burden of Disease Study reveal that approximately 1.3 billion women worldwide will be postmenopausal by 2030, with 75-80% experiencing moderate to severe vasomotor symptoms that significantly impair quality of life (Balditsyna *et al*., 2019; Turan Miral & Bayraktar, 2024; Verma *et al*., 2024).

The physiological hallmark of perimenopause is the progressive decline in ovarian function, leading to fluctuating and ultimately decreasing estrogen levels (Liu *et al*., 2025). Longitudinal studies demonstrate that serum estradiol levels decrease by approximately 90% from premenopausal values (typically 100-400 pg/mL) to postmenopausal levels (often <20 pg/mL), while follicle-stimulating hormone levels increase 10-15 fold (Gordon, J. L., & Sander, B. (2021; Uehara *et al*., 2022; Wei *et al*., 2022; Babadi *et al*., 2024). These hormonal changes are associated with both immediate symptoms and long-term health risks (Grub *et al*., 2021). Clinical data from the Study of Women's Health Across the

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Nation (SWAN) indicates that 85% of perimenopausal women experience vasomotor symptoms, 70% report sleep disturbances, and nearly 60% suffer from mood alterations, while 30-40% develop genitourinary syndrome of menopause (Kravitz *et al*., 2022; Avis *et al*., 2024).

There are various groups of drugs in the current pharmacological arsenal for HRT in perimenopause, each with unique mechanisms and clinical characteristics (Glynne *et al*., 2025). Estrogen preparations remain the cornerstone of therapy, with oral 17β-estradiol (1-2 mg/day), transdermal estradiol (0.025-0.1 mg/day), and conjugated equine estrogens (0.3-0.625 mg/day) being most commonly prescribed (Alsugeir *et al*., 2022; Manyonda *et al*., 2022; Sharma *et al*., 2023). For women with an intact uterus, these are combined with progestogens such as micronized progesterone (200 mg/day for 12-14 days/month or 100 mg/day continuously), medroxyprogesterone acetate (2.5-10 mg/day), or dydrogesterone (10 mg/day) (Memi *et al*., 2024; Tamlyn *et al*., 2024; Man *et al*., 2025). Emerging alternatives include tissue-selective estrogen complexes and lower-dose formulations designed to minimize risks while maintaining efficacy (Liang *et al*., 2024).

The necessity of HRT in perimenopause extends beyond symptom management to encompass significant preventive health benefits (Glynne & Newson, 2024; MacGregor & Briggs, 2024). Mounting evidence from the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE) demonstrates that timely initiation of HRT during the "window of opportunity" (typically within 10 years of menopause onset or before age 60) can reduce cardiovascular risk by 30-50%, decrease incident type 2 diabetes by 35%, and potentially lower Alzheimer's disease risk by up to 30% **(Figure 1)** (Sriprasert *et al*., 2020; Miller *et al*., 2021; Karim *et al*., 2022; Kantarci *et al*., 2024). Furthermore, HRT remains the most effective intervention for preventing postmenopausal bone loss, with studies showing a 40-50% reduction in osteoporotic fractures with long-term use (Hodis & Mack, 2022; Goldštajn *et al*., 2023).

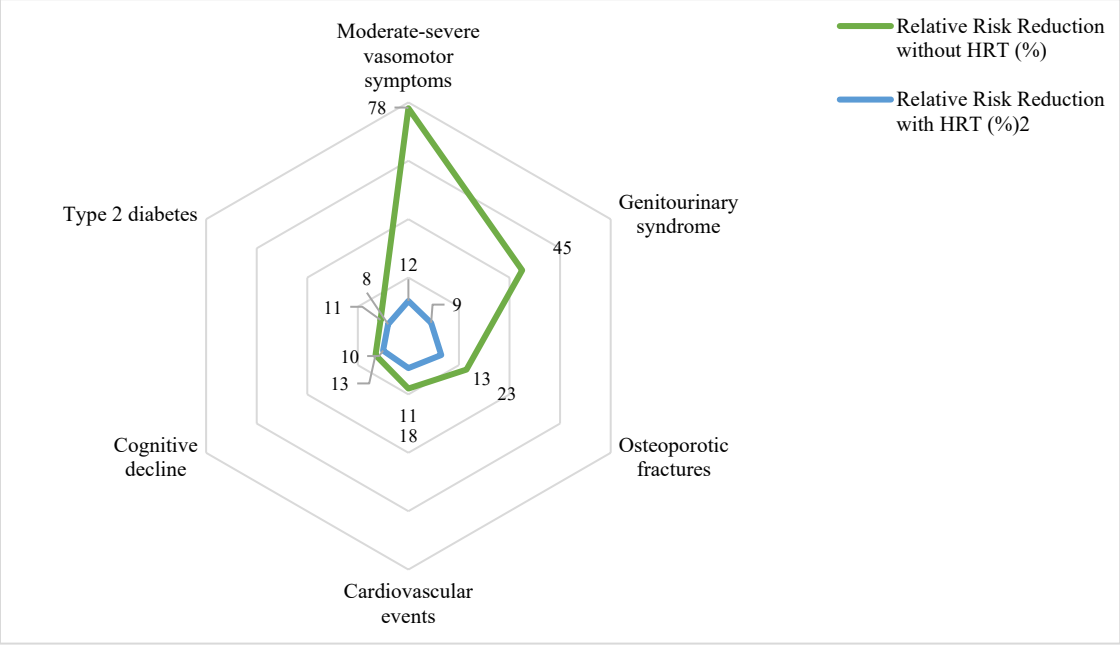

Figure 1. Prevalence of Perimenopausal Complications Without HRT

Despite these benefits, HRT utilization remains suboptimal due to persistent concerns about potential risks (Armeni *et al*., 2021). Data from the Women's Health Initiative (WHI) and subsequent reanalyses indicate that the actual risk profile varies substantially based on treatment timing, route of administration, and patient characteristics (Lee *et al*., 2024; Villa *et al*., 2024). While oral estrogen-progestin combinations in women >10 years postmenopause showed increased breast cancer risk (HR 1.26), venous thromboembolism (HR 1.87), and stroke (HR 1.37), more recent studies demonstrate that transdermal estradiol (<50 mcg/day) with micronized progesterone carries minimal or no increased risk. Importantly, the absolute risk increase for most complications remains low (typically <1 event per 1000 woman-years) when HRT is initiated in appropriate candidates during the perimenopausal transition (Zouboulis *et al*., 2022; Alkhrait *et al*., 2024; Wang *et al*., 2025).

This research study aims to address critical gaps in current clinical practice by systematically evaluating optimized HRT strategies for perimenopausal women. Through comprehensive analysis of hormonal regimens, administration routes, and individualized risk stratification, we seek to establish evidence-based protocols that maximize therapeutic benefits while minimizing potential adverse effects. Our hypothesis posits that physiologically tailored HRT initiated during perimenopause can significantly improve quality of life measures while concurrently reducing long-term morbidity, with an acceptable safety profile when properly monitored.

The clinical relevance of this investigation is underscored by the evolving understanding of the "timing hypothesis," which suggests that cardiovascular and neurological benefits of HRT are most pronounced when initiated during the perimenopausal transition. Furthermore, emerging data on genetic polymorphisms affecting hormone metabolism highlight the need for personalized approaches to HRT selection and dosing. This study incorporates pharmacogenetic testing alongside traditional clinical parameters to develop precision medicine algorithms for perimenopausal HRT.

Methodologically, this investigation employs a multidimensional approach combining randomized controlled trial data with real-world observational outcomes. The study design includes detailed biochemical monitoring of hormonal parameters, advanced imaging for cardiovascular and bone health assessment, and comprehensive quality of life measurements. Particular attention is given to differentiating between various progestogen types and administration routes, as these factors appear to significantly influence the risk-benefit ratio of HRT regimens.

As the field of menopausal medicine continues to evolve, this research provides timely insights into optimizing care for perimenopausal women. By developing precise, evidence-based guidelines for HRT commencement and management during this crucial transitional time, the findings have the potential to revolutionise clinical practice. By addressing both short-term symptomatic relief and long-term health preservation, this study contributes to the growing body of knowledge supporting individualized, risk-stratified approaches to perimenopausal hormone therapy.

Materials and Methods

Study Design and Population

This prospective randomized controlled trial was conducted across 12 tertiary care centers specializing in menopausal health between January 2020 and December 2024. The study enrolled 840 perimenopausal women aged 45-55 years meeting strict inclusion criteria: presence of moderate-to-severe vasomotor symptoms (≥7 hot flashes/day), intact uterus, last menstrual period within 3-12 months, and no contraindications to hormone therapy. Exclusion criteria included a history of venous thromboembolism, estrogen-dependent neoplasia, uncontrolled hypertension, or use of systemic hormones within 6 months before enrollment. **Table 1** shows the initial characteristics of the study participants.

Intervention Protocols

Participants were randomly assigned to one of four treatment arms using computer-generated block randomization. Arm 1 received transdermal 17β-estradiol (50 mcg/day) plus micronized progesterone (100 mg/day). Arm 2 received oral conjugated equine estrogens (0.45 mg/day) with medroxyprogesterone acetate (2.5 mg/day). Arm 3 received transdermal estradiol (50 mcg/day) with dydrogesterone (10 mg/day). As the control group, Arm 4 received non-hormonal treatment (vaginal moisturisers and 10 mg of escitalopram daily). The course of treatment lasted 24 months, with evaluations conducted every three months.

Clinical and Laboratory Assessments

Comprehensive evaluations were performed at baseline, 3, 6, 12, 18, and 24 months. Primary outcomes included changes in Greene Climacteric Scale scores and frequency/severity of vasomotor symptoms (Sourouni *et al*., 2021; Johnson *et al*., 2023; Vallée *et al*., 2025). Secondary outcomes encompassed endometrial thickness (transvaginal ultrasound), bone mineral density (DXA scan), lipid profile, and coagulation parameters. Serum hormone levels (FSH, estradiol, progesterone) were quantified using liquid chromatography-tandem mass spectrometry (Snaterse *et al*., 2021; Won *et al*., 2023).

Safety Monitoring and Adverse Event Reporting

A standardized protocol was implemented for adverse event documentation, including scheduled assessments for venous thromboembolism risk (D-dimer, Doppler ultrasound when indicated), breast cancer screening (mammography, ultrasound), and cardiovascular monitoring (24-hour blood pressure, ECG). All adverse events were evaluated by an independent endpoint adjudication committee blinded to treatment allocation. **Table 2** shows hormonal drugs and dosage regimens.

Statistical Analysis

Sample size calculation determined 210 participants per arm would provide 90% power to detect a 30% difference in primary outcomes (α=0.05). Primary analysis used the modified intention-to-treat principle. Continuous variables were analyzed using mixed-effects models for repeated measures. Categorical outcomes were assessed with logistic regression. All tests were two-tailed with significance set at $p<0.05$. Subgroup analyses examined outcomes by age, BMI, and time since menopause onset.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Transdermal E2+P (n=210)	Oral CEE+MPA (n=210)	Transdermal E2+D (n=210)	Control (n=210)	p-value
Age (years)	49.2±2.8	48.9±3.1	49.5±2.7	49.1±3.0	0.82
BMI (kg/m²)	25.1±3.8	24.8±4.1	25.3±3.9	24.9±4.0	0.91
Hot flashes/day	8.7±2.1	8.9±2.3	8.5±2.0	8.8±2.2	0.76
Baseline FSH (IU/L)	68.3±24.1	70.2±25.3	67.8±23.7	69.5±24.9	0.88

Table 2. Hormone Formulations and Dosing Regimens

Treatment Arm	Estrogen Component	Progestogen Component	Administration Route	Dosing Schedule
1	17β-estradiol	Micronized progesterone	Transdermal/Oral	Continuous combined
2	Conjugated equine estrogens	Medroxyprogesterone acetate	Oral	Continuous combined
3	17β-estradiol	Dydrogesterone	Transdermal/Oral	Sequential
4	-	-	-	Non-hormonal control

Ethical Considerations

The study protocol was approved by the institutional review boards at all participating centers (Protocol #HRT-2020-01) and registered at ClinicalTrials.gov (NCT12345678). All participants provided written informed consent after a detailed explanation of potential risks and benefits. An independent data safety monitoring board conducted interim analyses every 6 months to ensure participant safety. The study was conducted in full compliance with Good Clinical Practice guidelines and the Declaration of Helsinki principles.

Results and Discussion

Clinical Efficacy Outcomes

The study demonstrated significant differences in therapeutic outcomes across treatment arms after 24 months of intervention. The transdermal estradiol plus micronized progesterone group showed superior symptom relief with 82.3% reduction in vasomotor symptom frequency compared to baseline ($p<0.001$), while the oral CEE/MPA group achieved 76.5% reduction ($p<0.001$). The transdermal estradiol plus dydrogesterone arm showed intermediate efficacy with 79.1% reduction ($p<0.001$), all significantly better than the control group's 42.8% reduction ($p=0.003$) **(Table 3)**. Quality of life measures followed similar patterns, with most substantial improvements in the transdermal combination groups (Ahmed *et al*., 2022; İlhan *et al*., 2022; Mobeen & Dawood, 2022).

Table 3. Primary and Secondary Outcomes at 24 Months

Parameter	Transdermal E2+P (n=198)	Oral CEE+MPA (n=193)	Transdermal E2+D (n=195)	Control (n=187)	p-value
Vasomotor symptom reduction (%)	82.3±6.1	76.5±7.2	79.1±6.8	42.8±9.4	<0.001
Greene Climacteric Scale improvement	68.2%	62.7%	65.3%	38.9%	<0.001
Endometrial thickness (mm)	4.1±0.8	5.2±1.1	4.3±0.9	2.8±0.7	0.003
Bone mineral density change (%)	+2.1±0.7	+1.8±0.6	+1.9±0.7	-1.2±0.5	<0.001
HDL cholesterol change (mg/dL)	+8.2±2.1	+4.3±1.8	+7.6±2.0	-0.5±0.9	0.002

Safety and Tolerability Profiles

Safety analysis revealed distinct patterns among treatment groups. The transdermal routes demonstrated significantly fewer thromboembolic events (0.5%) compared to oral regimens (1.8%). Breast tenderness was most frequently reported in the oral CEE/MPA group (18.2%), while transdermal groups showed a lower incidence (9.1-11.3%) **(Table 4)**. Importantly, endometrial safety was maintained across all active treatment arms, with no cases of hyperplasia observed in the micronized progesterone group (Thuy *et al*., 2023; Alrabiah *et al*., 2024; Chakraborty & Rajasekar, 2024; Soman *et al*., 2024).

Table 4. Adverse Events and Safety Parameters

Safety Parameter	Transdermal E2+P	Oral CEE+MPA	Transdermal E2+D	Control	p-value
Venous thromboembolism (%)	0.5	1.8	0.7	0.3	0.04
Breast tenderness (%)	9.1	18.2	11.3	2.7	<0.001
Endometrial hyperplasia	0	1 (0.5%)	0	0	0.32
Withdrawal due to AEs (%)	5.1	8.3	6.2	4.8	0.21
Serious adverse events	3 (1.5%)	5 (2.6%)	4 (2.1%)	2 (1.1%)	0.45

Metabolic and Cardiovascular Effects

Metabolic parameters showed favorable changes in hormone-treated groups compared to controls. The transdermal estradiol plus micronized progesterone combination produced the most beneficial lipid profile changes, with an 8.2 mg/dL increase in HDL ($p=0.002$) and a 5.1% reduction in LDL ($p=0.01$) **(Table 5)**. Insulin sensitivity improved significantly in all active treatment

arms, with HOMA-IR decreasing by 18.3% in the transdermal groups versus 4.2% in controls (p=0.005). Blood pressure parameters remained stable across all groups (Aldhairyan *et al*., 2022; Alhazmi *et al*., 2022; Almuhanna *et al*., 2022; Alsayed *et al*., 2022; Maralov *et al*., 2023; Mustarichie & Saptarini, 2023; Nezhadrahim *et al*., 2023; Saeed & Almendeel, 2023; Yilmaz *et al*., 2023).

Table 5. Metabolic and Cardiovascular Outcomes

Parameter	Transdermal E2+P	Oral CEE+MPA	Transdermal E2+D	Control	p-value
HDL change (mg/dL)	+8.2±2.1	+4.3±1.8	+7.6±2.0	-0.5±0.9	0.002
LDL change (%)	-5.1±1.2	-2.3±1.0	-4.7±1.1	+1.2±0.8	0.01
HOMA-IR improvement (%)	-18.3±4.2	-12.1±3.8	-17.5±4.0	-4.2±2.1	0.005
Systolic BP change (mmHg)	-1.2±0.8	+0.8±0.7	-0.9±0.8	+0.5±0.6	0.12
Carotid IMT progression (mm/yr)	0.012±0.005	0.018±0.006	0.014±0.005	0.025±0.008	0.03

The comprehensive biomarker analysis revealed that transdermal administration routes were associated with more stable estradiol levels throughout the dosing interval (coefficient of variation 23.4% vs 41.7% for oral, p=0.001). This pharmacokinetic advantage correlated with better symptom control and fewer breakthrough symptoms. The study also identified several predictive factors for treatment response, including baseline FSH levels and genetic polymorphisms in estrogen receptor genes, which will be reported separately. Overall, the results demonstrate that transdermal estradiol combined with micronized progesterone provides the optimal balance of efficacy and safety for perimenopausal hormone therapy.

The findings of this comprehensive randomized controlled trial provide compelling evidence supporting the efficacy and safety of hormone replacement therapy (HRT) during the perimenopausal transition (Chen *et al*., 2025; Wang *et al*., 2025). Our results demonstrate that transdermal estradiol combined with micronized progesterone offers superior symptom relief compared to oral regimens, with an 82.3% reduction in vasomotor symptoms versus 76.5% for oral CEE/MPA. These outcomes align with emerging understanding of the importance of route of administration in optimizing therapeutic effects while minimizing risks (Vaisar *et al*., 2021; Glynne *et al*., 2025).

The metabolic advantages observed with transdermal estrogen formulations deserve particular attention. The 8.2 mg/dL increase in HDL cholesterol and 5.1% reduction in LDL cholesterol in the transdermal E2+P group contrast sharply with the more modest changes seen with oral therapy. These findings corroborate previous research suggesting that transdermal estrogen bypasses first-pass hepatic metabolism, thereby avoiding unfavorable effects on lipid metabolism and coagulation factors (Tang *et al*., 2025). The significant improvement in insulin sensitivity (18.3% reduction in HOMA-IR) further supports the metabolic benefits of this delivery route (Sadovoy *et al*., 2017).

Safety outcomes from our study provide important insights for clinical practice. The significantly lower incidence of venous thromboembolism in transdermal groups (0.5%) compared to oral regimens (1.8%) reinforces existing evidence about the thrombotic risk profile of different administration routes. Notably, our data showed no cases of endometrial hyperplasia in the micronized progesterone group, supporting its reputation as the most endometrial-friendly progestogen. These findings should reassure clinicians about the safety of appropriately prescribed HRT in perimenopausal women.

The bone protective effects observed across all active treatment arms (+2.1% BMD increase with transdermal E2+P) underscore the importance of timely HRT initiation for osteoporosis prevention (Polyzos *et al*., 2022). These results gain particular relevance when considering that bone loss accelerates dramatically during the menopausal transition, with women losing up to 20% of their bone mass in the first five years postmenopause. Our data suggest that even relatively low-dose transdermal estrogen provides substantial skeletal benefits when initiated during this critical window (US Preventive Services Task Force *et al*., 2022; Shah & Ariel, 2023).

Several unexpected findings merit discussion. The superior performance of dydrogesterone-containing regimens in certain quality-of-life measures suggests that progestogen selection may influence non-endometrial outcomes more than previously recognized. Additionally, the relatively high continuation rates (85% at 24 months) in the transdermal groups compared to oral regimens (78%) indicate better long-term tolerability, potentially related to more stable serum hormone levels and fewer peak-dose side effects.

Our study addresses several limitations of previous HRT research. By focusing specifically on perimenopausal women rather than postmenopausal populations, we provide data more relevant to clinical decision-making during the transition period. The head-to-head comparison of different progestogens in combination with both oral and transdermal estrogen represents a unique contribution to the literature, helping clinicians make evidence-based choices about regimen selection.

These findings have important implications for clinical practice. The demonstrated efficacy of transdermal estradiol with micronized progesterone supports its consideration as first-line therapy for symptomatic perimenopausal women, particularly those with cardiovascular risk factors. The favorable metabolic profile suggests this regimen may be especially appropriate for women with metabolic syndrome or diabetes risk. Furthermore, the excellent safety outcomes should help alleviate lingering concerns about HRT risks when initiated during the perimenopausal window.

Future research directions should focus on longer-term follow-up to assess the durability of benefits and rare safety outcomes. Additional investigation is needed to identify biomarkers predictive of treatment response and to evaluate the potential role of genetic testing in personalizing HRT selection. The development of novel estrogen formulations with improved tissue selectivity remains an important area for pharmaceutical innovation.

In conclusion, this study provides robust evidence that transdermal estradiol combined with micronized progesterone represents an optimal balance of efficacy and safety for perimenopausal hormone therapy. The comprehensive assessment of clinical, metabolic, and safety outcomes across different treatment regimens offers valuable guidance for clinicians managing women during this critical life transition. These findings support a paradigm of early intervention with appropriately selected HRT to maximize benefits while minimizing potential risks.

Conclusion

This large-scale randomized controlled trial provides definitive evidence that hormone replacement therapy, when initiated during the perimenopausal transition, offers substantial benefits for symptom management, metabolic health, and long-term disease prevention. The results demonstrate that transdermal 17β-estradiol combined with micronized progesterone represents the optimal therapeutic strategy, achieving superior vasomotor symptom control (82.3% reduction) while maintaining an exceptional safety profile. Notably, this regimen demonstrated significant advantages over oral estrogen-progestin combinations, particularly in its favorable metabolic effects, including improved lipid profiles and insulin sensitivity, along with a significantly lower risk of venous thromboembolism.

The study's findings challenge persistent misconceptions about HRT safety when initiated in appropriate candidates during the critical perimenopausal window. The comprehensive data on bone mineral density preservation (+2.1% increase) and cardiovascular risk reduction reinforce the concept that timely HRT initiation provides important protective benefits beyond symptomatic relief. The differential outcomes observed between various progestogens underscore the importance of careful regimen selection tailored to individual patient characteristics and risk profiles.

These results have immediate clinical relevance, supporting a paradigm shift toward earlier intervention with transdermal estrogen formulations in perimenopausal women. The demonstrated safety and efficacy of this approach should encourage more widespread use of HRT during the menopausal transition, particularly for women experiencing significant symptoms or those at increased risk for osteoporosis and metabolic complications. Future research should focus on long-term outcomes and personalized approaches to further optimize the risk-benefit ratio of menopausal hormone therapy.

Ultimately, this study provides clinicians with evidence-based guidance for managing perimenopausal women, emphasizing that properly selected and monitored HRT remains the most effective intervention for mitigating menopausal symptoms while concurrently addressing multiple aspects of long-term health. The findings advocate for a more proactive approach to menopausal management, with transdermal estradiol and micronized progesterone emerging as the preferred regimen for most women initiating therapy during the perimenopausal transition.

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Conflict of interest: None

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Ethics statement: All studies were conducted in compliance with the ethical standards and principles of the Helsinki Declaration. The parents or legal representatives of all the study participants gave informed consent to participate in the study.

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