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Analysis of the effectiveness and influencing factors of Bushen Huoxue formula in treating diminished ovarian reserve

A retrospective cohort study

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Abstract

Diminished ovarian reserve (DOR) is characterized by reduced ovarian follicle quantity and quality, contributing to female infertility. While hormone replacement therapy (HRT) is commonly used, its efficacy is limited and associated with adverse effects. Traditional Chinese medicine (TCM), using multi-target herbal formulations that may support ovarian function through endocrine modulation and microcirculatory improvement, has shown promise in improving ovarian function, though high-quality clinical evidence remains scarce. This study evaluates the efficacy of the Bushen Huoxue Formula in treating DOR and to identify predictors of treatment response. This retrospective cohort study included 122 DOR patients allocated to 3 groups: HRT (n = 32), combined HRT and TCM (n = 32), and TCM alone (n = 58). The primary outcome was the change in anti-Müllerian hormone (ΔAMH) levels after 3 months. Nonparametric tests assessed intergroup differences. Spearman correlation and a generalized linear model were used to evaluate associations between baseline factors and ΔAMH. Subgroup analyses were conducted by age, AMH level, and parity. Compared with the HRT group, both the TCM and combined groups showed significantly greater AMH improvements (generalized linear model: $B = 0.300$ and 0.270, respectively; both $P < .001$). Parity was a negative predictor of ΔAMH ($B = -0.123$, $P = .009$), while age, baseline AMH, and T4 were not independently associated. Subgroup analyses showed greater treatment effects in patients < 40 years, nulliparous, and with baseline AMH > 0.2 ng/mL ($P = .007$–<0.001). Bushen Huoxue Formula, either alone or combined with HRT, significantly improves AMH in DOR patients, particularly in younger, nulliparous women with moderate ovarian reserve. These findings support the use of TCM as a potential strategy to enhance ovarian function.

Abbreviations: AFC = antral follicle cunt, AMH = anti-Müllerian hormone, ART = assisted reproductive technology, BHF = Bushen Huoxue formula, BMI = body mass index, DHEA = dehydroepiandrosterone, DOR = diminished ovarian reserve, E2 = estradiol, FSH = follicle-stimulating hormone, GLM = generalized linear model, HPO = hypothalamic-pituitary-ovarian axis, HRT = hormone replacement therapy, IQR = interquartile range, LH = luteinizing hormone, RCT = randomized controlled trial, SLE = systemic lupus erythematosus, T3 = triiodothyronine, T4 = thyroxine, TCM = traditional Chinese medicine, TSH = thyroid-stimulating hormone.

Keywords: Bushen Huoxue formula, diminished ovarian reserve, effectiveness, hormone replacement therapy, influencing factors, retrospective study, traditional Chinese medicine

1. Introduction

Diminished ovarian reserve (DOR) is a major challenge in reproductive medicine, characterized by a decline in the quantity and quality of ovarian follicles, ultimately impairing female fertility potential.[1,2] This condition imposes both physiological and psychological burdens on affected individuals and has growing public health implications.[3–5] In recent years, the incidence of DOR has risen significantly, particularly among younger women under 40, underscoring the need for early identification and effective intervention strategies.[6,7] DOR has a complex and multifactorial etiology, involving genetic predispositions, autoimmune diseases, environmental exposures, medical interventions and age-related decline.[8–10] Pathological DOR implies a significantly premature and accelerated process.[11,12] Molecular mechanisms such as oxidative stress, mitochondrial

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dysfunction, and impaired DNA repair have been implicated in its progression.[11,13–16]

Clinically, treatment options for DOR are limited. While hormone replacement therapy (HRT) can partially alleviate perimenopausal symptoms, it does not significantly improve oocyte quality or fertility outcomes, and its long-term use poses health risks.[17–20] There is thus an urgent need for the exploration of safer and more effective alternative or adjunctive therapeutic approaches.

Traditional Chinese medicine (TCM), with its emphasis on holistic regulation and individualized therapy, has shown potential in DOR treatment. According to TCM theory, DOR is closely related to kidney and blood stasis. Furthermore, treatment strategies often focus on modulating endocrine function and enhancing microcirculation, which are believed to improve endocrine function, microcirculation, and follicular development through multi-target mechanisms.

Although some preliminary studies suggest that TCM may improve ovarian reserve indicators and pregnancy outcomes,[21–23] high-quality clinical evidence remains insufficient, limiting its broader acceptance in modern reproductive medicine.

To address this gap, we conducted a retrospective cohort study to evaluate the real-world clinical effectiveness of a traditional Chinese herbal formula designed to support ovarian function and improve microcirculation in patients with DOR. We compared ovarian reserve indicators (AMH, FSH) between groups receiving different treatment strategies and explored factors influencing treatment efficacy. Our findings of TCM into comprehensive DOR management and to inform future prospective research.

2. Methods

2.1. Study population

2.1.1. Diagnostic criteria: DOR was diagnosed based on a serum AMH level of <1.1 ng/mL, with antral follicle count of fewer than 7 as a supplementary reference.[24] Serum AMH levels were measured using the Elecsys® AMH assay (Roche Diagnostics GmbH, Mannheim, Germany) on the Cobas 8000 platform, based on the electrochemiluminescence immunoassay (ECLIA) method.

2.1.2. Inclusion criteria: Participants were eligible for inclusion if they met the following criteria:

1. Women aged between 20 and 45 years;
2. Diagnosis of DOR as defined above;
3. No current or recent fertility plans (no active attempts to conceive within the past 6 months).

2.1.3. Exclusion criteria: Participants were excluded if they met any of the following conditions:

1. Pregnant or breastfeeding;
2. Hisrory of immune dysfunction (e.g., due to radiotherapy, chemotherapy, AIDS, or systemic lupus erythematosus);
3. Use of medications known to improve ovarian response, such as coenzyme Q10 or dehydroepiandrosterone (DHEA), during the study period. Patients with a history of assisted reproductive technology (ART) treatment were not excluded. Both multiparous and nulliparous women were included in the study population.

2.2. Ethical statement

This study was approved by the Ethics Committee of Dongfang Hospital, Beijing University of Chinese Medicine (Approval No. JDF-IRB-2025050402; approved in March 2025). Patients were recruited from the gynecology outpatient clinic of Dongfang Hospital between January 2021 and December 2024. All participants provided informed consent for their medical records to be used for research purposes. Patient data were anonymized and handled with strict confidentiality throughout the study.

2.3. Exposure variables

The exposure variable in this study was the treatment regimen, classified into 3 groups. Patients were grouped based on the actual treatment regimens they received during routine clinical care, as documented in their electronic medical records. Treatment decisions were made collaboratively between physicians and patients. Therefore, group allocation was not randomized but reflected real-world clinical practice. The HRT group received HRT alone, comprising oral estradiol (1 mg/day) and progesterone (10 mg/day) starting on the fifth day of the menstrual cycle, administered for 21 consecutive days followed by a 7-day drug-free interval, in repeated 28-day cycles for 3 months. The Combined group received both HRT and a TCM intervention, the Bushen Huoxue Formula (BHF) (composed of Dipsaci Radix, Taxilli Herba, Cuscutae Semen, Angelicae Sinensis Radix, Paeoniae Rubra Radix, Salviae Miltiorrhizae Radix et Rhizoma, Cyperi Rhizoma, Rosae Chinensis Flos, Asini Corii Colla granules, Astragali Radix, Poria, and Curcumae Radix), administered as a daily dose divided into morning and evening portions, half an hour after meals, with suspension during menstruation. The detailed composition of the BHF is provided in Table S1, Supplemental Digital Content, https://links.lww.com/MD/P436. The TCM group received the BHF alone, following the same administration protocol as the combined group. Throughout the treatment period, patients in all groups were instructed to avoid strenuous exercise, restrict alcohol intake, and undergo regular hormonal monitoring. The rationale for establishing the combined group was based on the research hypothesis that the BHF would serve as the main therapeutic component for improving the core symptoms of DOR, while HRT would act as a supportive auxiliary treatment.

Subsequent efficacy analyses focused on examining the independent contribution of the BHF and evaluating potential synergistic or antagonistic effects within the combined intervention.

Potential confounding factors included age, body mass index (BMI), smoking and alcohol consumption histories, menstrual duration and cycle length, age at menarche, gravidity, parity, baseline AMH level, thyroid function parameters (TSH, T3, T4), ovarian reserve-related hormones (FSH, LH, E2), and histories of chronic pelvic inflammatory disease and ovarian surgery.

2.4. Follow-up protocol

Follow-up evaluations were conducted via structured telephone interviews at predefined intervals, specifically 3 months following the completion of treatment. Clinical outcomes were obtained from electronic medical records, while intervention adherence was assessed through patient self-reports. To minimize attrition bias, standardized operating procedures were implemented: at each follow-up time point, participants were contacted by telephone up to 3 times, supplemented by 2 reminder text messages if necessary; inclusion in the final analysis required the completion of at least 2 assessment points, including the baseline evaluation; and participants lost to follow-up were excluded from the statistical analyses.

2.5. Outcome measures

The primary outcome measure was the change in AMH levels (ΔAMH) 3 months after the completion of the treatment cycle. Secondary outcome measures included levels of 6 sex hormones.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk). The normality of continuous variables was assessed using the

Kolmogorov–Smirnov test, which indicated that these variables were not normally distributed. Consequently, nonparametric methods were used. Continuous variables among the 3 treatment groups were compared using the Kruskal–Wallis *H* test, while paired comparisons before and after treatment within groups were analyzed with the Wilcoxon signed-rank test. Categorical variables were compared using the Chi-squared (χ^2) test.

Associations between baseline characteristics and the changes in AMH (ΔAMH) were analyzed according to variable type: Spearman rank correlation was applied for continuous variables (e.g., age, BMI, TSH, gravidity, parity, etc); the Mann–Whitney *U* test was used for binary categorical variables (e.g., smoking status, alcohol use, thyroid disease history, etc); and the Kruskal–Wallis *H* test was used for categorical variables with more than 2 categories (e.g., menstrual blood volume).

The treatment group, as the primary exposure variable, was included in a multivariate generalized linear model (GLM) to assess its independent effect on ΔAMH, adjusting for age, BMI, and baseline TSH. To assess potential multicollinearity among covariates, particularly between age and reproductive history variables (e.g., parity), we calculated the variance inflation factor. All variance inflation factor (VIF) values were below 2, with age and parity both showing values around 1.131, indicating no significant collinearity. This suggests that age maintained statistical independence from other included variables and was therefore retained as an independent predictor in the multivariate model. Subgroup analyses stratified by age (<40 vs ≥40 years), baseline AMH level (≤0.2 ng/mL vs >0.2 ng/mL), and parity (nulliparous vs parous) were performed to explore treatment effect heterogeneity. Interaction plots were generated to visually assess potential differences in treatment effects across subgroups.

All tests were 2-sided, and $P < .05$ was considered statistically significant. Effect sizes, including 95% confidence intervals and partial eta-squared (η^2), were reported for GLM analyses and significant group comparisons.

3. Results

3.1. Study flow and baseline characteristics

Among the 239 patients who met the study's inclusion criteria, 47 were excluded due to nonadherence to the medication protocol, and 70 were excluded for incomplete follow-up data. Ultimately, 122 patients were included in the final analysis: 32 received HRT alone, 32 received combined HRT and the TCM compound intervention (BHF), and 58 received the TCM compound treatment alone (Fig. 1). Except for T4 levels, no statistically significant differences were observed among the groups in terms of demographic characteristics, lifestyle factors, medical history, or reproductive health indicators ($P > .05$) (Table 1).

3.2. Analysis of treatment effects

3.2.1. Intragroup changes in AMH levels:. Wilcoxon signed-rank tests were conducted to assess within-group changes in AMH levels before and after treatment. In the HRT group, the median AMH level decreased significantly from 0.335 ng/mL (IQR: 0.095–0.608) to 0.110 ng/mL (IQR: 0.020–0.455) (W = 80.000, $Z = -2.426$, $P = .015$, $R = 0.43$). In the combined group, the median AMH level increased significantly from 0.220 ng/mL (IQR: 0.090–0.395) to 0.375 ng/mL (IQR: 0.160–0.740) (W = 480.500, $Z = 4.050$, $P < .001$, $R = 0.72$). Similarly, in the TCM group, the median AMH level rose significantly from 0.370 ng/mL (IQR: 0.200–0.700) to 0.610 ng/mL (IQR: 0.270–0.910) (W = 1164.500, $Z = 3.634$, $P < .001$, $R = 0.49$) (Fig. 2A).

3.2.2. Analysis of FSH/LH ratio:. No significant changes in the FSH/LH ratio were observed before and after treatment in any of the 3 groups (all $P > .05$, Wilcoxon signed-rank test) (Fig. 2B).

3.2.3. Intergroup comparison of ΔAMH:. The Kruskal–Wallis *H* test identified significant differences in ΔAMH among the 3 groups ($H = 26.340$, $P < .001$). Post hoc comparisons using Bonferroni-corrected Dunn tests showed that the median ΔAMH in the combined group (0.130 [IQR: 0.060–0.310]) was significantly higher than that in the HRT group (–0.080 [IQR: –0.240–0]) ($Z = -4.680$, corrected $P < .001$). Similarly, the TCM group demonstrated a significantly greater improvement (0.090 [IQR: 0–0.290]) compared with the HRT group ($Z = -4.390$, corrected $P < .001$). No significant difference was observed between the Combined and TCM groups ($Z = 0.923$, corrected $P = 1.000$) (Fig. 2C).

3.3. Exploration of influencing factors

3.3.1. Univariate analysis: associations between baseline characteristics and ΔAMH:. Nonparametric tests were employed to evaluate associations between baseline variables and ΔAMH. Among continuous variables (assessed by Spearman rank correlation analysis), age ($r = -0.188$, $P = .038$) and parity ($r = -0.259$, $P = .004$) were significantly negatively correlated with ΔAMH, indicating that older age and higher parity may attenuate the improvement in ovarian reserve following treatment. In contrast, BMI ($r = -0.042$), menstrual parameters (menstrual duration: $R = 0.116$; menstrual cycle length: $r = -0.043$), thyroid function indicators (T3–TSH: *r* ranging from 0.038 to –0.066), and metabolic markers (ALT, AST, GLU: *r* ranging from –0.024 to 0.014) were not significantly associated with ΔAMH (all $P > .05$).

For categorical variables, the treatment group demonstrated a highly significant association with ΔAMH ($H = 26.340$, $P < .001$, $\varepsilon^2 = 0.216$), consistent with findings from intergroup comparisons (Section 3.2). No significant associations were observed for menstrual blood flow ($H = 0.682$), behavioral factors (smoking: $U = 0.000$; alcohol consumption: $U = 0.207$), or historical disease characteristics (history of thyroid disease: $U = 0.701$; history of pelvic surgery: $U = 0.153$ to 0.615) (all $P > .05$).

These results suggest that treatment modality was the primary determinant of ΔAMH, while age and parity emerged as key negative predictors (Table 2).

3.3.2. Multivariate regression analysis:. To identify independent factors associated with ΔAMH, a GLM was constructed using an identity link function and assuming a normal distribution for the dependent variable. The model demonstrated a good fit, as indicated by a significant Omnibus test ($\chi^2 = 32.533$, degrees of freedom = 6, $P < .001$), suggesting that the included variables collectively explained a significant portion of the variance in AMH changes.

Among the covariates, treatment group and parity emerged as significant predictors. Compared with the HRT group (reference category), both the TCM group ($B = 0.300$, 95% CI: 0.179–0.421, $P < .001$) and the Combined group ($B = 0.270$, 95% CI: 0.130–0.410, $P < .001$) exhibited significantly greater improvements in AMH levels, indicating that patients receiving the BHF, either alone or in combination with HRT, achieved superior enhancement of ovarian reserve compared with those receiving HRT alone.

Additionally, parity was negatively associated with ΔAMH ($B = -0.123$, 95% CI: –0.216 to –0.031, $P = .009$), suggesting that women with a history of childbirth exhibited relatively lower improvements in AMH. In contrast, age, baseline AMH (AMH_pre), and T4 levels were not significantly associated with ΔAMH (all $P > .05$) (Table 3).

3.4. Subgroup analysis

Through subgroup analyses (Table 4) and visualization of interaction plots (Fig. 3), this study systematically evaluated how

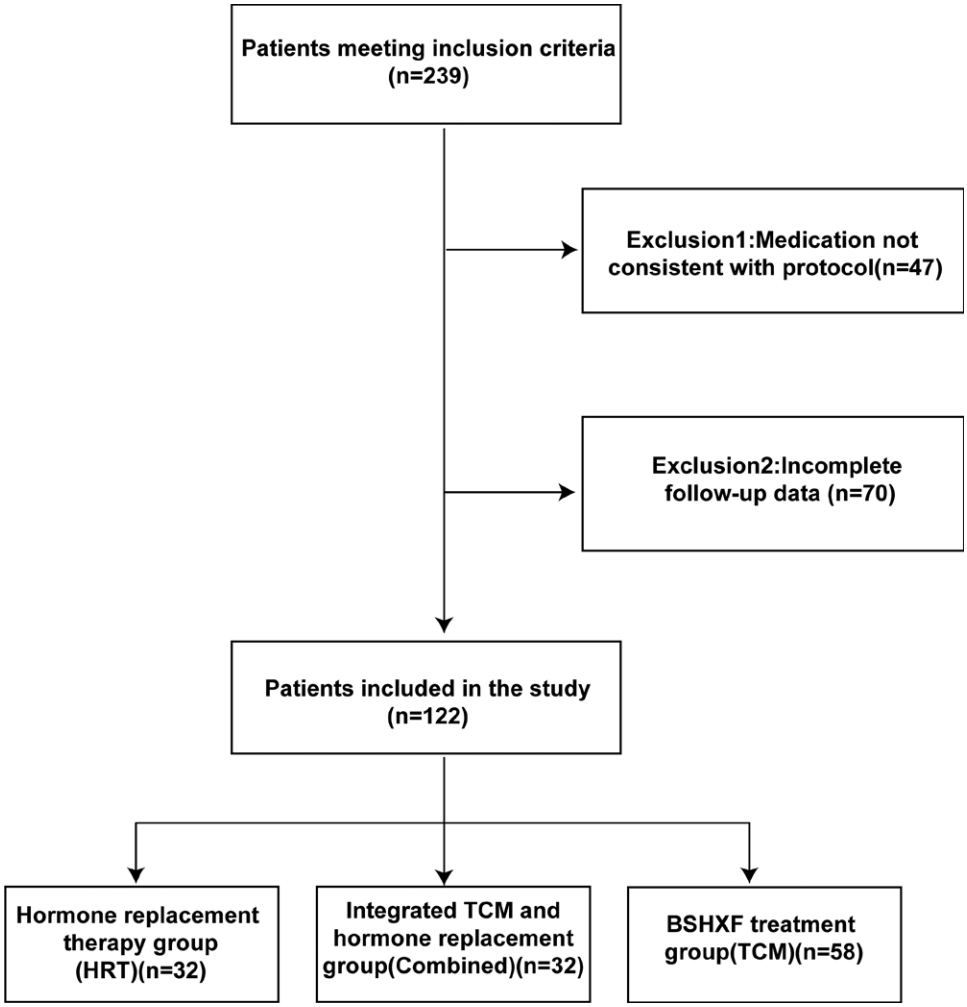

Figure 1. Flowchart of workflow. A total of 239 patients met the initial inclusion criteria. Following exclusion of 47 patients due to nonadherence to the medication regimen and 70 patients due to incomplete follow-up data, 122 patients were included in the final analysis. Participants were allocated into 3 groups: HRT alone (n = 32), combined HRT and TCM compound intervention (BHF) (n = 32), and TCM compound intervention alone (n = 58). BHF = Bushen Huoxue formula, HRT = hormone replacement therapy, TCM = Traditional Chinese medicine.

baseline characteristics moderated the effects of different treatment regimens. Age, baseline ovarian reserve status, and parity significantly influenced therapeutic outcomes.

Among patients aged < 40 years, both the TCM group (ΔAMH = 0.175 ± 0.317) and the combined group (ΔAMH = 0.266 ± 0.206) exhibited significant increases in AMH levels, while the HRT group showed a decline (ΔAMH = −0.124 ± 0.229) (P = .007, partial η^2 = 0.189).

In patients aged ≥ 40 years, although the improvements were slightly attenuated compared with younger patients, the TCM and Combined groups still demonstrated significantly greater benefits compared to HRT alone (P = .003, partial η^2 = 0.170).

Among patients with a baseline AMH > 0.2 ng/mL (indicating relatively preserved ovarian reserve), the nonhormonal treatments (Combined group:ΔAMH = 0.219 ± 0.258; TCM group: ΔAMH = 0.178 ± 0.372) were significantly more effective than HRT (ΔAMH = −0.187 ± 0.280) (P < .001, partial η^2 = 0.209). In contrast, among patients with baseline AMH ≤ 0.2 ng/mL (severely DOR), no significant differences in ΔAMH were observed among the 3 groups (P = .088).

Subgroup analysis based on parity showed that among nulliparous women, both the TCM (ΔAMH = 0.230 ± 0.376) and Combined (ΔAMH = 0.218 ± 0.202) groups achieved significantly better outcomes compared to the HRT group (ΔAMH = −0.101 ± 0.258) (P < .001, partial η^2 = 0.194). However, among parous women, no significant differences were detected across the 3 groups (P = .237).

Interaction plots further illustrated that the subgroup comprising patients aged < 40 years, nulliparous, and with baseline AMH > 0.2ng/mL derived the greatest benefit from nonhormonal interventions (Fig. 3A–C). These findings highlight the importance of considering age, fertility desire, and baseline ovarian reserve status in developing individualized treatment strategies.

4. Discussion

This retrospective cohort study aimed to assess the impact of the BHF either alone or in combination with HRT on the AMH levels of patients with DOR and to explore relevant influencing factors. The core findings of the study revealed that compared to the HRT group, patients treated with BHF (TCM group) or BHF combined with HRT (combined group) showed a significant and clinically meaningful improvement in AMH levels after treatment (GLM analysis: TCM group B = 0.300, P < .001; combined group B = 0.270, P < .001, both compared to the HRT group). This advantage was particularly pronounced in certain subgroups of patients. This discussion will focus on the key findings of the study, discussing their potential mechanisms, clinical significance, as well as the strengths and limitations of

Table 1

Baseline characteristics of patients by treatment groups.

Characteristic	HRT (n = 32)	Combined (n = 32)	TCM (n = 58)	*P*-value
Age (yr)	41.50 (37.00–44.00)	39.00 (35.50–42.00)	40.50 (36.00–43.00)	.151
BMI (kg/m^2)	22.86 (19.57–25.33)	21.49 (19.76–23.99)	21.71 (19.81–25.63)	.841
Menstrual duration (d)	5 (5–7)	5 (5–6)	5 (5–7)	.881
Menstrual cycle length (d)	28 (26–30)	28 (25.5–30)	28 (25–30)	.844
Menarche (yr)	14 (13–15)	14 (12–15)	14 (13–15)	.556
Menstrual blood flow				
Normal	11	13	29	.85
Reduced by 1/3	16	13	21	
Reduced by 1/3	4	5	7	
Spotting	1	1	1	
Gravidity	1 (0–2)	1 (0–2)	1 (0–2)	.313
Parity	0 (0–1)	1 (0–2)	0 (0–1)	.156
FSH (baseline) (mIU/mL)	11.65 (7.79–20.63)	10.80 (8.11–17.95)	10.75 (7.60–13.60)	.549
LH (baseline) (mIU/mL)	5.39 (3.87–10.05)	4.74 (3.64–7.96)	4.84 (3.40–7.22)	.696
E2 (baseline) (pg/mL)	48.45 (29.45–81.75)	41.30 (22.15–83.30)	47.45 (30.60–92.50)	.588
PRL (baseline) (mIU/mL)	232.00 (124.50–282.00)	223.50 (14.64–358.40)	245.45 (110.09–391.00)	.340
P (baseline) (ng/mL)	0.25 (0.21–0.46)	0.32 (0.20–0.50)	0.38 (0.24–0.73)	.119
T (baseline) (ng/dL)	15.10 (8.56–25.80)	12.60 (0.81–22.85)	13.00 (0.62–25.30)	.616
AMH (baseline) (ng/mL)	0.34 (0.09–0.62)	0.22 (0.09–0.41)	0.37 (0.20–0.70)	.074
T3 (ng/dL)	104.00 (89.40–116.00)	113.00 (100.49–131.00)	106.00 (87.60–119.00)	.056
T4 (ng/dL)	7.53 (6.65–8.40)	8.46 (7.30–10.08)	7.70 (6.77–8.97)	.038*
FT3 (pg/mL)	2.82 (2.55–3.20)	3.02 (2.60–3.18)	2.91 (2.61–3.19)	.784
FT4 (ng/dL)	1.27 (1.14–1.36)	1.17 (1.11–1.31)	1.25 (1.08–1.34)	.422
TSH (Miu/mL)	2.36 (1.75–3.23)	2.07 (1.74–3.13)	2.07 (1.74–2.62)	.771
ALT (U/L)	13.45 (10.60–19.95)	15.60 (11.85–20.90)	15.15 (12.60–21.90)	.633
AST (U/L)	16.75 (14.85–21.30)	18.00 (15.70–22.30)	18.95 (15.50–21.80)	.692
GLU (mmol/L)	5.21 (5.01–5.56)	5.17 (4.68–5.56)	5.22 (4.95–5.54)	.599
CREA (μmol/L)	60.75 (54.65–67.70)	57.80 (51.75–65.30)	58.65 (54.60–64.10)	.465
Smoke				
No	29	31	52	.470
Yes	3	1	6	
Alcohol				
No	23	28	47	.286
Yes	9	4	11	
Thyroid disease history				
No	30	31	55	.840
Yes	2	1	3	
History of hysteroscopic				
No	21	22	41	.884
Yes	11	10	17	
History of laparoscopic surgery				
No	27	29	49	.687
Yes	5	3	9	

The table presents the general demographic characteristics, lifestyle factors, medical history, and reproductive health-related indicators for the 3 treatment groups: HRT group, combined group, and TCM group. Comparisons were made between the groups and *P*-values were derived using the Kruskal–Wallis *H* test for continuous variables and the Chi-square test for categorical variables. No significant differences were found between the groups in terms of age, BMI, menstrual duration, or hormonal levels ($P > .05$). A significant difference in T4 levels was observed across the groups ($P = .04$). Additionally, menstrual blood flow and lifestyle factors (including smoking, alcohol consumption, and thyroid disease) showed no significant differences ($P > .05$).

ALT = alanine aminotransferase, AMH = anti-Müllerian hormone, AST = aspartate aminotransferase, BMI = body mass index, CREA = creatinine, E2 = estradiol, FSH = follicle-stimulating hormone, FT3 = free triiodothyonine, FT4 = free thyroxine, GLU = glucose, HRT = hormone replacement therapy, LH = luteinizing hormone, PRL = prolactin, TCM = Traditional Chinese medicine, TSH = thyroid-stimulating hormone.*$P < .05$.

the research, in combination with existing literature and theoretical frameworks.

4.1. Potential mechanisms of BHF in improving ovarian reserve

The most striking finding of this study was that BHF (whether used alone or combined with HRT) significantly outperformed HRT in improving AMH levels. It is noteworthy that the AMH levels in the HRT group actually showed a statistically significant decline after treatment ($P = .015$), which aligns with the general understanding that HRT, primarily aimed at supplementing exogenous hormones to alleviate symptoms of low estrogen, is unlikely to reverse substantial ovarian reserve depletion.[25,26] In contrast, the TCM and Combined groups saw a significant increase in AMH, suggesting that BHF may have the potential to directly or indirectly improve ovarian reserve function and delay follicular depletion.

From a TCM perspective, DOR is thought to result from systemic deficiencies and impaired internal circulation, which are believed to disrupt reproductive and endocrine functions.[27] The BHF adheres to the therapeutic principles of enhancing systemic vitality and improving blood flow. Ingredients in BHF, such as Cortex Eucommiae, Sang Ji Sheng, and Tu Si Zi, aim to support neuroendocrine regulation and may help regulate the function of HPO axis, thereby stabilizing the endocrine environment.[28,29] Additionally, blood-invigorating herbs like Angelica Sinensis are used to improve the microcirculation in the pelvis and ovaries, increase local blood supply and nutrition, and eliminate metabolic waste products.[30,31] Modern pharmacological research suggests that several active components in BHF (such as flavonoids,

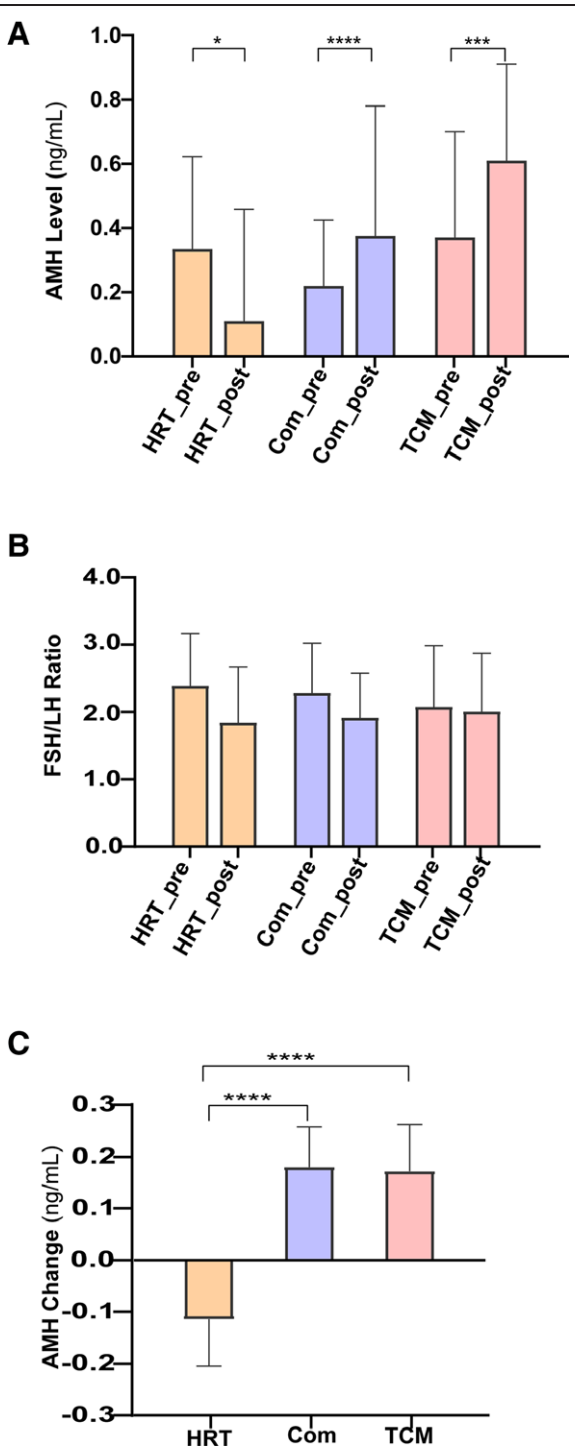

Figure 2. Changes in AMH levels and FSH/LH ratios before and after treatment across the 3 groups. (A) Intragroup changes in AMH levels before and after treatment. The HRT group showed a significant decrease in median AMH levels ($P = .015$), while both the combined group and the TCM group exhibited significant increases (both $P < .001$). (B) Intragroup changes in FSH/LH ratio before and after treatment. No significant changes were observed in any of the 3 groups (all $P > .05$). (C) Intergroup comparisons of ΔAMH. The Combined group and the TCM group demonstrated significantly greater improvements in ΔAMH compared with the HRT group (both corrected $P < .001$), with no significant difference between the combined and TCM groups (corrected $P = 1.000$). Statistical analyses were performed using Wilcoxon signed-rank tests for intragroup comparisons and Kruskal–Wallis H tests with Bonferroni-corrected Dunn post hoc tests for intergroup comparisons. AMH = anti-Müllerian hormone, FSH = follicle-stimulating hormone, HRT = hormone replacement therapy, LH = luteinizing hormone, TCM = Traditional Chinese medicine.

Table 2

Statistical associations between baseline variables and ΔAMH.

Variable	Statistical method	Test statistics (r, H, or, U)	P-value
Age (yr)	Spearman correlation	−0.188	.038*
BMI (kg/m^2)	Spearman correlation	−0.042	.647
Menstrual duration (d)	Spearman correlation	0.116	.202
Menstrual cycle length (d)	Spearman correlation	−0.043	.636
Menarche (yr)	Spearman correlation	−0.003	.975
Gravidity	Spearman correlation	−0.165	.069
Parity	Spearman correlation	−0.259	.004**
T3 (ng/dL)	Spearman correlation	0.038	.679
T4 (ng/dL)	Spearman correlation	0.053	.564
FT3 (pg/mL)	Spearman correlation	0.013	.890
FT4 (ng/dL)	Spearman correlation	−0.081	.373
TSH (Miu/mL)	Spearman correlation	−0.066	.468
ALT (U/L)	Spearman correlation	−0.024	.793
AST (U/L)	Spearman correlation	−0.023	.798
GLU (mmol/L)	Spearman correlation	−0.013	.886
CREA (μ mol/L)	Spearman correlation	0.014	.882
Treatment group	Kruskal–Wallis H test	26.340	<.001***
Menstrual blood flow	Mann–Whitney U test	0.682	.877
Smoke	Mann–Whitney U test	0.000	1.000
Alcohol	Mann–Whitney U test	0.207	.649
Thyroid disease history	Mann–Whitney U test	0.701	.402
History of hysteroscopic	Mann–Whitney U test	0.153	.696
History of laparoscopic surgery	Mann–Whitney U test	0.615	.433

P-values are derived from Spearman's rank correlation (for continuous variables), Kruskal–Wallis H test (for categorical variables with more than 2 groups), or Mann–Whitney U test (for binary categorical variables), as appropriate. ε^2 (Epsilon squared) was reported as the effect size for Kruskal–Wallis tests.

ALT = alanine aminotransferase, AMH = anti-Müllerian hormone, AST = aspartate aminotransferase, BMI = body mass index, GLU = glucose, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid-stimulating hormone. *$P < .05$.**$P < .01$.*** $P < .001$.

polysaccharides, and alkaloids) may exert multi-target synergistic effects, such as antioxidant stress, reduction of free radical damage to follicles and granulosa cells, anti-inflammatory actions to improve the ovarian microenvironment, inhibition of granulosa cell apoptosis to protect existing follicles, and even regulation of signaling pathways related to follicle growth and development, such as PI3K/Akt and MAPK pathways.[32–36] This multi-faceted, holistic regulatory characteristic may be key to BHF's superior performance in improving AMH compared to the single-mechanism approach of HRT. In our study, the therapeutic effect of the Combined group was similar to that of the TCM group ($P = 1.000$), suggesting that BHF might be the main driver of improving AMH, while HRT in the combined regimen may play a more supportive role in stabilizing cycles or co-improving symptoms, rather than directly enhancing AMH.

4.2. Analysis of key factors influencing therapeutic efficacy

Through multivariate GLM analysis, this study accurately identified key factors influencing the improvement in AMH levels. Parity was confirmed as an independent negative predictor of AMH change ($B = –0.123$, $P = .009$), suggesting that women with a history of childbirth might have a relatively lower ovarian reserve responsiveness to treatment. This could be attributed to the cumulative depletion of ovarian function during pregnancy and childbirth processes, leading to further reduction of the follicular pool or diminished sensitivity to interventions.[37] Furthermore, although both age and parity were initially considered related, multicollinearity diagnostics confirmed that their effects were statistically independent. The significant negative association between parity and ΔAMH persisted even after adjusting for age, suggesting a distinct biological mechanism potentially linked to cumulative ovarian exposure and reproductive history.

Table 3

Multivariable GLM for predictors of AMH change (dependent variable: ΔAMH).

Variable	*B* estimate	SE	95% CI lower	95% CI upper	Wald χ^2	*P*-value
Intercept	0.029	0.251	−0.463	0.522	0.014	.907
Group						
HRT (reference)	–	–	–	–	–	–
Combined	0.270	0.071	0.130	0.410	14.436	<.001
TCM	0.300	0.062	0.179	0.421	23.699	<.001
Age (yr)	0.000	0.006	−0.012	0.012	0.001	.975
Parity	−0.123	0.047	−0.216	−0.031	6.805	.009
AMH_pre (ng/mL)	−0.100	0.083	−0.262	0.062	1.459	.227
T4 (nmol/L)	−0.008	0.005	−0.019	0.002	2.587	.108

The GLM was constructed using an identity link function and assuming a normal distribution for the dependent variable (ΔAMH). The treatment group was included as a fixed factor, with the HRT group as the reference. Age, parity, baseline AMH level, and baseline T4 level were included as covariates. A significant Omnibus test ($\chi^2 = 32.533$, degrees of freedom = 6, $P < .001$) indicated good model fit. *B*: regression coefficient; 95% CI: 95% confidence interval.

AMH = anti-Müllerian hormone, CI = confidence interval, , GLM = generalized linear model, HRT = hormone replacement therapy, SE = standard error, TCM = traditional Chinese medicine.

Table 4

Comparison of ΔAMH among three intervention groups across different subgroups (GLM adjusted for b and T4).

Subgroup	Group	N	ΔAMH (mean ± SD, ng/mL)	*P*-value†	Partial η^2
Age < 40 years	HRT	10	−0.124 ± 0.229	.007**	0.189
	Combined	18	0.266 ± 0.206		
	TCM	25	0.175 ± 0.317		
Age ≥ 40 years	HRT	22	−0.110 ± 0.264	.003**	0.170
	Combined	14	0.069 ± 0.183		
	TCM	33	0.169 ± 0.370		
Baseline AMH ≤ 0.2 ng/mL	HRT	13	−0.008 ± 0.150	.088	0.120
	Combined	15	0.135 ± 0.156		
	TCM	15	0.152 ± 0.266		
Baseline AMH > 0.2 ng/mL	HRT	19	−0.187 ± 0.280	<.001***	0.209
	Combined	17	0.219 ± 0.258		
	TCM	43	0.178 ± 0.372		
Parity = 0	HRT	20	−0.101 ± 0.258	<.001***	0.194
	Combined	27	0.218 ± 0.202		
	TCM	40	0.230 ± 0.376		
Parity ≥ 1	HRT	12	−0.137 ± 0.245	.237	0.092
	Combined	5	−0.028 ± 0.187		
	TCM	18	0.041 ± 0.222		

P-values are derived from general linear models adjusted for baseline AMH and T4 levels.

AMH = anti-Müllerian hormone, GLM = generalized linear model, HRT = hormone replacement therapy, TCM = traditional Chinese medicine.

† *P*-values indicate the significance of the treatment effect within each subgroup.

** $P < .01$.

*** $P < .001$.

Although age showed a negative correlation with ΔAMH in univariate analysis ($P = .038$), it did not reach statistical significance after adjustment for other covariates in the GLM model ($P = .975$). While age was not an independent predictor in the multivariate analysis, subgroup analyses indicated that age acts as a moderating factor influencing the magnitude of treatment effects. In subgroups stratified by age (<40 years and ≥ 40 years), both the TCM and Combined groups demonstrated significant superiority over the HRT group ($P = .007$ and $P = .003$, respectively), with slightly higher effect sizes (Partial η^2) observed in the younger subgroup. This indicates that although BHF benefits patients across different age ranges, younger patients may derive greater benefit, consistent with the biological principle that earlier intervention during ovarian aging yields better outcomes.

Similarly, although baseline AMH level was not a significant predictor of ΔAMH in the GLM analysis ($P = .227$), when used as a stratification factor, it significantly moderated the treatment effects. Among patients with baseline AMH > 0.2 ng/mL (indicative of relatively better ovarian reserve), the advantages of the TCM and Combined groups were highly significant ($P < .001$, Partial $\eta^2 = 0.209$). However, among those with baseline AMH ≤ 0.2 ng/mL (indicative of severely DOR), intergroup differences did not reach statistical significance ($P = .088$). This strongly suggests that the therapeutic efficacy of BHF may depend on the presence of a sufficient quantity or functional capacity of residual follicles or granulosa cells as a basis for action. When ovarian reserve is extremely depleted, the effectiveness of any intervention may be substantially diminished, a phenomenon often referred to as the "floor effect."

4.3. Clinical implications and recommendations for individualised treatment

The findings of this study carry important clinical implications. Firstly, they provide objective evidence supporting BHF as an effective treatment option for DOR, particularly in improving the key biomarker AMH. Secondly, the results of the subgroup analyses highlight the necessity for individualized treatment strategies. For patients aged under 40 years, with no history of childbirth (Parity = 0), and a baseline AMH > 0.2 ng/mL, BHF monotherapy or combined therapy with HRT should be prioritized, as these patients are expected to achieve significantly greater improvements in AMH compared with HRT alone. This group typically has a stronger fertility desire and relatively better ovarian responsiveness, and BHF may improve their ovarian

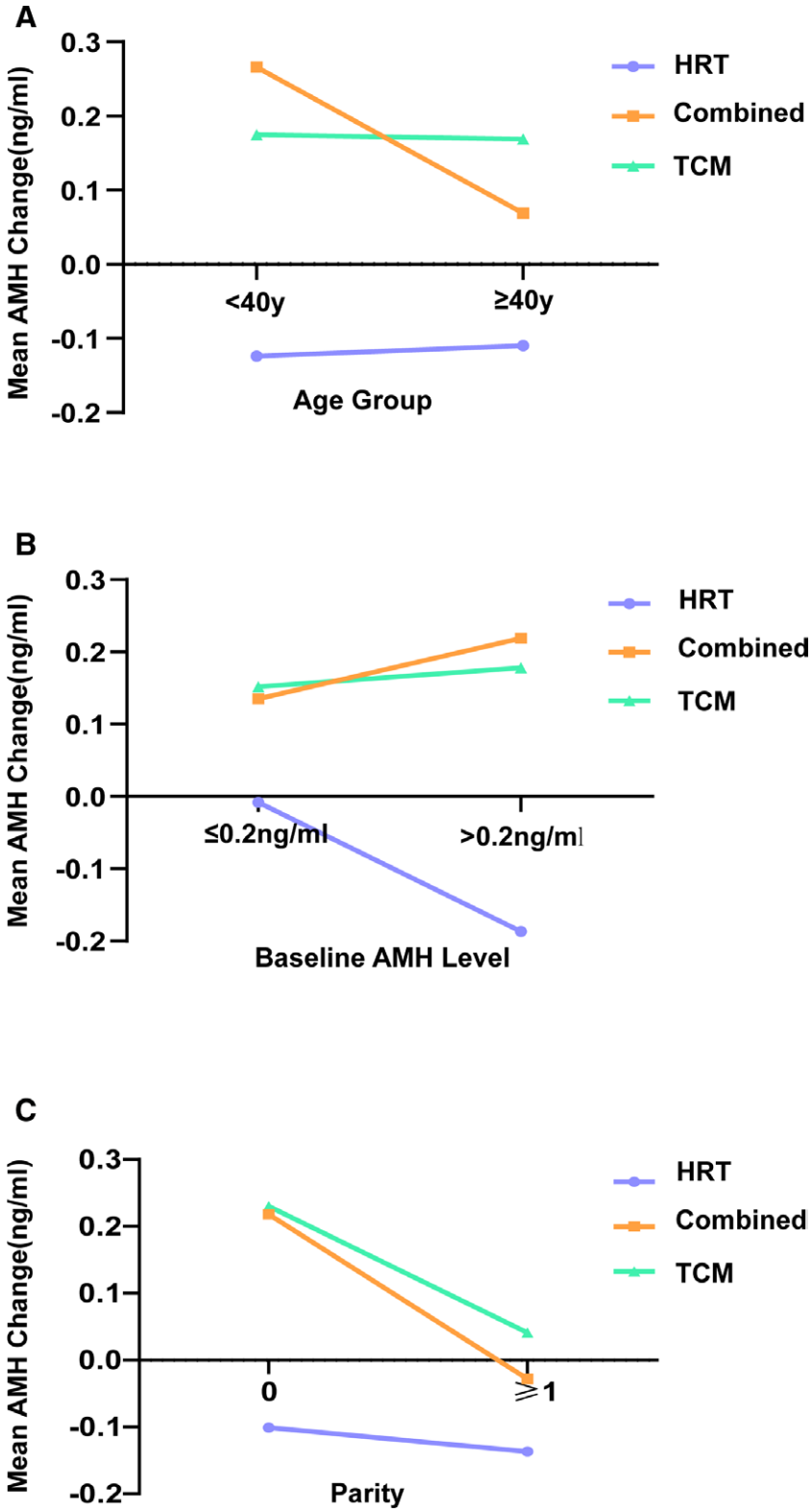

Figure 3. Interaction plot of subgroup analysis: moderating effect of baseline characteristics on treatment efficacy. This plot illustrates the interaction effects of different subgroups (based on age, ovarian reserve status, and parity) on treatment outcomes (ΔAMH). The results indicate that patients under 40 years of age, with baseline AMH > 0.2 ng/mL, and nulliparous women showed significant improvements in AMH levels with nonhormonal treatments (TCM and combined groups). In patients aged ≥ 40 years and those with baseline AMH ≤ 0.2 ng/mL, there were smaller differences in treatment effects, suggesting that individualized treatment strategies should prioritize factors such as age, fertility desires, and baseline ovarian reserve. AMH = anti-Müllerian hormone, TCM = Traditional Chinese medicine.

microenvironment and follicular quality, thus creating more favorable conditions for subsequent natural conception or ART treatments.

For patients who are older, have a history of childbirth, or present with extremely low baseline AMH levels, although the relative advantage of BHF diminishes or becomes nonsignificant,

the fact that the TCM and Combined groups still showed either improvement or a less pronounced decline in AMH compared with the HRT group suggests that BHF remains a potential therapeutic option. Particularly within a combined treatment strategy, it may exert auxiliary or quality-of-life enhancing effects. In these patients, treatment expectations should be carefully assessed, and thorough communication is warranted.

Additionally, although baseline T4 levels differed significantly between groups ($P = .04$), GLM analysis indicated that T4 was not an independent predictor of AMH change ($P = .108$). Nevertheless, the clinical impact of thyroid function on ovarian function should not be overlooked,[38–42] and future studies should explore potential interactions between thyroid status and the therapeutic efficacy of BHF.

4.4. Research strengths and limitations

This study possesses several notable strengths: it employed a retrospective cohort design, incorporating real-world clinical data, thereby conferring good external validity; the inclusion of an HRT control group and a combined treatment group allowed for direct comparison of different intervention strategies; the application of GLM models to control for confounding factors, coupled with detailed subgroup analyses, enabled in-depth exploration of heterogeneity in treatment effects and provided a basis for individualized therapeutic recommendations; the primary outcome measure, AMH, is internationally recognized as one of the gold standards for assessing ovarian reserve.

However, this study also has some limitations: the retrospective design inherently carries the risk of selection and information biases, for example, patient compliance data relied partly on self-report; the relatively limited sample size (n = 122), particularly in certain subgroups, may have affected statistical power; longer-term outcomes and direct impacts on reproductive endpoints, such as clinical pregnancy rates and live birth rates, were not assessed; there was no stratification by TCM syndrome types, which may have masked variations in efficacy across specific TCM patterns; the composition of the BHF was fixed, precluding exploration of the effects of dose adjustments or modifications in herbal components; not all potential confounding factors were accounted for, such as detailed nutritional status and environmental exposure histories.

4.5. Future research directions

Building on the findings and limitations of this study, future research should prioritize the design of large-scale, multicentre, RCTs to further validate the efficacy and safety of BHF in treating DOR, explore its underlying molecular mechanisms using advanced techniques such as metabolomics, proteomics, and single-cell sequencing, integrate more comprehensive outcome measures including antral follicle count and oocyte quality assessments, investigate the influence of different TCM syndromes or DOR subtypes on treatment efficacy, and assess the potential synergistic effects of combining BHF with ART technologies to optimize fertility strategies for DOR patients.

5. Conclusion

The results of this study demonstrate that BHF, whether used alone or in combination with HRT, confers significant advantages in improving AMH levels among patients with DOR, outperforming HRT monotherapy. Treatment modality and patients' reproductive history were identified as key factors influencing the extent of AMH improvement, with BHF showing particularly pronounced efficacy in younger patients (<40 years), those with higher baseline AMH levels, and those without previous childbirth.

This study provides new clinical evidence supporting the use of TCM interventions for DOR and suggests that such approaches may help delay ovarian functional decline and improve fertility potential. Future research should aim to validate these findings through prospective, multicentre, randomized controlled trials, clarify the long-term impact on reproductive outcomes, and further explore strategies for optimizing individualized treatment.

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