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REVIEWER'S REPORT

Manuscript No.: IJAR-59676

Title: Menopausal Hormone Therapy in Perimenopause and Menopause: Indications, Benefits, Risks, and Individualized Care,

Recommendation:

Accept as it is .....

Accept after minor revision.....

Accept after major revision .....

Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality		x		
Techn. Quality		x		
Clarity			x	
Significance			x	

Reviewer's ID: JPR-142

Detailed Reviewer's Report

The manuscript addresses an important and clinically relevant topic concerning menopausal hormone therapy during perimenopause and menopause. It provides a broad overview of therapeutic indications, potential benefits, associated risks, cardiovascular considerations, breast cancer outcomes, endometrial protection, and nonhormonal alternatives. The manuscript is generally well organized, and the authors demonstrate an effort to distinguish established clinical evidence from areas of continuing uncertainty.

Major revisions are recommended regarding the transparency and reproducibility of the literature-search methodology, clarification of the manuscript's original contribution, and strengthening of the critical interpretation of clinical evidence. The authors should provide the complete search strategy and the appendix referenced in the methodology. The distinction between randomized controlled trial findings and observational evidence should be maintained consistently throughout the manuscript.

The discussion of cardiovascular outcomes, timing of hormone therapy initiation, venous thromboembolism, and breast cancer risk would benefit from stronger comparative interpretation of recent clinical guidelines. The reference list should also be carefully updated and checked, particularly where older studies support contemporary clinical recommendations.

Furthermore, the clinical applicability section should be strengthened by providing a more practical framework for individualized treatment selection, considering reproductive stage, uterine status, cardiovascular risk, contraindications, and availability of therapeutic alternatives. The discussion of treatment accessibility and regulatory considerations in Morocco also requires better contextual justification. The four tables provide useful information but require improvements in readability, consistency, and clinical interpretation. Incorporating a concise clinical decision-making algorithm or conceptual figure would substantially improve the practical value of the review.

Detailed reviewer comments

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A. General comments

The manuscript provides a broad overview of menopausal hormone therapy, addressing indications, therapeutic benefits, potential adverse effects, timing of initiation, cardiovascular considerations, breast cancer risk, endometrial protection, and nonhormonal alternatives.

The authors have made a reasonable effort to distinguish established clinical benefits from areas where evidence remains uncertain. The discussion of the Women's Health Initiative (WHI), timing hypothesis, transdermal estrogen, and individualized risk assessment is particularly relevant.

Nevertheless, the manuscript currently reads predominantly as a descriptive narrative review. Greater critical synthesis, improved methodological transparency, and stronger clinical interpretation are required to enhance its scientific contribution.

B. Major comments requiring revision

1. Literature-search methodology

The authors describe a targeted narrative review based primarily on PubMed, Cochrane summaries, and professional society recommendations. However, the search strategy is insufficiently detailed to allow independent reproducibility.

The authors should:

- Provide complete search strings for each search concept.
- Clarify the number of records identified and the approach used to select relevant publications, if documented.
- Explain the criteria used to prioritize guidelines, randomized controlled trials, systematic reviews, and observational studies.
- Provide the stated Appendix A, including search queries and selection details. It is referenced in the manuscript but is not present in the supplied nine-page document.
- Clarify how conflicting recommendations were evaluated.

The authors should retain the narrative-review designation and avoid suggesting systematic-review-level comprehensiveness.

2. Strengthen the originality and scientific contribution

The manuscript covers several established aspects of menopausal hormone therapy, but the unique contribution over existing guidelines and narrative reviews is not sufficiently articulated.

I recommend introducing a more clinically oriented synthesis integrating:

- Patient-specific risk stratification.
- Selection of estrogen formulation and route.
- Progestogen requirements according to uterine status.
- Cardiovascular and thromboembolic risk assessment.
- Monitoring and reassessment strategies.

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A practical individualized treatment framework would substantially improve the manuscript's clinical utility.

3. Improve the interpretation of cardiovascular evidence

The discussion of the timing hypothesis, ELITE, KEEPS, and cardiovascular outcomes is useful. However, the authors should more explicitly distinguish surrogate vascular outcomes from actual clinical cardiovascular events.

The comparison between ESE and IMS recommendations should also be supported by a more detailed explanation of their differing interpretations of early initiation and cardiovascular outcomes.

Avoid presenting early initiation as evidence of cardiovascular protection in individual patients.

4. Update and strengthen the reference base

Although the manuscript incorporates several recent guidelines and publications from 2024–2026, some important clinical claims rely on older evidence.

Examples include:

- Reference 13: Cochrane review on oral estrogen and combined estrogen-progestogen therapy, 2004.
- Reference 14: Local estrogen for vaginal atrophy, 2016.
- Reference 20: Hormone replacement therapy and metabolic syndrome, 2006.
- Reference 26: ESTHER study, 2007.
- Reference 27: Transdermal and oral hormone therapy and stroke, 2010.

These studies may remain relevant as foundational evidence, but the authors should incorporate more recent evidence where available and explain why older studies remain important.

5. Improve clinical applicability and treatment recommendations

The manuscript discusses several treatment options, including transdermal estradiol, micronized progesterone, levonorgestrel intrauterine devices, vaginal estrogen, fezolinetant, and elinzanetant.

However, the practical decision-making process is not sufficiently developed.

The authors should clarify how treatment choices differ according to:

- Presence or absence of a uterus.
- Perimenopause versus established menopause.
- Isolated genitourinary symptoms versus systemic vasomotor symptoms.
- Previous venous thromboembolism or cardiovascular disease.
- Breast cancer history.
- Diabetes and hypertension.
- Contraindications and availability of alternative treatments.

A concise clinical decision-making algorithm would be valuable.

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6. Clarify the applicability to Moroccan healthcare settings

The section titled Applicability to care in Morocco is relevant, but its connection to the overall manuscript requires improvement.

The authors should explain why Morocco is selected as the specific healthcare context and provide available evidence regarding local treatment accessibility, regulatory approval, affordability, and monitoring infrastructure.

If reliable national information is unavailable, the section should be presented explicitly as a discussion of implementation considerations rather than established national practice.

7. Improve the discussion of newer nonhormonal treatments

The discussion of fezolinetant and elinzanetant is relevant and contemporary. However, the authors should ensure that the safety and monitoring recommendations reflect the latest applicable prescribing information.

In particular, the elinzanetant prescribing information should be checked against its latest 2026 update, rather than relying solely on an earlier label.

8. Strengthen the conclusion

The conclusion is scientifically reasonable but mainly repeats the central message of individualized prescribing.

The authors should provide a more decisive clinical synthesis emphasizing:

- When systemic therapy is appropriate.
- When local or nonhormonal treatment is preferable.
- Why cardiovascular prevention and diabetes prevention should not be independent indications.
- The importance of periodic reassessment and shared decision-making.

C. Minor comments

1. Ensure that all abbreviations are defined at their first occurrence.
2. Standardize the terminology for menopausal hormone therapy (MHT) and hormone replacement therapy (HRT).
3. Check consistency in the presentation of relative risks, odds ratios, hazard ratios, confidence intervals, and units.
4. Ensure that all tables have consistent formatting and readable text.
5. Improve the readability of Tables 1–4, particularly the dense content in Tables 2 and 4.
6. Verify that every table citation corresponds to the appropriate reference in the main text.
7. Correct and standardize reference formatting, including journal names, volume, issue, page numbers, publication dates, and DOI links.
8. Reference 34 should clearly indicate its May 2025 amendment.
9. Reference 37 should provide the direct URL to the relevant FDA safety communication rather than a general drug-safety webpage.
10. Ensure that the final manuscript includes all appendices mentioned in the text.

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