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Hyperbaric oxygen therapy for male infertility: a systematic review and meta-analysis on improving sperm quality and fertility outcomes

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Abstract

Hyperbaric oxygen therapy has emerged as a potential adjunctive treatment for male infertility, as it targets various sperm abnormalities and improves fertility outcomes. This systematic review and meta-analysis synthesized data from randomized controlled trials to evaluate the efficacy of hyperbaric oxygen therapy in treating male infertility. A comprehensive literature search identified nine eligible studies, which were assessed for quality using the Jadad scale and analyzed for heterogeneity. The meta-analysis revealed significant improvements in sperm survival, density, morphology, normal sperm rates, and motility following hyperbaric oxygen therapy, with an increased clinical pregnancy rate. Subgroup analyses based on infertility etiology and treatment duration further elucidated the heterogeneity of male infertility stemming from the etiology of infertility. Despite the high robustness of the meta-analysis results, the study is limited by the small number of included trials and potential publication bias. In conclusion, when combined with conventional treatments, hyperbaric oxygen therapy significantly enhances sperm parameters and fertility, underscoring its role as an effective adjunctive therapy for male infertility.

Key Words: asthenospermia; chronic bacterial prostatitis; hyperbaric oxygen; idiopathic male infertility; male infertility; meta-analysis; oligospermia; sperm; teratospermia; varicocele

Introduction

Hyperbaric oxygen therapy (HBOT) refers to a medical technique that involves inhaling pure oxygen or high-concentration oxygen under high-pressure conditions to treat hypoxic and ischemic diseases. The first hyperbaric chamber was produced in 1860, and in the same year, it was successfully utilized to treat carbon monoxide poisoning.[1] This therapy has undergone significant improvements over the years and has become an important adjunctive treatment in clinical practice because of its noninvasive nature, high safety profile, ease of operation, and minimal side effects. It is widely applied in the treatment of various conditions, including inflammation, immune disorders, and even depression.[2-5] Approximately 15% of couples worldwide experience infertility, with approximately 50% of these cases attributed to male factors.[6] Traditionally, procreation is regarded as a crucial component of marriage; thus, male infertility can lead to emotional detachment between partners and create a tense family atmosphere, potentially resulting in the dissolution of the marriage.

The etiology of male infertility is complex and includes abnormalities in sperm quantity, motility, and function, such as azoospermia, oligospermia, asthenozoospermia, and teratozoospermia. Additionally, conditions such as varicocele can lead to impaired testicular function, whereas idiopathic male infertility remains without a clear cause. Given this complexity, the treatment of male infertility in clinical practice is diverse. The pharmacological treatment of male infertility primarily relies on antioxidants (such as vitamin E and L-carnitine), hormone therapy (including gonadotropins and testosterone), and antimicrobial agents targeting sperm abnormalities caused by urogenital infections. The mechanism of action of antioxidants involves reducing oxidative stress damage to sperm, thereby improving sperm motility; however, their efficacy is limited, and they are mainly applicable to mild to moderate sperm abnormalities. Hormone therapy functions by regulating the hypothalamic–pituitary–gonadal axis, which can ameliorate oligospermia and asthenozoospermia due to endocrine disorders. Nonetheless, this approach is only suitable for endocrine-related sperm abnormalities, with limited effectiveness against organic causes. Furthermore, the use of hormones inevitably leads to potential side effects, such as the suppression of endogenous gonadal function. Antimicrobial agents are specifically indicated for sperm abnormalities resulting from infections, but prolonged antibiotic use may lead to the development of resistance.[7-12] In the context of surgical interventions for male infertility, varicocele repair via varicocelectomy is a specific procedure aimed at addressing varicocele. However, this technique necessitates a high level of technical skill and equipment support, resulting in prolonged surgical duration and significant costs for patients. Additionally, assisted reproductive technologies such as *in vitro* fertilization, intracytoplasmic sperm injection, and microdissection testicular

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sperm extraction are primarily indicated for cases of severe oligospermia and asthenozoospermia. Although assisted reproductive technologies have resolved numerous issues associated with male infertility, they are associated with high financial burdens and potential physical trauma. Furthermore, the implications of possible genetic abnormalities in embryos warrant further investigation.[13-16] Common pharmacological interventions include antioxidants such as vitamin E, coenzyme Q10, L-carnitine, and selenium.[7-9] Surgical options, such as varicocele ligation and microdissection testicular sperm extraction, are also employed on the basis of specific vascular pathologies.[13,14] Considering the positive outcomes observed with HBOT in various diseases, clinical applications have begun to explore its use as an adjunctive treatment for male infertility, yielding promising results. However, the literature is limited in sample size, and there is considerable variability in study design and efficacy assessment criteria. Consequently, there is currently insufficient evidence from randomized controlled trials to substantiate these findings. This study aims to conduct a systematic review and meta-analysis of the available research to provide evidence-based recommendations for the clinical use of HBOT as an adjunctive treatment for male infertility.

Data and Methods

Literature search

The protocol complies with the PRISMA 2020 guidelines (Additional file 1) and was registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (registration No. INPLASY2024120101) on December 24, 2024. A comprehensive search was conducted in the following databases: Cochrane, PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), VIP, and WanFang Data. Additionally, other sources, such as nondatabase publications released by traditional media, were also considered. The search period was extended from the establishment of the database until December 2024. The keywords used included oligospermia, azoospermia, asthenospermia, teratospermia, male infertility, and HBOT.

Inclusion and exclusion criteria for the literature

The inclusion criteria were as follows: (1) clinical data collected through randomized controlled trials; (2) a clear diagnosis of male infertility, such as oligospermia, asthenospermia, and teratospermia; (3) a treatment approach involving the use of HBOT either as a standalone treatment or in conjunction with other modalities, such as pharmacological or surgical interventions. The control group, on the other hand, received treatment through either pharmacotherapy or surgical procedures alone; and (4) language was restricted to Chinese and English.

The exclusion criteria were as follows: (1) duplicate studies, review articles, animal experiments, case reports, etc.; (2) studies from which the required data could not be obtained and for which the authors could not be contacted; and (3) studies involving subjects taking antitumor drugs, antiepileptic medications, or other substances that may adversely affect spermatogenesis and sperm motility.

Data extraction: Two authors independently conducted an initial screening of all study titles and abstracts to exclude irrelevant citations. In cases of disagreement between the two reviewers, a third researcher made the final judgment, and the third researcher's decision was considered authoritative. The specific screening process is detailed in **Figure 1**. The key indicators for data extraction included the authors, publication year, and the means and standard deviations of various treatment parameters for both the treatment and control groups (e.g., sperm density, motility, viability, sperm abnormality rate, and pregnancy rates). The two researchers assessed the quality of the included studies on the basis of the Jadad scale,[17] and the results were visualized via Stata software (Version 16.0, Stata Corp., College Station, TX, USA). According to the Jadad scale, studies were categorized as low quality (0–2 points) or high quality (3–5 points).

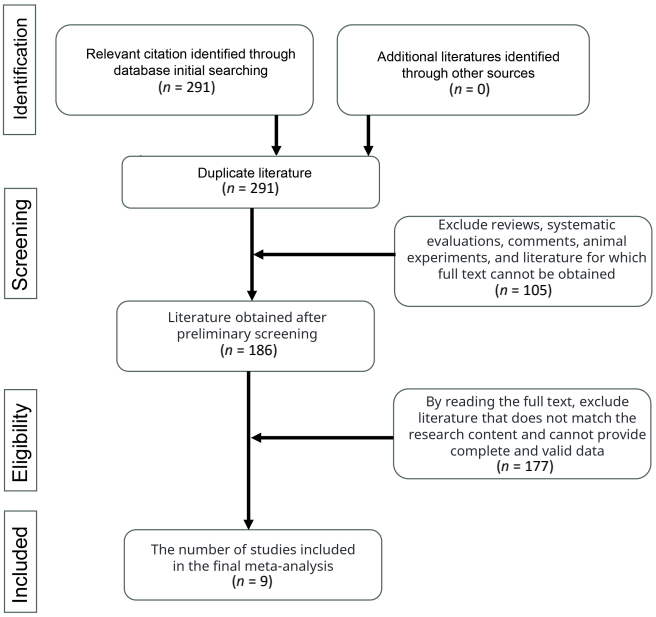

Figure 1 | Flowchart of the literature selection process for hyperbaric oxygen therapy in the treatment of male infertility.
The literature search was conducted across multiple databases, including Cochrane, PubMed, Web of Science, CNKI, VIP, and WanFang Data. Additionally, other sources, such as nondatabase publications released by the media, were also considered.

Statistical analysis

Data processing and analysis were conducted via Stata 16.0 software. The *Q* test and I^2 statistic were employed to assess the heterogeneity among studies. When $P > 0.1$ and $I^2 < 50\%$, there was good homogeneity among the results of the studies, and a fixed-effects model was utilized. Conversely, if $P \leq 0.1$ and/or $I^2 \geq 50\%$, heterogeneity among the results may be present, leading to the selection of a random effects model to mitigate heterogeneity and enhance the credibility of the findings. Continuous data are represented as weighted mean differences (WMDs) with corresponding 95% confidence intervals (95% *CI*s), whereas categorical data are expressed as risk ratios with 95% *CI*s. Subgroup analyses were performed to reduce heterogeneity. A funnel plot was used to assess the potential for publication bias. Sensitivity analyses were conducted by systematically excluding individual studies to observe whether the results significantly changed, thereby evaluating the robustness of the findings.

Results

Study selection and characteristics

A comprehensive search across multiple databases yielded a total of 291 articles related to HBOT for male infertility. After excluding duplicates, review articles, and studies that could not be accessed, a total of nine articles were ultimately included in the meta-analysis. The selection process is illustrated in **Figure 1**. The basic data of the included studies are summarized in **Table 1**. Information regarding the duration of the disease is presented in **Additional Table 1**. The quality assessment was conducted via the Jadad scale, and the risk of bias evaluation is presented in **Additional Figure 1**.

Table 1 | Basic characteristics of the literature on hyperbaric oxygen therapy for male infertility

Study	Year	Number	Age (yr)	Measures of intervention	Cause of infertility	Therapy course (mon)	Outcome indicator	Jadad score	Abstinence time
Wang et al.[20]	2002	Intervention group: 19 Control group: 19	30.5±3.6 (27–42)	Intervention group: Usual care + HBO Control group: Usual care	Asthenozoospermia	4	①②③④⑥	2	/
Zheng et al.[18]	2006	Intervention group: 32 Control group: 51	26±4 (21–38)	Intervention group: Antibiotic + HBO Control group: Antibiotic	CBP	6	①③⑥	3	5–7 d
Zheng et al.[23]	2006	Intervention group: 56 Control group: 40	Intervention group: 28±5 (24–38) Control group: 27±4 (24–37)	Intervention group: Spermatovenous ligation + HBO Control group: Spermatovenous ligation	VC	1	①②③⑤⑥	3	5–7 d
Jin et al.[22]	2007	Intervention group: 40 Control group: 40	Intervention group: 28±5 (23–38) Control group: 29±6 (22–40)	Intervention group: Spermatovenous ligation + HBO Control group: Spermatovenous ligation	VC	1	①③	3	5 d
Zhang et al.[25]	2007	Intervention group: 37 Control group: 37	31.5 (22–41)	Intervention group: Spermatovenous ligation + HBO Control group: Spermatovenous ligation	VC	3	①②⑤	3	4–5 d
Zheng et al.[21]	2013	Intervention group:96 Control group: 84	27±5 (21–44)	Intervention group: Pentoxifylline, Vitamin E + HBO Control group: Pentoxifylline, Vitamin E	Idiopathic male infertility	3	①②③⑤⑥	3	5–7 d
Metelev et al.[26]	2015	Intervention group: 30 Control group: 60	Intervention group: 28.8 ± 12.2 Control group: 29.3±10.5	Intervention group: IVF + HBO Control group: IVF	Idiopathic male infertility	2	⑥	3	/
Yuan and Zheng[19]	2016	Intervention group: 68 Control group: 68	31.2 (26–44)	Intervention group: Usual care + HBO Control group: Usual care	Asthenozoospermia	6	①②③④⑥	2	/
Özgök Kangal and Özgök[24]	2021	Intervention group: 9 Control group: 9	35.4±6.9	Intervention group: Spermatovenous ligation + HBO Control group: Spermatovenous ligation	VC	6	①	3	/

① Sperm density; ② sperm motility; ③ sperm viability rate; ④ sperm abnormality rate; ⑤ normal sperm rate; and ⑥ pregnancy rate. CBP: Chronic bacterial prostatitis; HBO: hyperbaricoxygentherapy; IVF: *in vitro* fertilization; VC: varicocele.

Results of the meta-analysis

Diagnostic results analysis

The analysis of sperm survival rates following HBOT in the treatment of male infertility included a total of six studies,[18-23] yielding a WMD of 22.99 (95% *CI*: 14.91–31.07, $P < 0.01$; **Figure 2A**). These results indicate that HBOT significantly enhances the viability of male sperm. For sperm density, eight studies[18-25] were included, resulting in a WMD of 14.90 (95% *CI*: 11.92–17.88, $P < 0.01$; **Figure 2B**). These results indicate that HBOT significantly enhances sperm density in males. The analysis of the sperm abnormality rate included two studies,[19,20] with a WMD of –16.79 (95% *CI*: –18.31 to –15.28, $P < 0.01$; **Figure 2C**), and the results indicate that treatment with HBO significantly improved the morphology of male sperm. For normal sperm rates, three studies[21,23,25] were analyzed, yielding a WMD of 15.34 (95% *CI*: 9.70–20.97, $P < 0.01$; **Figure 2D**), and the results indicate that HBOT significantly increases the number of normal sperm in males. The analysis of sperm motility included five studies,[19-21,23,25] with a WMD of 23.91 (95% *CI*: 18.53–29.29, $P < 0.01$; **Figure 2E**), and the results indicate that treatment with HBO significantly increases the motility of normal sperm in males. Finally, the clinical pregnancy rate, which was based on six studies,[19-21,23,25,26] demonstrated a risk ratio of 3.45 (95% *CI*: 1.38–8.73, $P < 0.01$; **Figure 2F**), and the results indicate that treatment with HBO significantly increased the clinical cure rate (pregnancy rate) in males.

Except for the sperm abnormality rate, all the other metrics exhibited heterogeneity among the included studies, suggesting the use of a random effects model for meta-analysis. The sperm abnormality rate was analyzed via a fixed effects model. These results indicate that HBOT significantly improves sperm survival, density, morphology, normal sperm rates, and motility while also increasing the clinical pregnancy rate in the treatment of male infertility.

Subgroup analysis

Given the high heterogeneity observed in the diagnostic results, it is essential to conduct a subgroup analysis to further explore the sources of this heterogeneity. Subgroup analyses were performed on the basis of the etiology of infertility and the duration of treatment for various indicators. Although heterogeneity was significantly reduced for sperm density and sperm viability, some heterogeneity remained (I^2 = 51% and 69%, respectively). Subgroup analyses based on the "sperm motility" and "normal sperm rate" indicators both effectively reduced heterogeneity ($I^2 < 50\%$), indicating that the etiology of infertility is a source of heterogeneity for these two indicators. The outcome measure of the sperm morphology rate could not be subjected to subgroup analysis because of the limited number of studies included in the review. The results of heterogeneity across each subgroup are displayed in **Table 2**, while the effect sizes for each subgroup are illustrated in **Additional Figure 2**.

Sensitivity analysis and publication bias assessment

A sensitivity analysis was conducted via a leave-one-out approach, whereby each study was sequentially excluded to perform a reanalysis of the remaining studies in the meta-analysis. The results indicated that there were no significant changes in outcomes before and after the exclusion of individual studies, suggesting that the meta-analysis results possess a high degree of robustness. Given that funnel plots rely heavily on visual assessment for detecting publication bias, the Egger and Begg methods were employed for evaluation. The analysis revealed varying degrees of publication bias in terms of sperm density, sperm motility, sperm viability, treatment metrics, and pregnancy rate metrics ($P > 0.05$), indicating a potential risk of bias in the publication of this meta-analysis. Owing to the insufficient number of included studies for other treatment metrics, a publication bias analysis was not performed for those indicators.

Discussion

The causes of male infertility are diverse. These conditions include conditions such as varicocele, which affects spermatogenesis in the testes; obstructive azoospermia, where sperm cannot be expelled owing to ductal obstruction; and abnormalities in sperm count, function, and morphology that prevent fertilization, as well as idiopathic male infertility, which may be associated with genetic, immunological factors, or undetected microlesions.[27-29] Given the complexity of the etiology of male infertility and the unique effects of HBOT on chronic ischemia, hypoxic diseases, and microcirculatory disorders, there has been a clinical trend toward combining HBOT with conventional treatments for male infertility to increase therapeutic efficacy. However, this approach has yet to receive adequate support from evidence-based medicine.[30,31]

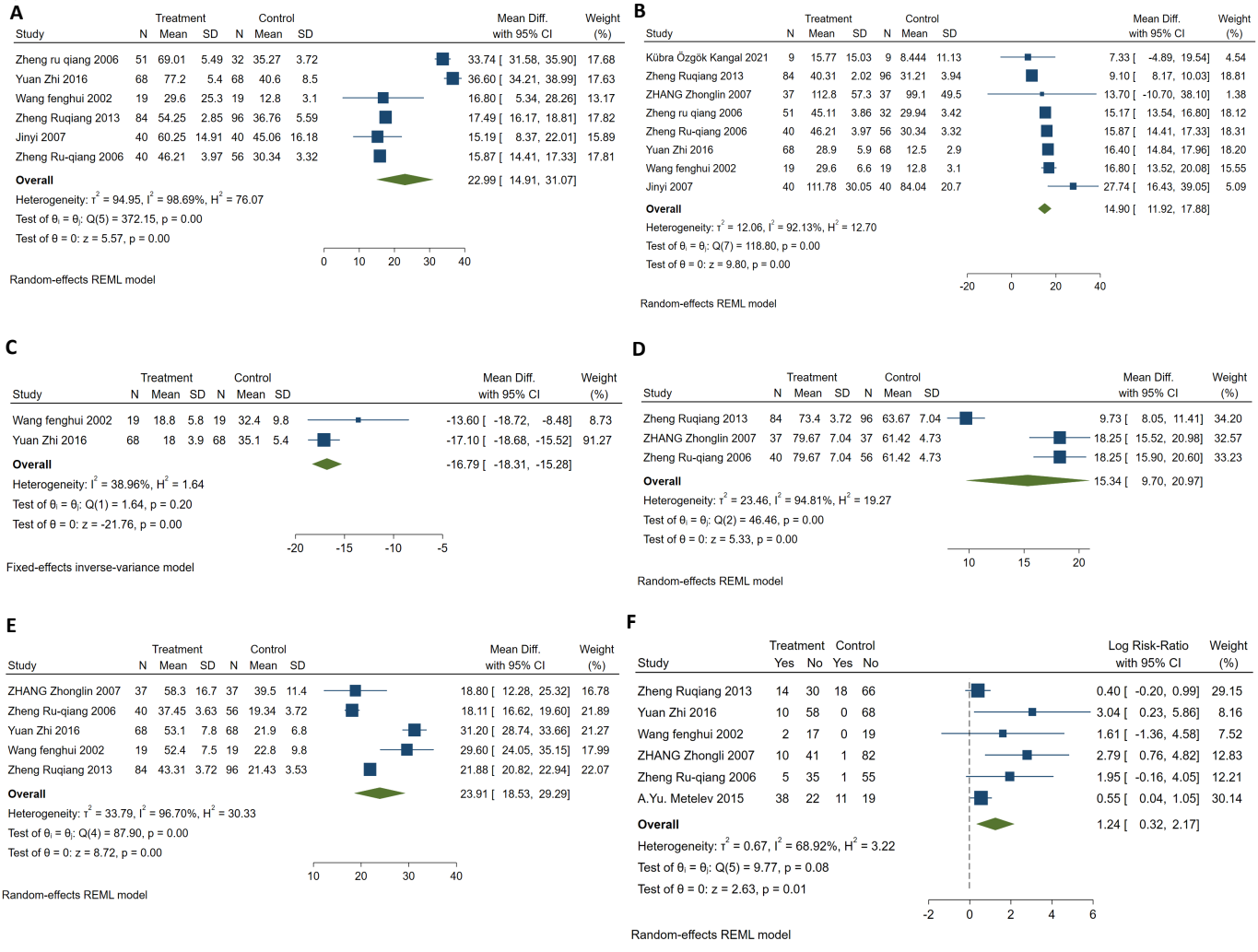

Figure 2 | Forest plot of the meta-analysis of hyperbaric oxygen therapy for the treatment of male infertility.
(A) Sperm viability; (B) sperm density; (C) sperm abnormality rate; (D) normal sperm rate; (E) sperm motility; (F) clinical cure rate (pregnancy rate). The effect size is represented as the log risk ratio.

Table 2 | Subgroup analysis of hyperbaric oxygen therapy treatment for male infertility

Subgroup analysis		Number of articles	I^2
Subgroup analysis based on the different etiologies of infertility			
Sperm density	VC	4	51%
	Asthenozoospermia	2	0%
	CBP	1	/
	Idiopathic male infertility	1	/
Sperm motility	Asthenozoospermia	2	0%
	VC	2	0%
	Idiopathic male infertility	1	0%
Normal sperm morphology rate	VC	2	0%
	Idiopathic male infertility	1	/
Subgroup analysis based on the different treatment courses			
Sperm viability rate	6 mon or longer	2	69%
	Less than 6 mon	4	0%

CBP: Chronic bacterial prostatitis; VC: varicocele.

In the meta-analysis of HBOT for male infertility, high heterogeneity was observed in all the study outcomes except for the sperm abnormality rate, which included only two studies. Subgroup analysis on the basis of the etiology of infertility revealed significantly reduced heterogeneity, indicating considerable variability in the effectiveness of HBOT for male infertility caused by different underlying factors. In terms of sperm motility, the combination of HBOT with other treatments was found to increase sperm motility in patients with oligoasthenozoospermia. This improvement may be attributed to the ability of HBOT to effectively increase the expression levels of various reproductive hormones in the body. Previous studies have confirmed that HBOT has notable advantages in improving the levels of follicle-stimulating hormone, luteinizing hormone, and testosterone,[32] and the role of these reproductive hormones in regulating sperm function is well established.[33,34]

Furthermore, in terms of normal sperm parameters, the combination of HBOT was more effective in increasing the normal sperm rate in patients with varicocele. Considering that the molecular mechanisms underlying infertility due to varicocele result from a combination of factors such as testicular microcirculation impairment, testicular ischemia and hypoxia, and the reflux of adrenal toxins,[27,35,36] one significant reason for the effectiveness of HBOT in treating varicocele may be its ability to address microcirculatory disturbances in the testis, thereby improving the survival environment of germ cells and increasing the number of normal sperm.

The duration of treatment is also a crucial factor influencing therapeutic efficacy. Compared with those treated for less than 6 months, subgroups treated for more than 6 months had better outcomes in terms of the "sperm survival rate." Another interesting phenomenon mentioned in some of the literature is the potential occurrence of a rebound effect, such as that observed with drugs, after the discontinuation of HBOT (e.g., after 3 months), where treatment outcomes may return to pretreatment levels.[19,20] This rebound effect may be because HBOT only temporarily alters intratesticular oxygen dissolution, increasing blood oxygen tension, which promotes the diffusion of oxygen from the blood to interstitial tissues. However, it does not address the underlying causes of the condition (e.g., it does not alter the vascular lesions associated with varicocele). To ensure that patients receive optimal therapeutic outcomes, we recommend minimizing interruptions to HBOT throughout the treatment process, thereby maintaining continuity and integrity of care. For patients with more severe conditions, it may be advisable to consider extending their duration in the hyperbaric oxygen chamber under strict medical evaluation and guidance, as well as increasing the frequency of treatments to maximize the therapeutic effects of HBOT. Additionally, during HBOT, patients may concurrently use medications that effectively improve microcirculation in the testicular vasculature. This synergistic approach, which combines pharmacological interventions with HBOT, may further increase treatment efficacy and promote the recovery of patients' reproductive systems.[37]

Notably, some studies have reported the use of HBOT alone for idiopathic male infertility. While this treatment significantly improved various sperm parameters, no difference was observed in the final pregnancy rate compared with that of the control group.[21] These findings suggest that HBOT for male infertility may yield better results when used in combination with other mainstream treatments. Furthermore, during HBOT, the induction of angiogenesis may improve erectile function, which could also be a potential reason for the increased clinical cure (pregnancy) rates.[38,39] In summary, the mechanism by which HBOT improves male infertility is likely through the promotion of testicular angiogenesis and the enhancement of microcirculation. This, in turn, may synergistically interact with pharmacological and surgical treatments to optimize the survival environment of germ cells, thereby significantly enhancing the efficacy of clinical interventions for male infertility.

We aimed to analyze the advantages and disadvantages of different combinations of HBOT with other treatment modalities, as well as their applicable scenarios. Unfortunately, we were unable to achieve this goal. There are two primary reasons for this: (1) The limited number of included studies, as many evaluations of treatment efficacy for male infertility were represented by only a single publication. (2) For certain outcome measures that included two or more studies, the results were relatively similar, failing to demonstrate any significant differences in efficacy among them (**Additional Figure 2**). Our work can only suggest that HBOT in conjunction with other treatment modalities may provide a synergistic effect.

The present meta-analysis has the following limitations: (1) the number of studies included in the analysis is relatively small, and most studies had a total sample size of less than 100 cases, which may affect the stability of the results; (2) the unwillingness of researchers to provide negative results or inconclusive studies may lead to bias in the meta-analysis, resulting in publication bias; (3) the majority of the studies included in this analysis focused on Chinese populations, which may limit generalizability due to regional and ethnic factors, and language bias could also impact the strength of the evidence and its applicability; and (4) the quality of the included literature was heterogeneous, with some studies exhibiting short follow-up periods and a lack of preliminary assessments of patients' psychological states and quality of life. To address these shortcomings, future research should focus on conducting larger-scale, multicenter randomized controlled trials to increase the stability and generalizability of the findings. Additionally, it is essential to incorporate more high-quality literature to mitigate the impact of publication bias, as well as to prioritize the evaluation of patients' psychological states and quality of life.

In summary, the results of this meta-analysis indicate that HBOT, when used in conjunction with other treatments, significantly improves sperm density, motility, and viability and reduces abnormalities, ultimately increasing male fertility. It is an effective adjunctive therapy for the treatment of male infertility.

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Conflicts of interest: *No authors declare competing interests.*

Data availability statement: *All data relevant to the study are included in the article or uploaded as additional files.*

Additional files:

Additional Figure 1: *Study flowchart.*

Additional Figure 2: *Forest plots of subgroup analyses for various sperm parameters.*

Additional Table 1: *The clinical course of the subjects included in the literature.*

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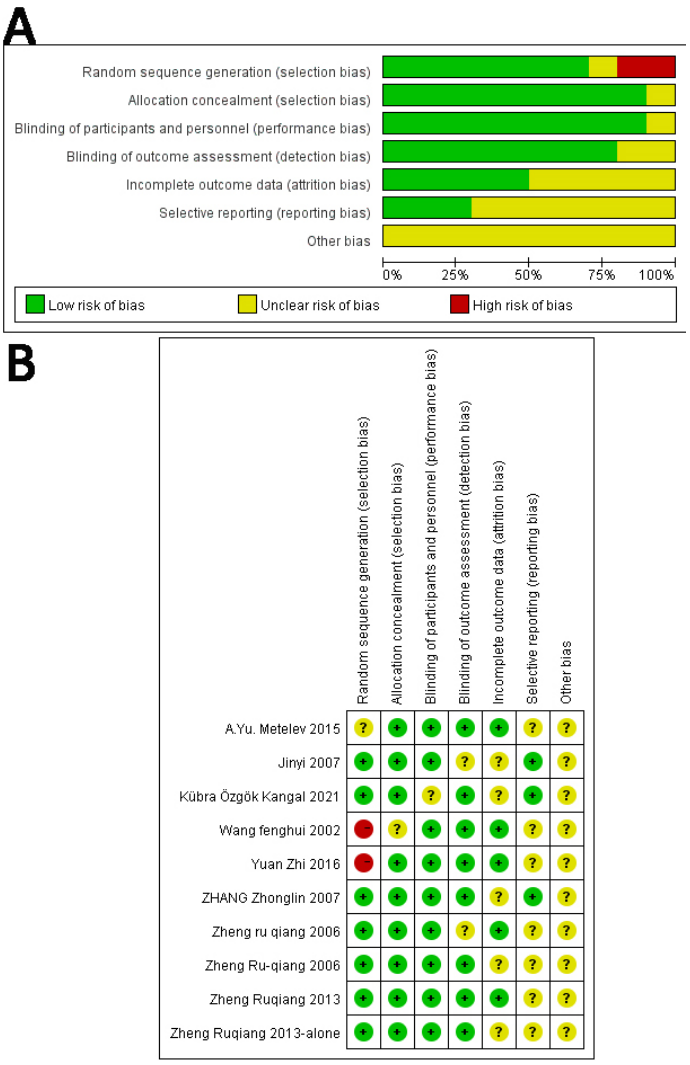
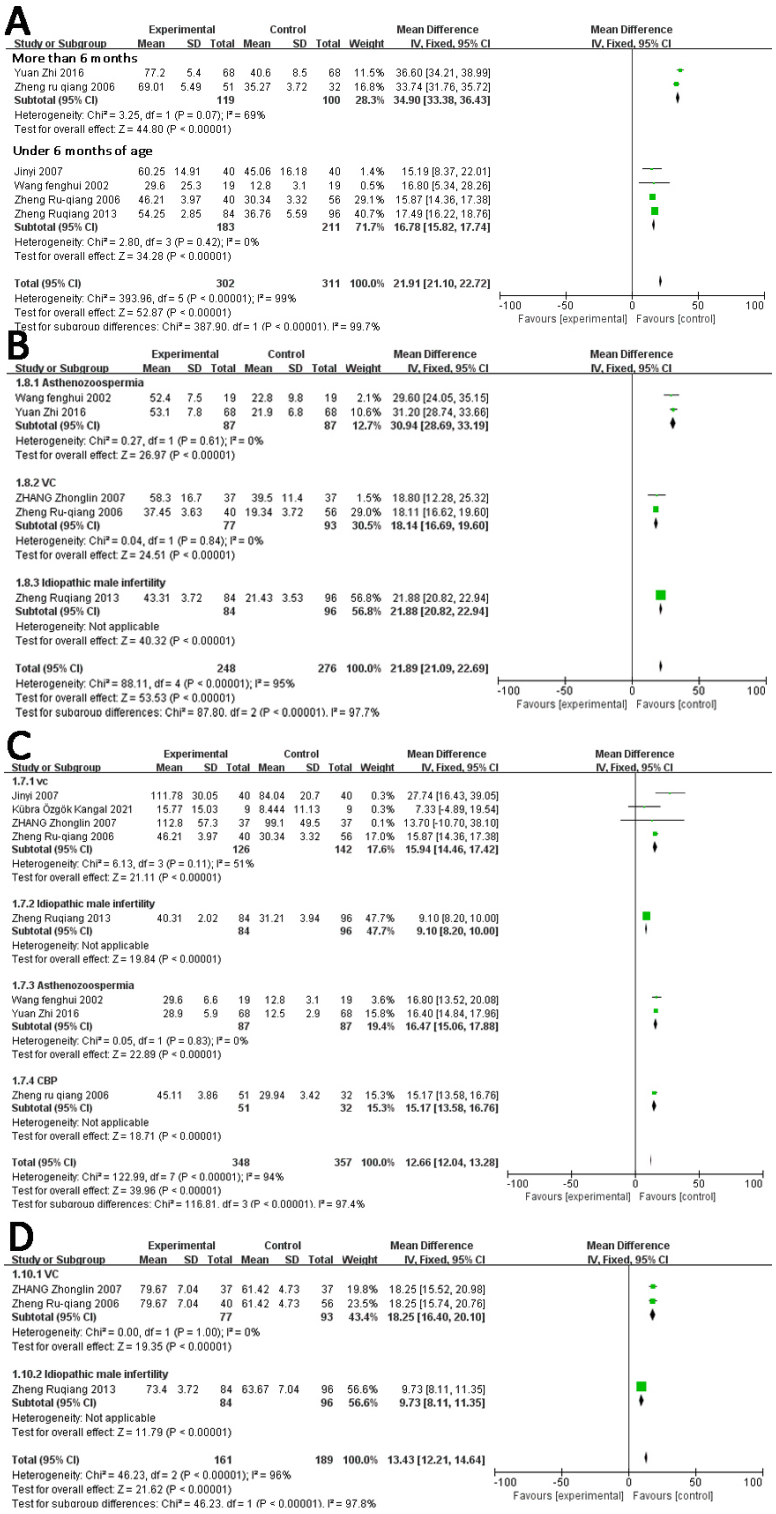


Additional Figure 1. Risk of bias evaluation.

(A) Risk of bias graph. (B) Risk of bias summary.



Additional Figure 2. Forest plots of subgroup analyses for various sperm parameters.

(A) Subgroup analysis of the sperm survival rate according to treatment duration. (B) Subgroup analysis of the sperm motility rate according to infertility etiology. (C) Subgroup analysis of sperm density on the basis of infertility etiology. (D) Subgroup analysis of the normal sperm rate according to infertility etiology. VC: Varicocele.

Additional Table 1: The clinical course of the subjects included in the literature

Study	Year	Course of disease	Cause of infertility
Wang et al.[19]	2002	The patient has been cohabiting for more than two years postmarriage, engaged in normal sexual activity, and expresses a desire for conception. Female infertility factors have been excluded, and despite years of treatment without resolution and the absence of any identified etiology, the patient has been confirmed through examination to have oligoasthenozoospermia.	Asthenozoospermia
Zheng et al.[17]	2006	The duration of infertility was 2 to 5 yr (2.5 ± 1.2 yr), during which no contraceptive methods were employed, and the couple engaged in regular, unprotected sexual intercourse for more than 1 yr without achieving pregnancy.	CBP
Zheng et al.[22]	2006	Infertility duration ranged from 3 to 9 yr (5.5 ± 3.2 yr).	VC
Jin et al.[21]	2007	/	VC
Zhang et al.[24]	2007	The duration of primary or secondary infertility ranges from 12 to 24 mon.	VC
Zheng et al.[20]	2013	Infertility duration was 1-8 yr (2.2 ± 1.2 yr) with no contraceptive use, regular and normal sexual activity, and despite the application of current diagnostic methods, no identifiable cause of infertility was found.	Idiopathic male infertility
Metelev et al.[25]	2015	/	Idiopathic male infertility
Yuan and Zheng[18]	2016	Cohabitation for more than 2 yr postmarriage without achieving pregnancy.	Asthenozoospermia
Özgök Kangal and Özgök[23]	2021	Patients who had a history of infertility for at least 1 yr	VC

CBP: Male infertility caused by chronic bacterial prostatitis; HBO: Hyperbaric oxygen therapy; IVF: in vitro fertilization; VC: varicocele.