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Coenzyme Q10 effect on semen parameters: Profound or meagre?

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Abstract

Coenzyme Q10 has shown promise in treating male infertility; however, there are inconsistencies across the published data. We undertook a quantitative meta-analysis by pooling data from three placebo-controlled randomised clinical trials (RCTs) in order to evaluate the efficacy of CoQ10 in improving semen parameters. Sperm count, sperm motility, sperm forward motility, sperm morphology and CoQ10 level in the seminal plasma were measured and quantitatively correlated with CoQ10 oral administration. Pooled analysis showed a significant impact of CoQ10 in improving sperm motility and forward motility, without a significant impact on sperm count, sperm morphology, ejaculate volume or seminal plasma level of CoQ10. Efficacy assessment suggested that CoQ10 shows better results at higher doses and when administered for a period of more than 3 months but not longer than 6 months. We conclude that CoQ10 has a profound effect on sperm motility and a meagre effect on all other parameters. Therefore, CoQ10 can be used for treating asthenozoospermic infertility with the dosage and duration depending upon the severity of the disorder and the patient's response to the treatment.

KEYWORDS

asthenozoospermia, Coenzyme Q10, CoQ10, male infertility, sperm motility

1 | INTRODUCTION

Semen quality has declined in the last four decades, and the incidence of infertility has increased significantly (Mishra, Negi, Srivastava, Singh, & Rajender, 2018). Infertility is defined as the failure to initiate a pregnancy after unprotected intercourse for one year or more (Zegers-Hochschild et al., 2009). Infertility is conceptually defined as decreased sperm count and/or motility as per the WHO (World Health Organization) 2010 criteria (Cooper et al., 2010). About 15% of couples are affected by this condition around the world (Agarwal, Mulgund, Hamada, & Chyatte, 2015). Male and female factors contribute almost equally to the aetiology, with some couples presenting with compound issues on both the sides (Kumar & Singh, 2015). Among various factors, oxidative stress has been accounted for infertility since the 1940s (Aitken & Baker, 2006; MacLeod, 1943; Saleh et al., 2003; Sharma & Agarwal, 1996; Tremellen, 2008; Wagner, Cheng, & Ko, 2018). Oxidative stress ensues when reactive oxygen radicals, hydrogen peroxide, hydroxyl species and super oxide anions overpower the antioxidant protection in the cells (Combelles, Gupta, & Agarwal, 2009; Sharma & Agarwal, 1996; Tremellen, 2008). High ROS-level in semen may lead to sub-fertility and even sterility (Adewoyin et al., 2017; Agarwal & Said, 2005; Rato et al., 2012). Latest research in this area shows that oxidative stress might contribute to 30%–80% of infertility in men (Bisht, Faiq, Tolahunase, & Dada, 2017). A few antioxidants have already been found effective in male infertility treatment, for example glutathione, vitamin C, vitamin E, astaxanthin and CoQ10, but there is still no well-standardised male infertility treatment convention (Majzoub & Agarwal, 2018; Omar et al., 2019).

CoQ10 or ubiquinone is a significant mitochondrial respiratory chain antioxidant that has shown promise in treating human male infertility (Balercia et al., 2009; Nadjarzadeh et al., 2011; Safarinejad, 2009). For this purpose, CoQ10 is generally prescribed alone or in combination with other antioxidants. Some studies

claim profound effect of CoQ10 in treating male infertility, while others deny a significant beneficial effect. Recent studies have warned against indiscriminate use of antioxidants without sufficient evidence of their beneficial effects (Gharagozloo & Aitken, 2011; Palani, 2018). To evaluate the beneficial effects of CoQ10, three randomised placebo-controlled trials have been conducted in infertile men. A meta-analysis has also been conducted, but this meta-analysis was conducted with inappropriate statistical measures to conclude that CoQ10 administration improves sperm motility (Lafuente et al., 2013). They concluded this on the basis of relative risk, which is appropriate for the birth occasion, but not for other semen parameters that are not dichotomous. Sperm motility, forward motility, seminal CoQ10 level and sperm morphology are not the occasions, and hence they ought not to be considered for relative risk. Consequently, there is no meta-analysis on the efficacy of CoQ10 in male infertility.

We undertook the present investigation to evaluate the impact of CoQ10 administration on semen parameters. Out of all in vivo studies, we included only placebo-controlled randomised clinical trials (RCTs) to quantitatively assess the efficacy of CoQ10 in improving semen parameters.

2 | MATERIALS AND METHODS

This exploration was excluded from endorsement by the Institutional Review Board since it was an orderly survey and meta-investigation. We received the ideal reporting flow chart from precise surveys and meta-analysis (PRISMA) to report the results of this systematic assessment (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 | Search strategy

The meta-analysis began with a descriptive record of double-blind, randomised, placebo-controlled trials that evaluated the impact of CoQ10 supplements on the semen parameters of males who had fertility problems not induced by pathological illnesses. The electronic databases like GoogleScholar, EMBASE, MEDLINE (PubMed), Science Citation Index (SCI) were used for literature review until June 2019. The search strategy included the combination of keywords such as "male infertility," "infertility," "Coenzyme Q10," "CoQ10," "ubiquinol" and "antioxidant." We also searched all databases of preliminary clinical trials, such as www.clinicaltrials.gov, www.controlled-trials.com and the WHO International Clinical Trials Registry Platform (www.who.int/trialsearch). We manually reviewed articles for identification of other studies and acquired the full text of all relevant studies.

2.2 | Inclusion and exclusion criteria

The hits obtained through literature search were subjected to well-defined inclusion/exclusion criteria to select the studies for pooled analysis. Inclusion criteria were as follows: (a) placebo-controlled randomised clinical trials (RCTs) that included placebo and CoQ10 treatment to evaluate the effects of CoQ10 administration on semen parameters, (b) inclusion of the patients was carried out according to the standard diagnostic parameters, (c) the purpose of all the studies was similar, (d) standard methods were used to conduct the trial, and (e) sufficient information and data were provided for inclusion of the study. The exclusion criteria consisted of the following: (a) the studies that failed to provide a detailed description of the subjects, raw data and other information required to specifically understand the study design and the data therein, (b) review articles, meta-analyses, case reports and research on males with disorders such as varicocele, cryptorchidism, and (c) the studies that administered CoQ10 along with other vitamins or antioxidants, which would confound the effect of CoQ10.

2.3 | Data extraction

Data were obtained using a spreadsheet to record study design, the number of subjects, dosage and duration, quantitative effects and the primary outcomes. Two authors (RV and SR) extracted the quantitative data, interventions provided and other information. The discrepancies were resolved by discussion, leading to a consensus.

2.4 | Quantitative data analysis

Comprehensive Meta-Analysis Software version 2 was used to perform all statistical analyses for this study (Comprehensive Meta-Analysis Program, version 2). Standard difference in mean (SDM) for each semen parameter was used as the 'effect size' with their respective 95% confidence intervals. We took 0.5 as a pre-and post-correlation value and the effect direction standardised by post-*SD* value.

The heterogeneity between the studies was quantitatively assessed using Q and I^2 statistics, considering *P* value of <.10 as statistically significant. Heterogeneity index (I^2) value < 25% means low heterogeneity, 50% means moderate heterogeneity and 75% corresponds to high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003; Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). Pooled effect size value was calculated using both the fixed effect and random effects models and high-resolution plots (forest plot) were generated. For drawing inference, fixed effect model was used when the heterogeneity was not significant, but random effects model was used in the presence of significant heterogeneity.

Treatment protocols for the dose and length of CoQ10 therapy were comparatively heterogeneous across the studies (Table 1). Balercia et al., 2009, Safarinejad, 2009 and Nadjarzadeh et al., 2011 administered oral CoQ10 for durations of 24, 26 and 12 weeks respectively (Table 1). Methodological information and other details for the included studies are given in Table 2. Since intermittent data were not available for any of these studies, base and end point values were considered for meta-analysis, irrespective of the dose and duration of treatment.

TABLE 1 CoQ10 dose and duration across three randomised controlled trials included in the meta-analysis

Study name	Placebo (number of subjects completing the trial)	CoQ10 (number of subjects completing the trial)	CoQ10 dose
Balercia et al. (2009)	27	28	200 mg daily
Safarinejad (2009)	96	98	300 mg daily
Nadjarzadeh et al. (2011)	24	23	200 mg daily

TABLE 2 Detailed description of each study included in the meta-analysis

Study details	Balercia et al. (2009)	Safarinejad (2009)	Nadjarzadeh et al. (2011)
Study type	Double-blind, randomised, placebo-controlled trial	Double-blind, randomised, placebo-controlled trial	Double-blind, randomised, placebo-controlled trial
Patients recruited	*n* = 60	*n* = 212	*n* = 60
Age group	27–39 years, mean = 32 years	21–42 years, mean = 28 years	25–46 years, mean = 34 years
Idiopathic infertility diagnosis	Asthenozoospermia	Oligoasthenoteratozoospermia	Oligoasthenoteratozoospermia
Inclusion criteria	More than two years, regular unprotected sex with a potentially fertile female	No child besides two years, regular sexual intercourse	No pregnancy during unprotected sex whole year
Genital diseases	Absent	Absent	Absent
Medical therapy	No medication for at least for 3 months before the study began	No medical therapy for at least 12 weeks before the study began	No medical therapy for at least 3 months before the study began
Intervention	CoQ10 200 mg, 2 times a day, placebo: 2 times a day, duration of treatment: 6 months, total 9 months study	CoQ10 300 mg, single daily dose, placebo single dose daily, duration of treatment: 26 weeks, total 20 months study	CoQ10 200 mg single daily dose, placebo: single daily dose, duration of treatment: 12 weeks, total 19 months study
Outcomes	Seminal parameters improved	Seminal parameters improved	Seminal parameters improved

The publication bias was investigated using funnel plot, followed by asymmetry assessment of the funnel plot by Egger's regression intercept test. The sensitivity analysis was done by removing one study at a time and calculating the overall effect on the rest of the studies.

3 | RESULTS

After literature screening, we identified 9 studies that evaluated the effect of CoQ10 with or without other supplements on semen parameters. Since the aim of this study was to evaluate the effect of CoQ10 only, we selected randomised placebo-controlled trials on CoQ10 for quantitative data analysis. Three randomised placebo-controlled trials on CoQ10 (Balercia et al., 2009; Nadjarzadeh et al., 2011; Safarinejad, 2009) were subjected to quantitative data analysis, and the remaining studies were used for qualitative analysis (Figure 1).

3.1 | Sperm concentration (million/ml)

All three studies analysed sperm concentration (million/ml). In the original investigations, only one study showed a significant improvement in sperm concentration (Safarinejad, 2009), while the two other studies showed no significant improvement. Heterogeneity test for sperm count showed a significant heterogeneity ($Q = 17.48$, $I^2 = 88.56$, $p = .00001$), suggesting the use of random effects model for inference. Pooled analysis showed no significant improvement in sperm concentration upon CoQ10 administration (SDM = 0.67, 95% CI = −0.10 to 1.45, $p = .089$; Figure 2 and Table 3). Funnel plot showed the lack of publication bias (Figure S1).

3.2 | Total sperm motility (%)

All three studies included in the meta-analysis evaluated sperm motility. In the original investigations, two studies showed a significant improvement in sperm motility (Balercia et al., 2009; Safarinejad, 2009), while the third study showed no significant improvement. Heterogeneity test for sperm motility showed no significant heterogeneity between studies ($Q = 4.48$, $I^2 = 55.43$, $p = .106$), suggesting the use of fixed effect model for inference. Pooled analysis showed a significant improvement in sperm motility upon CoQ10 administration (SDM = 1.47, 95% CI = 1.22–1.73, $p = .000$; Figure 2 and Table 3). Funnel plot showed the lack of publication bias (Figure S1).

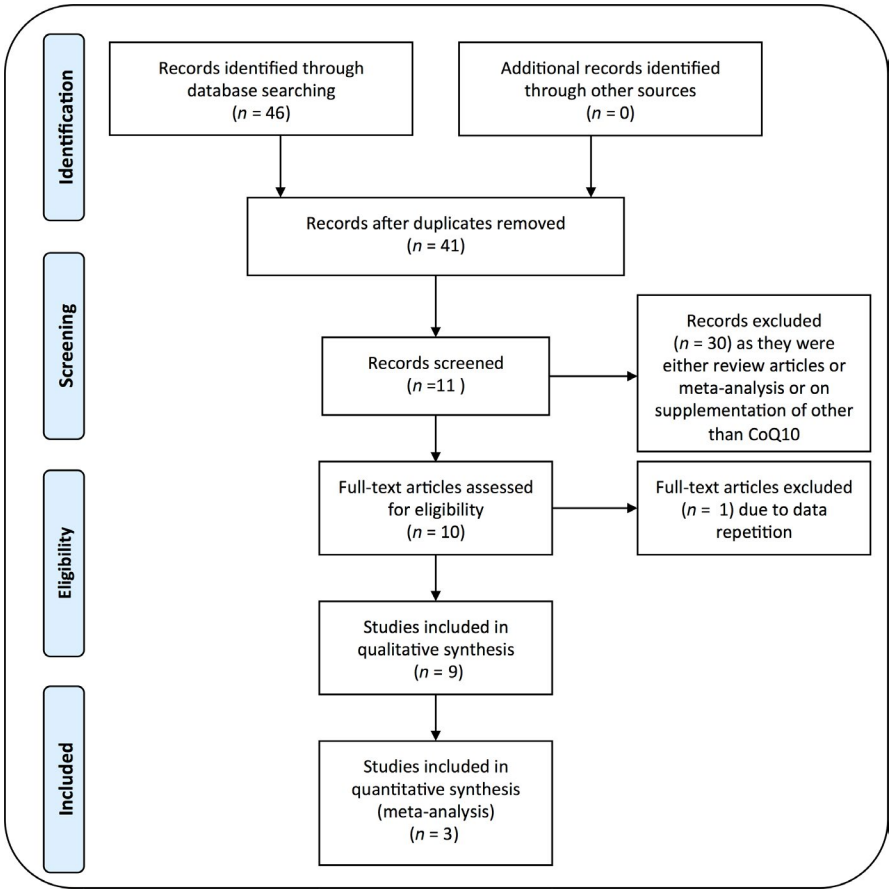

FIGURE 1 PRISMA flow chart for the screening of studies for meta-analysis

3.3 | Forward motility (%)

Only two studies (Balercia et al., 2009; Nadjarzadeh et al., 2011) had analysed forward motility, of which one claimed a significant improvement in forward motility (Balercia et al., 2009), while the other reported no improvement (Nadjarzadeh et al., 2011). Heterogeneity test for sperm forward motility showed no significant heterogeneity between studies (Q = 2.11, I^2 = 52.80, p = .145), suggesting the use of fixed effect model for inference. Pooled analysis showed a significant improvement in sperm forward motility upon CoQ10 administration (SDM = 0.66, 95% CI = 0.27–1.06, p = .001; Figure 2 and Table 3).

3.4 | Sperm morphology (%)

Two studies (Nadjarzadeh et al., 2011; Safarinejad, 2009) evaluated sperm morphology, of which one reported a significant improvement in sperm morphology (Safarinejad, 2009), while the other found no significant improvement (Nadjarzadeh et al., 2011). Heterogeneity test for sperm morphology showed a significant heterogeneity between studies (Q = 3.44, I^2 = 70.93, p = .06), suggesting the use of random effects model for inference. Pooled analysis showed no significant improvement in sperm morphology upon CoQ10 administration (SDM = 1.24, 95% CI = −0.56 to 3.03, p = .176; Figure 3 and Table 3).

3.5 | CoQ10 level in seminal plasma (ng/ml)

Two studies (Balercia et al., 2009; Safarinejad, 2009) had analysed seminal level of CoQ10, but Nadjarzadeh et al., (2011) did not present this data; however, the authors presented these data in their later study on the same patients (Nadjarzadeh et al., 2014). Out of three, two studies reported a significant improvement in seminal plasma CoQ10 level (Balercia et al., 2009; Safarinejad, 2009), while the third reported no significant improvement (Nadjarzadeh et al., 2011). Heterogeneity test for CoQ10 level showed a significant heterogeneity between studies (Q = 107.04, I^2 = 98.13, p = .000), suggesting the use of random effects model for inference. Pooled analysis showed no significant improvement in seminal CoQ10 level upon CoQ10 administration (SDM = 2.11, 95% CI = −0.21 to 4.43, p = .074; Figure 3 and Table 3). Funnel plot showed the lack of publication bias (Figure S1).

3.6 | Ejaculate volume (ml)

Two studies (Nadjarzadeh et al., 2011; Safarinejad, 2009) presented semen volume data, both of which reported no significant improvement in ejaculate volume. Heterogeneity test for ejaculate volume showed no significant heterogeneity between studies (Q = 0.01, I^2 = 0, p = .90), suggesting the use of fixed effect model for inference. Pooled analysis showed no significant improvement in

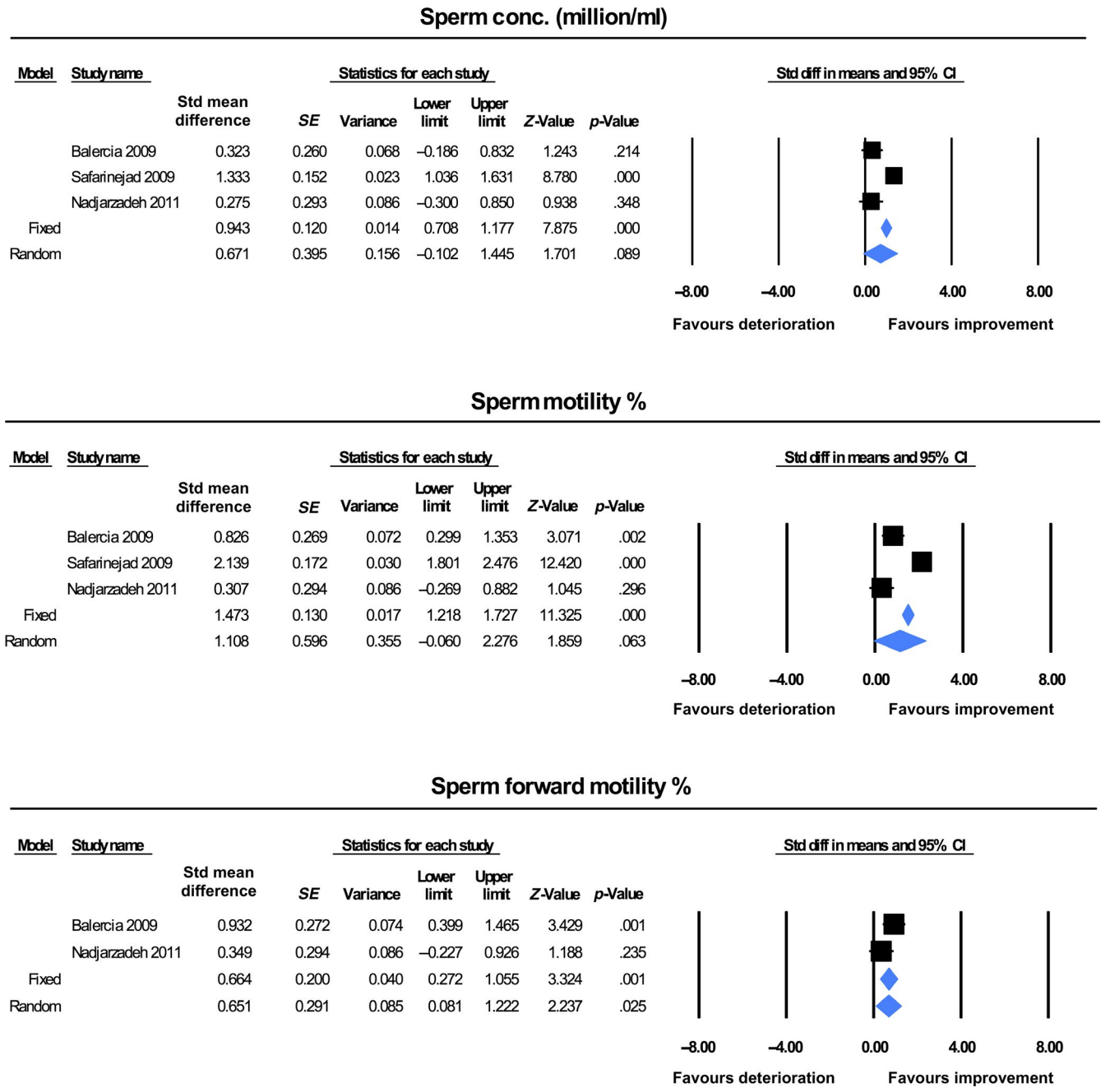

FIGURE 2 Forest plot for meta-analysis on sperm concentration (million/ml), sperm motility (%) and sperm forward motility (%). The *Z* value shows the degree and direction of relationship, whereas the *p* value shows the significance of the relationship. The horizontal bar shows the range of mean with a square in the centre. The direction of the projection of the horizontal bar shows the direction of the association. The diamond-shaped box shows the pooled OR and its width indicates the 95% CI

sperm morphology upon CoQ10 administration (SDM = 0.057, 95% CI = −0.19 to 0.30, p = .647; Figure 3 and Table 3).

4 | DISCUSSION

Various studies on male infertility support the role of CoQ10 in improving sperm motility (Ahmadi, Bashiri, Ghadiri-Anari, & Nadjarzadeh, 2016; Balercia et al., 2004). The purpose of this quantitative assessment was to provide a critical evaluation of the effect of CoQ10 administration on semen parameters in infertile men. To strictly evaluate the impact of CoQ10 on semen parameters, we included only double-blind, placebo-controlled, randomised clinical trials. We found that CoQ10 administration results in significant improvements in sperm motility and forward sperm motility without a significant improvement in sperm count, sperm morphology and ejaculate volume. These results suggest that CoQ10 can be the therapy of choice for asthenozoospermia, but not for oligozoospermia. The improvement in sperm motility upon CoQ10 administration may be explained on the basis of improvement in mitochondrial function,

TABLE 3 Summary of the results of meta-analyses for different semen parameters

Study parameters	Meta-analysis model chosen	SDM (95% CI)	*p* Value	Number of patients
Sperm conc.	Random	0.67 (−0.10 to 1.44)	.089	296
Sperm motility	Fixed	1.47 (1.22–1.73)	.000	296
Forward motility	Fixed	0.66 (0.27–1.06)	.001	102
Sperm morphology	Random	1.24 (−0.56 to 3.03)	.176	241
Seminal CoQ10 level	Random	2.11 (−0.21 to 4.43)	.074	296
Ejaculate volume	Random	0.06 (−0.19 to 0.30)	.647	241

which is supported by in vivo studies in various biological systems (Gvozdjáková et al., 2014), including in ageing (Hernández-Camacho, Bernier, López-Lluch, & Navas, 2018).

Various studies used different doses and durations of CoQ10 administration. There were significant variations in the outcomes of these studies, which in addition to unknown factors can be attributed to the dose and duration. The three RCT studies administered 200–300 mg for a duration of 12–26 weeks. Among the studies included in this meta-analysis, Safarinejad (2009) used the highest dose (300 mg) for the longest duration (26 weeks), which incidentally also showed the most significant improvement in most of the parameters. Recent investigations suggested that a higher daily dose of CoQ10 (400–600 mg) gives better results in comparison with 200 mg dose (Alahmar, 2019). Furthermore, it is seen that the noticeable improvement is seen after a minimum of 3 months of treatment (Alahmar, 2019). Nevertheless, treatment beyond 6 months does not show further improvement (Alahmar, 2019; Safarinejad, 2009). The latter is important as some recent studies have shown that extreme consumption of antioxidants can change the oxidation–reduction equilibrium to reductive stress, which is as damaging as oxidative stress (Henkel, Sandhu, & Agarwal, 2019).

Evidence suggest that semen quality has decreased significantly over the last 40 years (Mishra et al., 2018; Sengupta, Dutta, & Krajewska-Kulak, 2017). Oxidative stress is established as a critical factor in male infertility pathophysiology with approximately 30–80 per cent of male infertility is considered to have contribution from high ROS (Showell et al., 2014). Higher ROS concentrations may damage plasma membrane, proteins and sperm DNA, imposing that suitable antioxidant capacity is critical to ensure male fertility (Darbandi et al., 2018). Previous studies on CoQ10 have established its antioxidant capacity, which improves total antioxidant capacity (TAC), superoxide dismutase (SOD) and catalase (CAT) activity (Alahmar, 2019; Balercia et al., 2009; Safarinejad, 2009). The effect of CoQ10 in improving mitochondrial function and sperm motility may be explained by improvement in the antioxidant capacity, which prevents the loss of cell integrity. Improvement in testosterone level or at least amelioration of the reduction in testosterone could be another mechanism underlying the action of CoQ10 (Banihani, 2018).

This meta-analysis had some limitations. Among the foremost is the less number of studies. Till date, only three placebo-controlled RCTs have been undertaken, most of which were small trials. Despite pooling from the available studies, the maximum sample size for any parameter was 296, which does not provide very high power to statistical analysis. It may be noted that the fixed effect model was used to draw the inferences for sperm motility and forward motility in the absence of heterogeneity. Since fixed effect model is less stringent in comparison with the random effects model, these results need support from more trials. For all other parameters, random effects model was used for drawing inference. Since heterogeneity is a significant player in drawing inference in meta-analysis, further large-scale trials would provide strength to these conclusions. Only one study had scored pregnancy achievement upon CoQ10 administration, limiting the possibility of undertaking a pooled analysis on this parameter.

5 | CONCLUSION

Data analysis across the studies, evidence from all studies and the quantitative synthesis from meta-analysis suggested that CoQ10 appears to have a profound effect on sperm motility, but this is subject to further studies on this. Nevertheless, the effect on other parameters was meagre. Based on this analysis, we conclude that CoQ10 appears to have a significant beneficial effect on sperm motility and forward motility without affecting sperm count. Therefore, CoQ10 can be the therapy of choice for asthenozoospermic infertility with a dose of 200–400 mg for a period of 3–6 months depending upon the severity and patient's response, which should be monitored on a monthly basis. There is evidence that CoQ10 in combination with other vitamins and antioxidants may improve overall semen quality. Certainly, large-scale randomised trials with or without combination with other vitamins and antioxidants are required for unambiguously establishing the importance of CoQ10 in treating male infertility.

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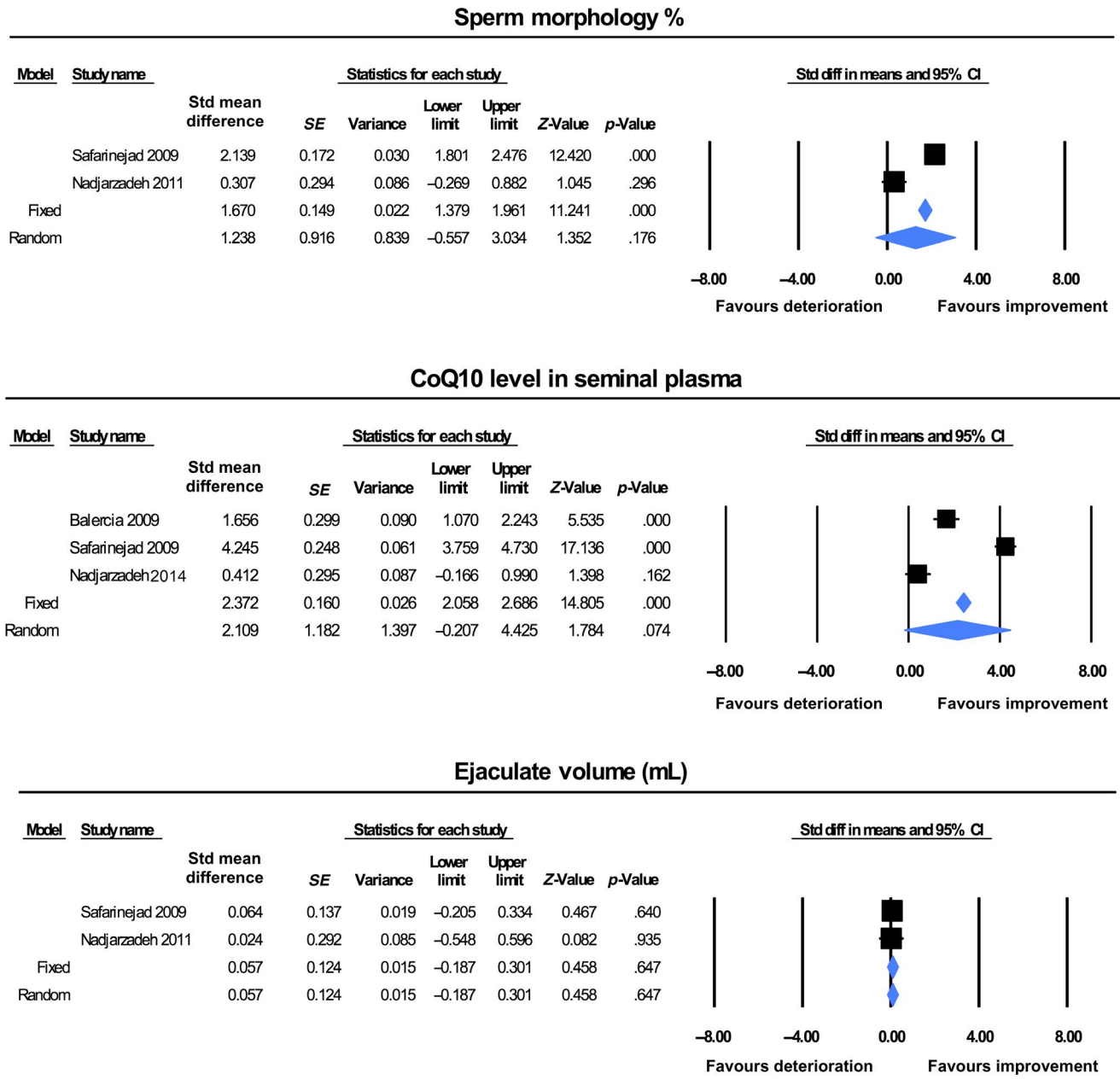

FIGURE 3 Forest plot for meta-analysis on sperm morphology (%), CoQ10 level in seminal plasma (ng/ml) and ejaculate volume (ml). The *Z* value shows the degree and direction of relationship, whereas the *p* value shows the significance of the relationship. The horizontal bar shows the range of mean with a square in the centre. The direction of projection of the horizontal bar shows the direction of association. The diamond-shaped box shows the pooled mean, and its width indicates the 95% CI

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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