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REVIEWER'S REPORT

Manuscript No.: JNHM- 165

Title: Efficacy of Individualized Homoeopathic Intervention in Functional Ovarian Cysts: A Systematic Review of Clinical Evidence with Emphasis on Ultrasonographic Outcomes,

Recommendation:

Accept after minor revision

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

Reviewer's Name: Bilqees Hamza

Detailed Reviewer's Report

The manuscript presents a systematic review evaluating clinical evidence published between 2015 and 2025 regarding the efficacy of Individualized Homoeopathy in treating functional ovarian cysts, focusing specifically on objective pre- and post-intervention ultrasonographic outcomes.

The primary conclusion of the review is that while individual case reports document post-treatment cyst resolution on ultrasound, the existing literature **fails to demonstrate causal efficacy**. This is due to critical design limitations in the primary sources—most notably the complete absence of concurrent control groups to account for the natural spontaneous regression of functional cysts.

2. Methodological & Synthesis Appraisal

Strengths

- **PRISMA Alignment:** The review explicitly applies PRISMA reporting principles (Figure 1), tracking records from initial database identification ($n=18$) down to final qualitative synthesis ($n=4$).
- **Appropriate Handling of Meta-Analysis:** The authors correctly refrained from constructing a pooled treatment-effect meta-analysis or statistical diamond. Aggregating small, uncontrolled case series (Figure 2) would create a mathematically misleading representation of efficacy.
- **Distinction Between Resolution and Causation:** The manuscript clearly differentiates between *observed post-treatment changes* (report-level findings) and *proven therapeutic efficacy* (causal inference).

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Methodological Weaknesses & Areas for Expansion

- **Extremely Restricted Sample Size:** The final synthesis relies on only 4 studies encompassing 13 total patients (Das et al., $n=3$; Banerjee & Basu, $n=1$; Rath et al., $n=5$; Bappa et al., $n=4$). The authors briefly mention excluding an earlier 2011 observational study ($n=73$) due to the 2015–2025 window restriction. The paper would benefit from a sensitivity analysis comparing the current 10-year window against broader historical data.
- **Inconsistent Cyst Classification:** The review notes that included studies frequently mixed *functional/simple* cysts (follicular, corpus luteum) with *complex* or unspecified benign cysts. The authors must emphasize this diagnostic ambiguity more strongly in their Risk of Bias evaluation, as non-functional cysts follow completely different natural histories.

3. Clinical & Scientific Risk-of-Bias Evaluation

The manuscript accurately identifies four major sources of bias that degrade the certainty of evidence to **Very Low** under GRADE criteria:

1. **Natural History & Spontaneous Regression (Primary Confounder):** Simple/functional cysts are physiological products of regular ovarian function that naturally resolve within 1 to 3 menstrual cycles (8–12 weeks, as recognized by O-RADS and SRU guidelines). Without a placebo or observation arm, spontaneous healing cannot be separated from remedy effect.
2. **Selection & Publication Bias:** Uncontrolled case series systematically suffer from reporting bias—clinicians publish striking successes while unresolved or worsened cases remain unreported.
3. **Lack of Imaging Standardization:** Primary studies failed to utilize blinded central radiologist reviews, fixed follow-up intervals, or standardized 3D volumetric calculations (relying instead on inconsistent 2D maximum diameter measurements).
4. **Safety & Adverse Event Ascertainment:** The included reports failed to prospectively track adverse events, emergency surgical interventions, or disease progression.

4. Constructive Recommendations for Manuscript Improvement

To elevate the manuscript for formal journal publication, the authors should address the following points:

- **Formalize Risk of Bias Tooling:** Replace generic Risk of Bias commentary with a standardized assessment tool tailored for uncontrolled observational data (such as the **JBI Critical Appraisal Checklist for Case Series** or **CARE guidelines**).
- **Expand Proposed RCT Protocol Parameters:** Section 4 outlines recommendations for future trial designs. Expand Table 3 to explicitly state exact primary diagnostic criteria (e.g., O-RADS

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Category 2 simple cysts $<6\text{ cm}$), explicit follow-up timepoints ($8\text{ to }12\text{ weeks}$), and statistical power calculations needed for future double-blind RCTs.

- **Refine Terminology Standardization:** Ensure clear operational definitions throughout the text distinguishing between **Complete Resolution** (total absence on imaging), **Partial Response** (pre-defined % diameter reduction), and **Spontaneous Involution**.

5. Final Review Verdict

Recommendation: Accept with Major Revisions

The review addresses an important clinical gap in complementary medicine evaluation. Its primary thesis—that objective ultrasound documentation in case reports is insufficient to prove causal efficacy without randomized controls—is scientifically sound and clinically essential. Incorporating a standardized appraisal checklist (like JBI) and expanding on diagnostic classification boundaries will render this manuscript ready for publication.