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Benefits of Empiric Nutritional and Medical Therapy for Semen Parameters and Pregnancy and Live Birth Rates in Couples with Idiopathic Infertility: A Systematic Review and Meta-analysis

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Abstract

Context: Empiric use of medical and nutritional supplements to improve semen parameters and pregnancy rates in couples with idiopathic infertility has reached global proportions, although the evidence base for their use in this setting is controversial.
Objective: We systematically reviewed evidence comparing the benefits of nutritional and medical therapy on pregnancy rates and semen parameters in men with idiopathic infertility.
Evidence acquisition: A literature search was performed using MEDLINE, Embase, LILACS, and the Cochrane Library (searched from January 1, 1990 to September 19, 2017). using the methods detailed in the Cochrane Handbook. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of evidence.
Evidence synthesis: The literature search identified 5663 citations, and after screening of abstracts and full texts, 61 studies (59 randomised controlled trials and two non-randomised comparative studies) were included. Pooled results demonstrated that pentoxyfylline, coenzyme Q10, L-carnitine, follicle-stimulating hormone, tamoxifen, and kallikrein all resulted in improvements in semen parameters. Individual studies identified several other medical and nutritional therapies that improved semen parameters, but data were limited to individual studies with inherent methodological flaws. There were limited data available on live birth and pregnancy rates for all interventions.

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The GRADE certainty of evidence for all outcomes was very low mainly owing to methodological flaws and inconsistencies in study design. Some outcomes were also downgraded owing to imprecision of results.
Conclusions: There is some evidence that empiric medical and nutritional supplements may improve semen parameters. There is very limited evidence that empiric therapy leads to better live birth rates, spontaneous pregnancy, or pregnancy following assisted-reproductive techniques. However, the findings should be interpreted with caution as there were some methodological flaws, as a number of studies were judged to be either at high or unclear risk of bias for many domains.
Patient summary: This review identified several medical and nutritional treatments, such as pentoxyfylline, coenzyme Q10, L-carnitine, follicle-stimulating hormone, tamoxifen, and kallikrein, that appear to improve semen parameters. However, there are limited data suggesting improvements in pregnancy and live birth rates. The lack of evidence can be attributed to methodological flaws in studies and the low number of pregnancies reported.

1. Introduction

Infertility is the inability of a sexually active couple not using contraception to achieve spontaneous pregnancy within 1 yr [1]. Approximately one in eight couples do not achieve pregnancy within 1 yr and seek medical treatment [2]. Infertility may be due to a male factor in approximately half of infertile couples and may include abnormal semen parameters (oligozoospermia, asthenozoospermia, teratozoospermia) or a combination of all three, known as oligoasthenoteratozoospermia (OAT), or azoospermia, although the condition is idiopathic in up to 25% of patients [3]. Idiopathic male infertility is clinically diagnosed after excluding all known causes of impaired spermatogenesis.

Medical and nutritional interventions have been used to treat male idiopathic infertility [2]. Many of these therapies are off-label and the evidence for their use is limited. Medical therapies include hormonal therapies that modulate the hypothalamic-pituitary-testicular axis. Gonadotropins (gonadotropin-releasing hormone [GnRH], luteinising hormone [LH], follicle-stimulating hormone [FSH], and human chorionic gonadotropin [hCG]) have all been used to treat idiopathic male infertility. FSH directly acts on Sertoli cells to stimulate spermatogenesis, while aromatase inhibitors act by inhibiting the peripheral conversion of testosterone to oestrogens, thereby reducing the negative feedback inhibition of oestrogens on the hypothalamic-pituitary-gonadal axis and promoting spermatogenesis.

While intratesticular testosterone is required for spermatogenesis, exogenous testosterone inhibits pituitary LH and FSH production via a classic negative feedback mechanism that leads to inhibition of spermatogenesis. Clomiphene and tamoxifen are selective oestrogen receptor modulators that block negative feedback at the level of the hypothalamus and the pituitary, thus increasing LH and FSH excretion from the anterior pituitary, which raises testosterone levels and stimulates spermatogenesis.

Many nutritional and herbal supplements exert their positive effects on male infertility by increasing seminal antioxidant capacity. While reactive oxygen species (ROS) are required for normal sperm function, excessive ROS production has been implicated in the pathophysiology of male infertility. Elevated ROS levels are associated with abnormal sperm development, function, and fertilising capacity, and sperm DNA damage. Sperm DNA damage has been associated with recurrent fertilisation failure and recurrent pregnancy loss from both natural conception and assisted reproductive technologies. Carnitines, *N*-acetyl cysteine, and selenium have antioxidant properties that protect sperm from the negative effects of ROS [4–6]. Zinc and selenium both play a role in testicular function, spermatozoa oxygen consumption, sperm chromatin stabilisation, and sperm capacitation, and may mediate intratesticular testosterone levels [6,7]. Several vitamins act as potent antioxidants, inhibiting free radical-induced damage to cell membranes and decreasing seminal ROS. Coenzyme Q10 (CoQ10) is implicated in mitochondrial bioenergetics, which is important in sperm maturation [8].

Systematic reviews assessing FSH, clomiphene citrate, gonadotropins, tamoxifen, and several nutritional therapies have previously revealed some improvement in sperm quality and spontaneous pregnancy rates [9–12]. Conversely, it has been shown that androgens, bromocriptine, α-blockers, systemic corticosteroids, and magnesium supplementation are ineffective [2]. The management of men with idiopathic infertility remains challenging, mainly because of the large numbers of different treatments and conflicting evidence from individual studies. Against this backdrop, we conducted this systematic review (SR).

In this study, we systematically reviewed evidence comparing the benefits of nutritional and medical therapy on pregnancy rates and semen parameters in men with idiopathic infertility.

2. Evidence acquisition

This SR was undertaken under the auspices of the European Association of Urology (EAU). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance and the Cochrane handbook for systematic reviews of interventions [13,14]. The protocol was registered at PROSPERO (CRD42016032976).

2.1. Literature search

We searched electronic databases including MEDLINE, MEDLINE In-Process, Embase, the Cochrane Controlled Trials Register, and LILACS from January 1990 to September 2017. Studies were limited to those written in the English language, and conference abstracts were excluded from the analysis. The complete search strategy is detailed in the Supplementary material. The detailed PICO search strategy is shown in Table 1.

2.2. Data collection and analysis

Two reviewers (R.P.P. and B.D.K.) independently screened abstracts and full texts. Any disagreements were resolved via discussion or consultation with a third reviewer (H.M.B.). Two reviewers independently extracted outcome data. Any disagreements were resolved via discussion or consultation with a third reviewer (M.I.O. or H.M.B.). Study authors were contacted to provide missing information.

The risk of bias (RoB) for each study included was independently assessed by two reviewers (R.P.P. and B.D.K.). Any disagreements were resolved via discussion or consultation with a third reviewer (M.I.O. or H.M.B.). We used the Cochrane RoB assessment tool for randomised controlled trials (RCTs) [14,15]. Nonrandomised studies were assessed using the ROBINS-I tool [16].

Meta-analysis (MA) was performed when more than one RCT demonstrated homogeneity of the population, comparison, outcome definition, methods, and timing of outcome measurement. For studies with multiple publications, only the most up-to-date or complete data for each outcome were used. A priori, a fixed-effects model was used to calculate pooled estimates of treatment effects across similar studies and their 95% confidence intervals (CIs). When clinical or methodological heterogeneity was suspected, a random-effects model was used. For continuous outcomes, each trial was summarised using the mean value for each group and standard deviation (SD), and combined as a mean difference (MD) if the same scale was used for the outcome measurement in more than one trial. We used an odds ratio (OR) for dichotomous outcomes. We identified heterogeneity by visually inspecting forest plots and using a standard χ^2 test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the MA. We planned to use a funnel plot to interpret publication bias. However, there were fewer than ten trials in the meta-analyses, so we did not use these plots, in accordance with the guidance in the Cochrane handbook. Quantitative synthesis was undertaken for nonrandomised studies.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence for each comparison [14]. The certainty of evidence for critical/important outcomes for decision-making was rated on study design, limitations in study design or execution (RoB), inconsistency of results, indirectness of evidence, imprecision, and publication bias. We calculated the optimal information size to judge imprecision and to assess the overall quality of evidence. We assumed $\alpha = 0.05$, $\beta = 0.20$, and an a priori anticipated intervention effect with MD of 10% across the two groups. The final optimal information size was 392 participants. The certainty of evidence was assessed by one reviewer (M.I.O.).

3. Evidence synthesis

3.1. Quantity of evidence identified and characteristics of the studies included

The literature search identified 5663 abstracts, and 226 were selected for full-text screening. A total of 61 studies (59 RCTs

Table 1 – PICO search strategy

P	Population	*Inclusion criteria*: • Male patients aged ≥18 yr with idiopathic male factor infertility • Couple infertility as defined by WHO and altered semen parameters according to the WHO manual used at the time of publication of the paper: oligozoospermia, asthenozoospermia, teratozoospermia, or azoospermia; AND idiopathic defined as exclusion of all known causes of impaired spermatogenesis (as defined by authors); if defined by the authors as different than above, the study is retained and the results presented as a subgroup analysis *Exclusion criteria*: • Idiopathic hypoganodatropic hypogonadism • Genetic alterations (eg, Kallmann syndrome, Klinefelter syndrome)
I	Intervention	• Nutritional therapy including: trace elements (zinc, copper), vitamin C, vitamin E, antioxidants, coenzyme Q10, herbal therapy, amino acids (arginine, carnitine), selenium, folic acid, omega fatty acids, food supplements, or other nutritional therapies not listed here, and/or • Medical therapy including: tamoxifen, clomiphene citrate, gonadotropins, aromatase inhibitors, or other medical therapies
C	Comparator	• Placebo • No treatment • Other experimental treatment as listed above under intervention
O	Outcomes	*Primary outcome*: • Effectiveness of medical or nutritional therapy for idiopathic male infertility in terms of live birth rate/pregnancy rate *Secondary outcome*: • Effectiveness of therapy for routine and functional semen parameters and the development of treatment-related adverse outcomes or side effects

WHO = World Health Organisation.

and two non-RCTs) met the inclusion criteria and were included in the SR [17–78]. The inclusion process is graphically illustrated in a PRISMA diagram in Fig. 1.

3.2. Baseline characteristics of the studies included

We extracted detailed baseline information for all of the studies included. Supplementary Tables 1 and 2 details the inclusion and exclusion criteria; the number of participants included in the studies; the intervention and comparator, including the number of participants in each arm; the definition of idiopathic infertility used; and the treatment duration.

3.3. RoB assessment

3.3.1. Cochrane RoB assessment for RCTs

Random sequence generation was judged to be high in 15, unclear in 22, and low in 22 studies. Allocation concealment was judged high in 14, unclear in 21, and low in 24 studies. Twenty-five studies were judged as high and five as unclear for blinding of participants and personnel. Fourteen studies were judged as having high RoB for blinding of outcomes, and 16 studies were judged as high and four as unclear for attrition bias. Three studies were judged as high and 30 as unclear for reporting bias. The RoB assessment is graphically represented in Fig. 2.

3.3.2. ROBINS-I

We identified two nonrandomised studies that were included in the SR [69,74]. ROBINS-I, a tool for assessing RoB in nonrandomised studies of interventions, revealed that the RoB for these two studies was critical. Detailed results are available in Supplementary Table 3.

3.4. GRADE

The certainty of evidence was assessed using GRADE. A number of studies had methodological issues, as discussed earlier for RoB assessment. Some evidence was also downgraded because of clinical and statistical heterogeneity, as judged from a high I^2 value or χ^2 statistic.

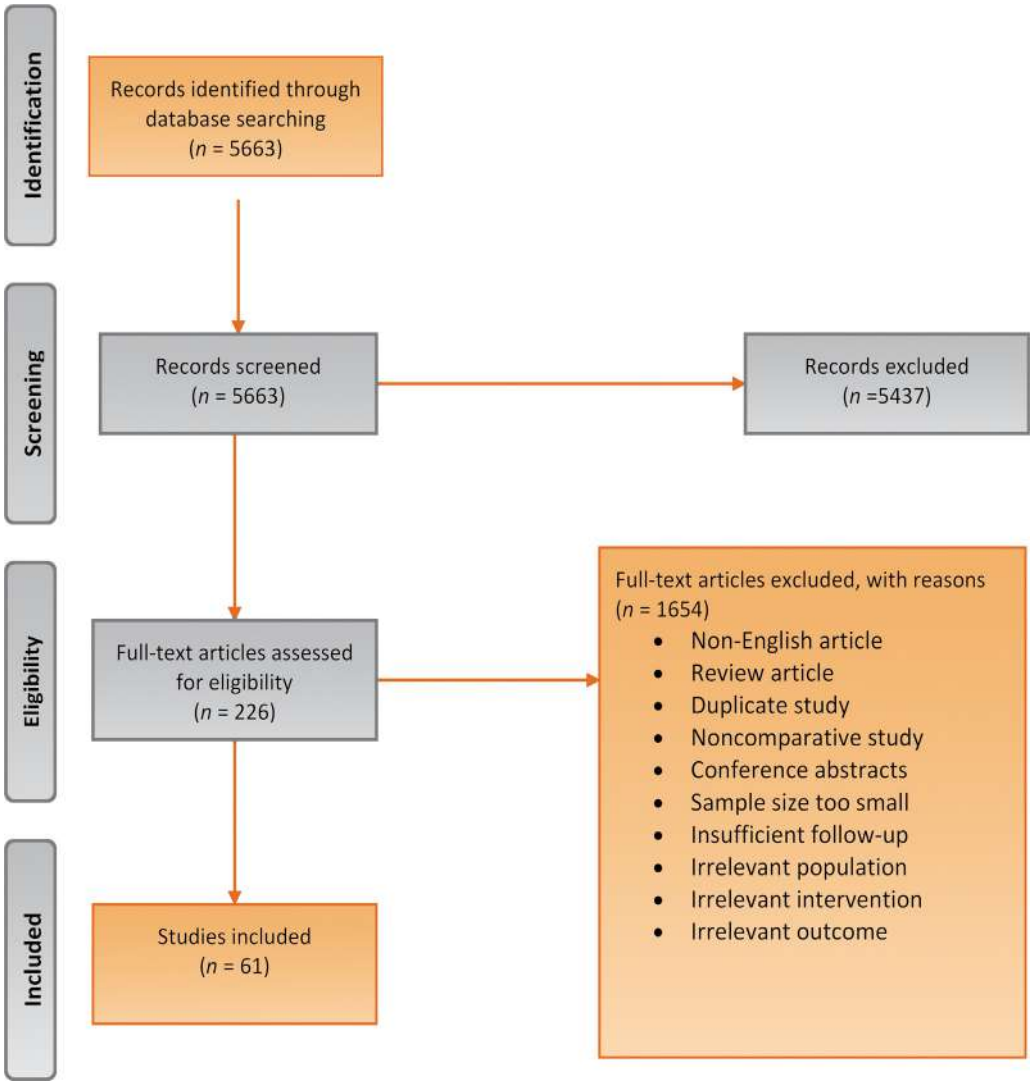

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart.

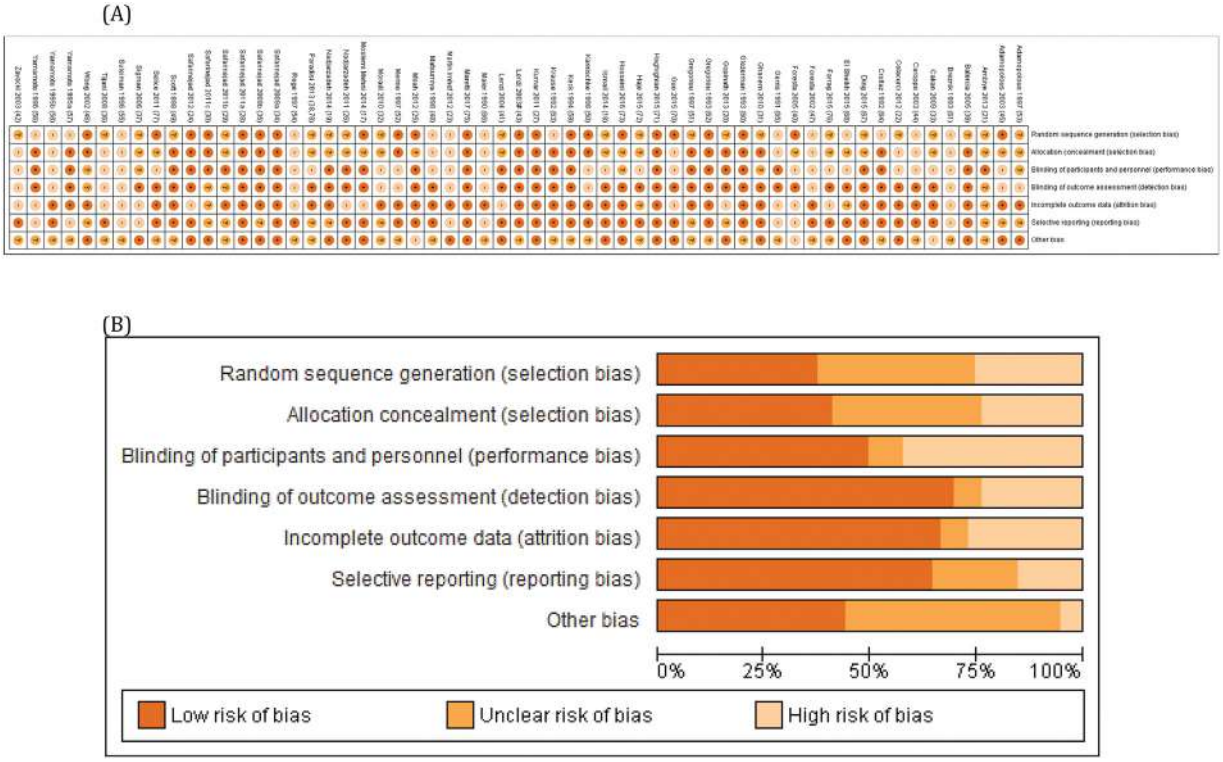

Fig. 2 – Risk of bias assessment. (A) Risk of bias summary according to the judgment of the review authors on each risk of bias item for each study included. The number in parentheses for each study corresponds to the reference number. (B) Risk of bias graph according to the judgment of the review authors for each risk of bias item presented as a percentage across all the studies included.

3.5. *Results for comparisons of interventions*

3.5.1. *Influence of intervention on live birth and pregnancy rates*

Data on live birth rates were reported in only four of the 61 studies [38,51,55,62,78]. In these studies, the number of confirmed live births was low. Data on pregnancy rates following intervention were included in 33 of the 60 studies. Pregnancies were achieved either spontaneously or with assisted reproductive techniques. In all of the studies we evaluated the number of pregnancies reported was very low and MA pooling of the results was not possible for the majority of comparisons. Therefore, the SR results focused mainly on the secondary outcome, that is, the effectiveness of therapy on routine and functional semen parameters. Data on live birth and pregnancy rates are shown in Supplementary Table 1 and Supplementary Figure 1.

3.5.2. *Results for changes in routine semen parameters following intervention*

Results for the following semen parameters are reported:

1. Sperm morphology reported as the percentage change before and after treatment across the groups; MA results are presented as the mean percentage difference (MPD) along with SD;
2. Sperm motility reported as the percentage change before and after treatment across the groups; MA results are presented as MPD along with SD; and
3. Sperm concentration reported as $\times 10^6$/ml; MA results are presented as the sperm count MD along with SD.

3.5.2.1. MA of change in semen parameters following intervention. Figs. 3–5 show forest plots generated from MA performed on data extracted from studies evaluating recombinant FSH versus placebo on changes in semen parameters (sperm morphology, motility, and concentration). Supplementary Figure 1 shows a forest plot generated from MA performed on data extracted from studies evaluating the same intervention comparison on changes in semen parameters where multiple studies evaluating the same comparison were assessed. These included placebo-controlled studies evaluating pentoxyfylline, CoQ10, L-carnitine and L-acetylcarnitine, recombinant FSH, tamoxifen, and kallikrein.

MA demonstrated a significant improvement in sperm concentration with the use of pentoxyfylline, CoQ10, and L-carnitine when compared with placebo (Supplementary Figure 1). Pentoxyfylline, CoQ10, L-carnitine, tamoxifen, and kallikrein led to a significant improvement in sperm motility. Pentoxyfylline, CoQ10, L-carnitine, L-carnitine + L-acetylcarnitine, and kallikrein led to a significant improvement in sperm morphology.

3.5.2.2. MA of change in semen parameters following intervention with pentoxyfylline versus placebo. Three studies evaluated pentoxyfylline against placebo [17,28,52]. In two studies

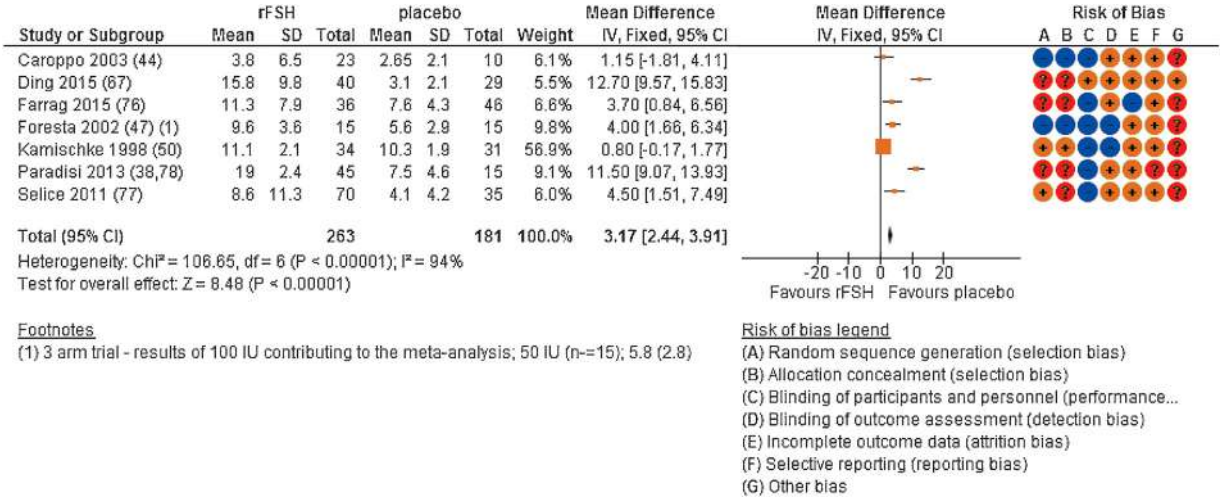

Fig. 3 – Effect of recombinant follicle-stimulating hormone (rFSH) versus placebo on sperm concentration. Reference numbers for the studies are in parentheses. CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

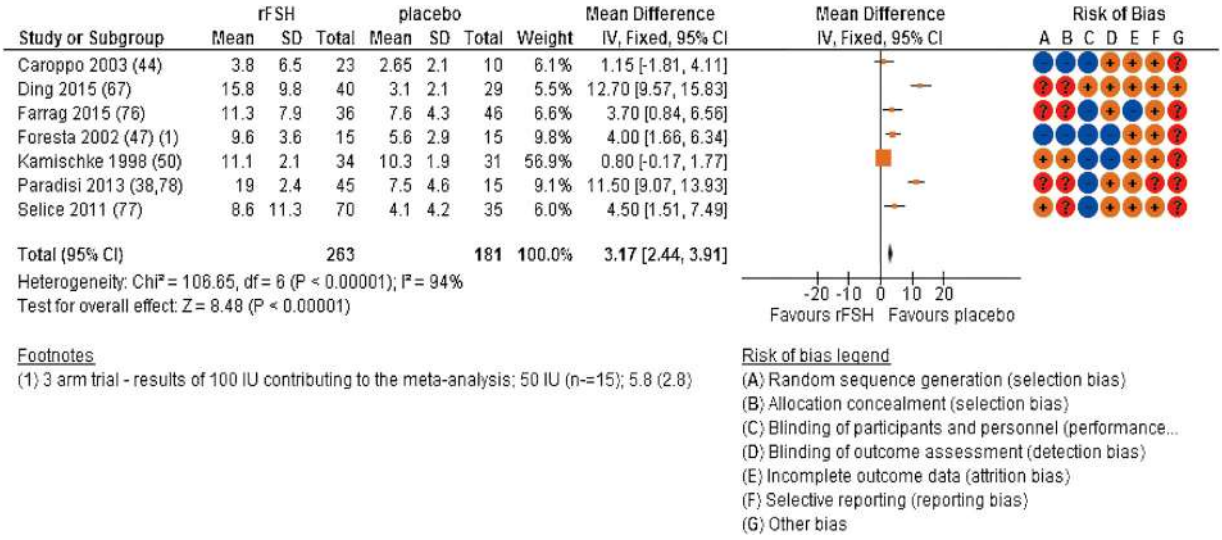

Fig. 4 – Effect of recombinant follicle-stimulating hormone (rFSH) versus placebo on sperm morphology. CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

the daily dose was 800 mg and in the remaining study it was 1200 mg. The treatment duration varied between 3 and 6 mo. Sperm concentration (MD 8.98 $\times$ 10^6/ml, 95% CI 8.06–9.90 $\times$ 10^6/ml; 413 participants; three studies; I^2 = 95%; $p < 0.0001$; low certainty), sperm motility (MPD 11.96, 95% CI 11.28–12.64; 413 participants; three studies; I^2 = 98%; $p < 0.0001$; low certainty), and sperm morphology (MPD 5.56, 95% CI 4.99–6.13; 413 participants; three studies; I^2 = 97%; $p < 0.0001$; low certainty) improved with treatment.

3.5.2.3. MA of change in semen parameters following intervention with CoQ10 versus placebo. Four studies evaluated CoQ10 against placebo [19,24,26,35]. The dose assessed was 300 mg daily in one study and 200 mg daily in the remaining three. The duration of therapy was 3 mo or 6 mo. Sperm concentration (MD 8.49 $\times$ 10^6/ml, 95% CI 7.62–9.37 $\times$ 10^6/ml; 432 participants; three studies; I^2 = 96%; $p < 0.0001$; low certainty), sperm motility (MPD 7.08, 95% CI 6.62–7.53; 432 participants; four studies; I^2 = 99%; $p < 0.0001$; low certainty), and sperm morphology (MPD 14.94, 95% CI 14.31–15.57; 432 participants; three studies; I^2 = 100%; $p < 0.0001$; low certainty) improved with treatment.

3.5.2.4. MA of change in semen parameters following intervention with L-carnitine versus placebo. Six studies evaluated L-carnitine treatment against placebo [17,37,39,41,43,72]. Studies

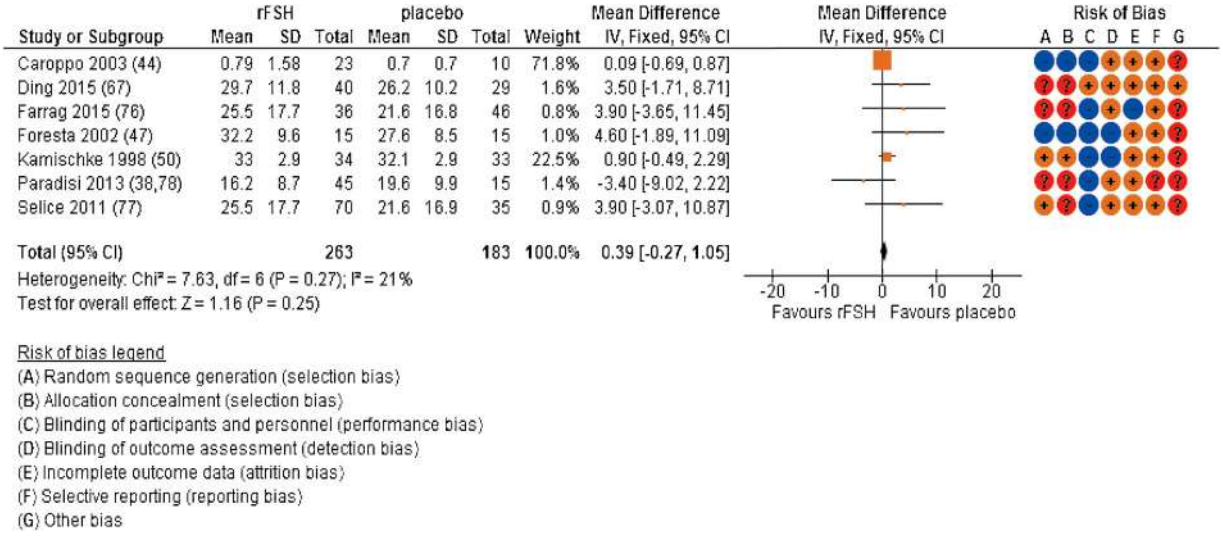

Fig. 5 – Effect of recombinant follicle-stimulating hormone (rFSH) versus placebo on sperm motility. CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation.

used a doses of 1 g, 2 g, or 3 g daily. The results showed no significant difference in pregnancy rate (OR 1.99, 95% CI 0.50–7.88; 90 participants; 2 studies; I^2 = 61%; p = 0.33; very low certainty). Sperm concentration (MD 6.57 × 10^6/ml, 95% CI 5.95–7.16 × 10^6/ml; 289 participants; four studies; I^2 = 99%; $p < 0.0001$; very low certainty) and sperm motility (MPD 18.38, 95% CI, 17.66–19.10; 289 participants; four studies; I^2 = 99%; $p < 0.0001$; very low certainty) appeared to improve with treatment, but not sperm morphology (MPD 1.94, 95% CI, 1.81–2.07; 199 participants; three studies; I^2 = 98%; $p < 0.0001$; very low certainty).

3.5.2.5. MA of change in semen parameters following intervention with L-carnitine + L-acetylcarnitine versus placebo. Three studies evaluated combined L-carnitine and L-acetylcarnitine treatment against placebo [37,39,41]. The duration of therapy in both studies was 6-mo and used 2 g of L-carnitine daily. The results showed no significant difference in pregnancy rate (OR 1.67, 95% CI 0.49–5.70; 111 participants; three studies; I^2 = 28%; p = 0.42; very low certainty). Sperm motility improved with treatment (MPD 4.22, 95% CI 0.48–7.97; 111 participants; three studies; I^2 = 90%; p = 0.03; very low certainty), although sperm concentration (MD 2.63 × 10^6/ml, 95% CI −2.82 × 10^6/ml to 8.08 × 10^6/ml; 86 participants; two studies; I^2 = 0%; p = 0.34; very low certainty) and sperm morphology (MPD −1.61, 95% CI −4.77 to 1.55; 86 participants; two studies; I^2 = 93%; p = 0.32; very low certainty) did not.

3.5.2.6. MA of change in semen parameters following FSH treatment versus placebo. While different FSH preparations are commercially available, the nine studies evaluating FSH treatment versus placebo used recombinant FSH [38,40,44,47,50,67,76–78]. The report by Paradisi and colleagues [78] in 2013 was the continuation of a study published in 2006 [38]. Therefore, we did not duplicate participants when extracting data from the two reports. All the studies used differing recombinant FSH regimes (50–300 IU administered daily or on alternate days). The duration of therapy was 3–4 mo in all studies. Pregnancy rates were higher for patients receiving recombinant FSH (OR 3.30, 95% CI 1.39–7.82; 343 participants; five studies; I^2 = 0%; p = 0.007; low certainty). Sperm concentration (MD 3.17 × 10^6/ml, 95% CI 2.44–3.91 × 10^6/ml; 444 participants; seven studies; I^2 = 94%; $p < 0.0001$; very low certainty) and sperm morphology (MPD 1.54, 95% CI 0.29–2.80; 446 participants; seven studies; I^2 = 97%; p = 0.02; very low certainty) appeared to improve with treatment, but not sperm motility (MPD 0.39, 95% CI −0.27 to 1.05; 476 participants; seven studies; I^2 = 21%; p = 0.25; very low certainty). It should be noted that the pooled estimate of effect on sperm morphology was strongly influenced by the study by Farrag and colleagues [76], and the result became nonsignificant on sensitivity analysis when we excluded the results from this study from the pooled estimate of treatment effect (MPD −0.02, 95% CI 0.49–0.45; 364 participants; six studies; I^2 = 77%; p = 0.94; very low certainty).

3.5.2.7. MA of change in semen parameters following kallikrein treatment versus placebo. Three studies evaluated kallikrein treatment versus placebo [56,59,60]. All the studies used differing kallikrein regimes (100–300 IU administered daily or on alternate days) and therapy duration (3–4 mo). The results showed no significant difference in pregnancy rate (OR 0.80, 95% CI 0.32–2.03; 193 participants; two studies; I^2 = 0%; p = 0.64; very low certainty). Although there was an improvement in sperm motility with kallikrein (MPD 2.69, 95% CI 2.05–3.32; 302 participants; three studies; I^2 = 86%;

$p < 0.00001$; very low certainty), a greater improvement in sperm concentration was seen in the placebo groups than following kallikrein treatment (MD −4.23, 95% CI −5.38 to −3.08; 213 participants; two studies; $I^2 = 76\%$; $p < 0.0001$; low certainty).

3.5.2.8. MA of change in semen parameters following tamoxifen treatment versus placebo. Three studies evaluated tamoxifen treatment versus placebo [33,63,72]. The duration of therapy was 3 mo. The results showed no significant difference for pregnancy rate (OR 2.48, 95% CI 0.67–9.23; 203 participants; two studies; $I^2 = 0\%$; $p = 0.17$, very low certainty). Sperm concentration (MD 2.62, 95% CI 1.63–3.61; 160 participants; two studies; $I^2 = 0\%$; $p < 0.0001$; low certainty), sperm motility (MPD 6.74, 95% CI 4.95–8.52; 287 participants; three studies; $I^2 = 67\%$; $p < 0.0001$; low certainty), and sperm morphology (MPD 0.59, 95% CI 0.41–0.77; 201 participants; two studies; $I^2 = 97\%$; $p < 0.0001$; very low certainty) improved with treatment.

3.6. Results from remaining RCTs, comparative studies, and nonrandomised trials

As shown in Supplementary Table 2, 24 studies were unique (ie, results reported in a single study) and therefore results could not be pooled. Treatments included nutritional supplements such as saffron, *Withania somnifera*, α-lipoic acid, omega fatty acids, selenium, *N*-acetyl cysteine, magnesium, Y-virilin, vitamin E, ginger, and a probiotic. Medical treatments included lisinopril, tranilast, testosterone, terazosin, bunazosin, GnRH, and mesterolone. One observational study assessed response to recombinant FSH response relative to a control group who received no treatment [69].

3.7. Discussion

3.7.1. Principal findings

We found some improvements in semen parameters, but owing to the short follow-up and low number of positive events, it is difficult to draw conclusions on pregnancy or live birth rates for any treatment. Many of the studies had methodological flaws and provided conflicting results when evaluating the same treatment. Random sequence generation was judged to be high in 11 and unclear in 33 studies. Allocation concealment was judged high in six and unclear in 36 studies. This was considered while assessing the overall certainty of evidence. As a result, the majority of outcomes were either rated as "low" or "very low" when assessing the certainty using the GRADE approach. Therefore, the findings of this SR should be interpreted with caution.

FSH and tamoxifen treatment resulted in improvements in sperm concentration, while sperm motility improved with tamoxifen and sperm morphology improved with FSH. However, data on pregnancy rates were limited by a low number of positive events. Contemporary SRs evaluating anti-oestrogens in the treatment of male infertility concluded that there was a 2.4 times higher chance of pregnancy if men were treated with anti-oestrogens, but this was based on historical data predominantly generated before 1990. Santi et al. [10] demonstrated similar findings with regards to improvements in semen parameters and pregnancy rates as in the present SR.

Nutritional supplements may have antioxidant activity [79,80]. Antioxidants may protect against free radical injury, with infertile men having higher ROS levels. It has been shown that antioxidants improve spermatogenic function and sperm DNA integrity [81,82]. Thus, reducing oxidative stress via nutritional antioxidant supplementation has the potential to improve semen parameters and ultimately pregnancy rates.

We found that antioxidants such as L-carnitine and CoQ10 appear to have a beneficial effect on sperm concentration, motility, and morphology. Selenium and N-acetyl cysteine also had a beneficial effect on all semen parameters. Again, data on pregnancy rates are limited by the low number of positive events.

Low carnitine levels have been observed in the semen of men with OAT [83] and sperm motility could be improved when exposed to L-carnitine [84]. However, the present MA of six studies showed only a marginal improvement in sperm concentration and motility.

CoQ10 plays an integral role in cellular respiration, and high seminal CoQ10 levels are associated with sperm motility and antioxidant capacity [85]. Although only four RCTs in this SR compared CoQ10 with placebo, the sperm concentration, motility, and morphology all appeared to improve with treatment, although none of these studies reported on live birth rates after treatment with CoQ10.

The most objective outcome measure to indicate the effectiveness of intervention for male fertility is the pregnancy rate or live birth rate, which is superior to assessment of sperm parameters, although most studies only reported on semen parameters. However, it must be noted that "fertility" potential also depends on the fertility status of the female partner, which clearly influences the outcome of any medical or nutritional intervention in the male partner. For instance, the diagnosis of relevant female factors such as endometriosis and tubal defects would require relatively invasive procedures, which are not routinely reported on.

3.7.2. Recommendations for future research

Our SR revealed that antioxidant nutrient supplements (eg, CoQ10, L-carnitine) significantly improved semen parameters and their utility in the treatment of male infertility should be the focus of future studies. The primary outcome of this review was not reported in the majority of studies. It is important that a core outcome set is developed for patients with infertility. This can be achieved by following the Core Outcome Measures in Effectiveness Trials or the International Consortium for Health Outcomes Measurement methodology.

In summary, well-designed and -conducted prospective studies are needed to identify optimum dosage regimens

and treatment durations while using pregnancy and live birth rates as primary outcome measures following therapeutic interventions. Future trials should follow the recommendations of the CONSORT statement.

3.7.3. Strengths and limitations of the review

The major strengths of this SR are that it is the first comprehensive literature search for all medical and nutritional treatments for idiopathic male infertility using a robust and transparent methodological approach based on the Cochrane handbook.

Major limitations of the review include significant heterogeneity among the studies identified. In addition, the possibility of publication bias cannot be completely eliminated and the majority of the studies were underpowered, with a small sample size.

4. Conclusions

This review indicates that medical treatment and nutritional supplementation may improve male fertility. Although there is some evidence that medical and nutritional supplements may improve semen parameters, there is very limited evidence that it leads to an increase in rates of spontaneous pregnancy or pregnancy via assisted reproductive techniques or in live birth rates.

Author contributions: Muhammad Imran Omar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pal, Kelly, Bruins, Diemer, Krausz, Tournaye, Kopa, Yuan, Omar, Minhas, Jungwirth.
Acquisition of data: Pal, Kelly, Bruins, Yuan, Omar.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2018.12.022.

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