What are the benefits of empiric nutritional and medical therapy on semen parameters, the pregnancy rate, and live birth rates in couples with idiopathic infertility? A systematic review and meta-analysis

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Abstract

Context: The 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 the evidence comparing the benefits of nutritional and medical therapy on pregnancy rate and semen parameters in men with idiopathic infertility.

Evidence acquisition: Literature search was performed using MEDLINE, EMBASE, LILACS and the Cochrane Library (searched from January 1st 1990 to September 19th 2017). We adopted the methods as detailed in the Cochrane Handbook. GRADE was adopted in order to assess certainty of evidence.

Evidence synthesis: Literature search identified 5663 citations, and after abstract and full-text screening 61 studies (59 RCTs and 2 non-randomised comparative studies) were included. Pooled results demonstrated that pentoxyfylline, co-enzyme Q10, L-carnitine, FSH, 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. GRADE certainty of evidence for all the outcomes was very low mainly due methodological flaws and inconsistencies with study design, and inconsistency. Some outcomes were also downgraded due 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 improved 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 has identified several medical and nutritional treatments such as pentoxyfylline, co-enzyme Q10, L-carnitine, FSH, Tamoxifen and kallikrein, appear to improve semen parameters. In spite of this, there are limited data suggesting pregnancy and live birth rates are increased, and is attributable to methodological flaws in studies and the low number of reported pregnancies.

1.1 Description of the condition

Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy within one year [1]. Approximately 1 in 8 couples do not achieve pregnancy within one year 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 is idiopathic in up to 25% of patients [3]. Idiopathic male infertility is clinically diagnosed after excluding all known causes of impaired spermatogenesis.

1.2 Description of the interventions

Medical and nutritional interventions have been utilised for treating male idiopathic infertility [2]. Many of these therapies are off-label, and the evidence for their usage is limited. Medical therapies include hormonal therapies, which modulate the hypothalamic-pituitary-testicular axis. Gonadotrophins [Gonadotropin Releasing Hormone (GnRH), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and human Chorionic Gonadotropin (hCG)] have all been used in treating idiopathic male infertility. FSH directly acts on Sertoli cells to stimulate spermatogenesis, whilst 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.

Whilst, intra-testicular testosterone is required for spermatogenesis, exogenous testosterone inhibits pituitary LH and FSH production due to a classic negative feedback mechanism leading to inhibition of spermatogenesis. Clomiphene and tamoxifen are Selective Estrogen 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. Whilst, reactive oxygen species (ROS) are required for normal sperm function, excessive production of ROS has been implicated in the pathophysiology of male infertility. Elevated ROS levels are associated with abnormal sperm development, function, fertilizing capacity and sperm DNA damage. Sperm DNA damage has been associated with recurrent failure of fertilisation and recurrent pregnancy loss from both natural conception and assisted reproductive technologies. Carnitines, N-Acetyl cysteine and selenium have antioxidant properties protecting sperm from the negative effects of ROS [4-6]. Zinc and selenium both play a role in testicular function, spermatozoa oxygen consumption, sperm chromatin stabilization, sperm capacitation and may mediate intra-testicular testosterone levels [6, 7]. Several vitamins act as potent antioxidants, inhibiting free-radical-induced damage to cell membranes, decreasing seminal ROS and inhibiting free-radical-induced damage. Coenzyme Q-10 (CoQ10) is implicated in mitochondrial bioenergetics, which is important in sperm maturation [8].

Systematic reviews assessing FSH, Clomiphene citrate, gonadotrophins, tamoxifen and several nutritional therapies have previously reported some improvement in sperm quality and spontaneous pregnancy rates [9-12]. Conversely, androgens, bromocriptine, α-blockers, systemic corticosteroids and magnesium supplementation have been shown to be ineffective [2]. The management of men with idiopathic infertility remains challenging, mainly due to large numbers of different treatments and conflicting evidence from individual studies. Against this backdrop, this systematic review (SR) was conducted.

1.3 Aims and objectives

We systematically reviewed the evidence comparing the benefits of nutritional and medical therapy on the pregnancy rate and semen parameters in men with idiopathic infertility.

2. Methods

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

2.1 Literature Search

Electronic databases included Medline, Medline In-Process, EMBASE, Cochrane Controlled Trials Register, and LILACS; January 1990, to September 2017. Studies were limited to those written in the English language whilst conference abstracts were excluded from analysis. The complete search strategy is available online in Supplementary Appendix 1.

The detailed PICO search strategy is shown in Table 1.

2.6 Data collection and analysis

Two reviewers (RP and BK) independently performed abstract and full-text screening. Any disagreements were resolved by discussion or by consulting a third reviewer (HMB). Two reviewers independently extracted outcome data. Any disagreements were resolved by discussion or by consulting a third reviewer (MIO or HMB). Study authors were contacted to provide missing information.

The 'risk of bias' (RoB) of each included study was independently assessed by two reviewers (RP and BK). Any disagreements were resolved by discussion or by consulting a third reviewer (MIO or HMB). We used Cochrane RoB assessment tool for RCTs [14, 15]. Non-randomised studies were assessed by using ROBINS-I tool [16].

Meta-analysis was performed when more than one randomised controlled trial 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 effect across similar studies and their 95% CIs. When clinical or methodological heterogeneity was suspected, then a random effects model was used. For continuous outcomes, each trial was summarised using the mean value for each group and SD, and combined as mean difference (MD) if the same scale was used for the outcome measurement in more than one trial. We used Odd Ratio (OR) for dichotomous outcomes. We identified heterogeneity by visually inspecting the forest plots and by using a standard Chi^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 meta-analysis. We planned to use a funnel plot to interpret publication bias. However, there were fewer than 10 trials in the meta-analyses, and therefore we did not use these plots as per guidance of the Cochrane Handbook. Quantitative synthesis was undertaken for non-randomised studies.

The GRADE approach was used to assess the certainty of evidence for each comparison [14]. 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 in order to judge imprecision and to assess the overall quality of evidence. We assumed an alpha of 0.05, a beta of 0.20, and an a priori anticipated intervention effect with a mean difference of 10% across the two groups. The final optimal information size was 392 participants. Certainty of evidence was assessed by the reviewer MIO.

3. Evidence synthesis

3.1. Quantity of evidence identified and characteristics of included studies

5663 abstracts were identified in the literature search, and 226 were selected for full-text screening. 61 studies (59 RCTs and 2 non-RCTs) met the inclusion criteria and were included in this SR [17-78]. The literature flow process is graphically illustrated in the PRISMA diagram (Figure 1).

3.2 Baseline Characteristics of included studies:

We extracted detailed baseline information on all of the included studies. The following information can be found in Supplementary Table 1 and Supplementary Table 2:

- Inclusion criteria
- Exclusion criteria
- Number of participants included in the studies
- Intervention and comparator, including number of participants in each arm
- Definition of idiopathic infertility
- Treatment duration

3.3. Risk-of-bias assessment

3.3.1 Cochrane risk of bias assessment of randomised controlled trials:

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. 25 studies were judged high and 5 unclear for the domain blinding of participants and personnel. 14 studies were judged high RoB from blinding of outcomes, and 16 studies were judged high and 4 unclear for attrition bias. Three studies were judged high and 30 as unclear for reporting bias. Risk of Bias assessment is graphically represented in Figure 2.

3.3.2 ROBINS-I

We identified 2 non-randomised studies, which were included in this SR [69, 74]. We used ROBIN-I, a tool for assessing risk of bias in non-randomised studies of interventions. Risk of Bias assessment of these two studies were judged critical [69, 74]. Detailed results are available in Supplementary Table 3.

3.4 GRADE:

Certainty of evidence was assessed by adopting GRADE. A number of studies had methodological issues as discussed earlier under risk of bias assessment. The evidence was also downgraded due to clinical and statistical heterogeneity. This was judged by high I^2 value; or χ^2 statistics.

3.5. Results of comparisons of interventions

3.5.1: Influence of Intervention on live birth rate and pregnancy rate

Data on live birth rates were reported in only 4/61 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 33/60 studies. Pregnancies were either spontaneous or with ART. In all the studies evaluated the number of pregnancies reported was very low and meta-analysis pooling the results was not possible for the majority of comparisons. Therefore, the results of this SR, focused mainly on the secondary outcome i.e. the effectiveness of therapy on routine and functional semen parameters. Data concerning the live birth rates and pregnancy rates are shown in Supplementary Table 1; and Supplementary Figure 1.

3.5.2. Results on changes in routine semen parameters following intervention

Results of the following semen parameters are reported:

- Sperm morphology reported as the percentage change before and after treatment across the groups; meta-analysis indicate mean percentage difference along with standard deviation (SD)
- Sperm motility reported as the percentage change before and after treatment across the groups; meta-analysis indicate mean percentage difference along with SD
- Sperm concentration reported as $X10^6$/ml; meta-analysis indicate the mean sperm count difference along with SD

3.5.2.1. Meta-analysis of change in semen parameters following intervention

Figures 3, 4 and 5 illustrate the Forest plots generated from meta-analysis performed on data extracted from studies evaluating Recombinant FSH v placebo on alterations in semen parameters (sperm morphology, sperm motility and sperm concentration). Supplementary Figures 1 illustrates the Forest plot generated from meta-analysis performed on data extracted from studies evaluating the same intervention comparison on alterations in semen parameters where multiple studies evaluating the same comparison were assessed. These included placebo controlled studies evaluating pentoxyfylline, CoQ10, L-carnitine and L-acetyl carnitine, recombinant FSH, tamoxifen and kallikrein.

Meta-analysis demonstrated a significant improvement with the use of pentoxyfylline, CoQ10, and L-carnitine on sperm concentration when compared with placebo (Supplementary Figure 1). Pentoxyfylline, CoQ10, L-carnitine, tamoxifen and kallikrein showed a significant improvement in sperm motility. Pentoxyfylline, CoQ10, L-carnitine, L-carnitine in addition to L acetyl carnitine and kallikrein showed a significant improvement in sperm morphology.

3.5.3.1 Meta-analysis of change in semen parameters following intervention with pentoxyfylline versus placebo:

Three studies evaluating pentoxyfylline against placebo were identified [17, 28, 52]. In 2 studies the daily dose was 800mg and in the remaining study it was 1200mg. The treatment duration varied between 3-6 months. Sperm concentration [mean sperm count difference (8.98 X 10^6/ml, 95% CI 8.06 X10^6/ml to 9.90 X10^6/ml; participants = 413; studies = 3; I^2 = 95%), P<0.0001, low certainty evidence], motility [mean percentage difference 11.96 (95% CI, 11.28 to12.64; participants = 413; studies = 3; I^2 = 98%), P<0.0001, low certainty evidence] and morphology improved with treatment [mean percentage difference 5.56, (95% CI, 4.99 to 6.13; participants = 413; studies = 3; I^2 = 97%), P<0.0001), low certainty evidence].

3.5.3.2 Meta-analysis 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 or 6 months. Sperm concentration [mean sperm count difference 8.49 X 10^6/ml (95% CI, 7.62 X10^6/ml to 9.37 X10^6/ml; participants=432; studies=3; I^2=96%) P<0.0001, low certainty evidence], motility [mean percentage difference 7.08 (95% C, 6.62 to 7.53; participants=432; studies=4; I^2=99%) P<0.0001, low certainty evidence] and morphology [mean percentage difference 14.94 (95% CI, 14.31 to 15.57; participants=432; studies=3; I^2 = 100%) P<0.0001, low certainty evidence] improved with treatment.

3.5.3.3. Meta-analysis of change in semen parameters following intervention with L-carnitine versus placebo:

Six studies evaluating L-carnitine treatment against placebo were identified [17, 37, 39, 41, 43, 72]. Studies used doses of 1g, 2g or 3g daily. The results were not statistically significant for pregnancy rate [(OR 1.99, 95% CI 0.50 to 7.88; participants=90; studies=2; I^2 = 61%) P=0.33, very low certainty evidence]. Sperm concentration [mean sperm count difference 6.57 X 10^6/ml (95% CI, 5.95 X 10^6/ml to 7.16 X 10^6/ml; participants=289; studies=4; I^2=99%) P<0.0001, very low certainty evidence] and motility [mean percentage difference 18.38 (95% CI, 17.66 to 19.10; participants=289; studies=4; I^2=99%) P<0.0001, very low certainty evidence] appeared to improve with treatment but not morphology [mean percentage difference 1.94 (95% CI, 1.81 to 2.07; participants=199; studies=3; I^2=98%) P<0.0001, very low certainty evidence].

3.5.3.4 Meta-analysis of change in semen parameters following intervention with L-carnitine with L-acetyl carnitine versus placebo:

Three studies evaluated combined L-carnitine with L-acetyl carnitine treatment against placebo [37, 39, 41]. The duration of therapy in both studies was 6-months and used 2g L- carnitine daily. The results were not statistically significant for pregnancy rate [(OR 1.67, 95% CI 0.49 to

5.70; participants=111; studies=3; I^2=28%), p=0.42, very low certainty evidence]. Sperm motility improved with treatment [mean percentage difference 4.22 (95% CI, 0.48 to 7.97; participants=111; studies=3; I^2=90%) P=0.03, very low certainty evidence], although sperm concentration [mean sperm count difference 2.63 X 10^6/ml (95% CI, -2.82 X 10^6/ml to 8.08 X 10^6/ml; participants=86; studies=2; I^2 = 0%) P=0.34, very low certainty evidence] and morphology [mean percentage difference -1.61 (95% CI, -4.77 to 1.55; participants=86; studies=2; I^2=93%) P=0.32, very low certainty evidence] did not.

3.5.3.5 Meta-analysis of change in semen parameters following FSH treatment versus placebo:

Whilst 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 published by Paradisi and colleagues in 2013 was the continuation of a study published in 2006. Therefore, we did not duplicate participants, whilst extracting data from the two reports [38, 78]. All studies used differing rFSH regimes, and used 50IU to 300IU administered daily or on alternate days. The duration of therapy was 3-4 months in all studies. The pregnancy rates were higher in patients receiving rFSH [(OR 3.30, 95% CI 1.39 to 7.82; participants=343; studies=5; I^2=0%), P=0.007, low certainty evidence]. Sperm concentration [mean sperm count difference 3.17 X 10^6/ml, 95% CI 2.44 X 10^6/ml to 3.91 X 10^6/ml; participants=444; studies=7; I^2=94%)) P<0.0001, very low certainty evidence] and morphology [mean percentage difference 1.54, 95% CI 0.29 to 2.80; participants=446; studies=7; I^2= 97%) P=0.02, very low certainty evidence] appeared to improve with treatment but not motility [mean percentage difference 0.39 (95% CI, -0.27 to 1.05; participants=476; studies=7; I^2=21%) P=0.25 very low certainty evidence]. It should be noted that the pooled estimate of effect on sperm morphology was strongly influenced by the study conducted by Farrag and colleagues, and the result became insignificant on sensitivity analysis after we excluded the results from this study from the pooled estimate of treatment effect [mean percentage difference -0.02, 95% CI 0.49 to 0.45; participants=364; studies=6; I^2=77%) P=0.94, very low certainty evidence] [76].

3.5.3.6 Meta-analysis 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 (between 100 IU to 300 IU administered daily or on alternate days) and duration of therapy (3-4 months). The results were not statistically significant for pregnancy rate [(OR 0.80, 95% CI 0.32 to 2.03; participants=193; studies=2; I^2= 0%), P=0.64, very low certainty evidence]. Although there was an improvement in sperm motility with kallikrein [mean percentage difference 2.69 (95% CI, 2.05 to 3.32; participants=302; studies=3; I^2=86%) P<0.00001, very low certainty evidence] a larger improvement in sperm concentration was seen in the placebo groups than following kallikrein treatment [mean difference -4.23 (95% CI -5.38 to -3.08; participants=213; studies=2; I^2=76%) P<0.0001, low certainty evidence].

3.5.3.7 Meta-analysis 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-months. The results were not statistically significant for pregnancy rate [(OR 2.48, 95% CI 0.67 to 9.23; participants=203; studies=2; I^2=0%), P=0.17, very low certainty evidence]. Sperm concentration [mean difference 2.62 (95% CI, 1.63 to 3.61; participants=160; studies = 2; I^2=0%) P<0.0001, low certainty evidence], motility [mean percentage difference 6.74 (95% CI, 4.95 to 8.52; participants=287; studies=3; I^2=67%) P<0.0001, low certainty evidence] and morphology [mean percentage difference 0.59 (95% CI, 0.41 to 0.77; participants=201; studies=2; I^2=97%) P<0.0001, very low certainty evidence] improved with treatment.

3.6 Results of remaining RCTs, comparative studies and non-randomised trials

As shown in Supplementary Table 2, 24 studies were unique i.e. reported in a single study and therefore results could not be pooled together. Treatments included nutritional supplements such as: saffron, Withania somnifera, alpha lipoic acid, omega fatty acids, selenium, N- Acetyl

Cysteine, magnesium, Y-Virilin, vitamin E, ginger and probiotic. Medical treatments included; lisinopril, tranilast, testosterone, terazosin, bunazosin, GnRH and mesterolone. An observational study assessed rFSH response relative to a control group who received no treatment [69].

4 Discussion:

4.1 Principal findings

We found some improvements in semen parameters, but due to the short follow-up and low number of positive events, it is difficult to draw conclusions on pregnancy or live birth rates with 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 6 and unclear in 36 studies. This was considered whilst assessing the overall certainty of evidence. As a result, the majority of outcomes were either rated as “low” or “very low” whilst assessing the certainty with GRADE approach. Therefore, the findings of this SR should be interpreted with caution.

FSH and tamoxifen treatment resulted in improvement in sperm concentration, whilst sperm motility improved with tamoxifen and sperm morphology improved with FSH. Data on pregnancy rate however, 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 prior to 1990. Santi et al demonstrated similar findings with regards to improvements in semen parameters and pregnancy rate, as in the present SR [10].

Nutritional supplements may have antioxidant activity [79, 80]. Antioxidants may protect against free radical injury, with infertile men having higher levels of ROS. Antioxidants have

been shown to improve spermatogenic function and sperm DNA integrity [81, 82]. Thus, reducing oxidative stress with the use of a nutritional antioxidant supplementation has the potential to improve semen parameters and ultimately pregnancy rates.

We found that anti-oxidants 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 reporting on pregnancy rates are limited by the low number of positive events.

Low levels of carnitine have been reported in the semen of men with OATs [83] and sperm motility could be improved when exposed to L-carnitine [84]. However, the present meta-analysis of 6 studies showed only a marginal improvement of sperm concentration and motility.

CoQ10 plays an integral role in cellular respiration and high seminal coenzyme Q levels are associated with sperm motility and antioxidant capacity [85]. Although there are only 4 RCTs in this review comparing CoQ10 with placebo, 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 measures to indicate the effectiveness of intervention on male fertility is pregnancy rate or live birth rate; which is superior to utilising 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.

Recommendations for future research:

In this SR, anti-oxidant nutrient supplements (e.g. co-enzyme Q10, L-carnitine) were shown to significantly improve 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 COMET or ICHOM methodology.

In summary, well conducted and designed prospective studies are needed to identify optimum dosage regimens and duration of treatments, whilst utilising pregnancy and live birth rates as primary outcome measures following therapeutic interventions. Future trials should follow the recommendations of the CONSORT statement.

4.2 Strengths and limitations of the review

The major strengths of this SR are:

- First review to perform a comprehensive literature search for all medical and nutritional treatments for idiopathic male infertility.
- Robust and transparent methodological approach based on Cochrane Handbook.

The major limitation of the review is:

- Significant heterogeneity among the identified studies
- The possibility of publication bias cannot be completed eliminated.
- Majority of the studies were under-powered with a small sample size.

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 spontaneous pregnancy, pregnancy rates with assistant reproductive techniques or live birth rates.

Author Contributions:
Study Concept and design: M.O, R.P, B.K, M.B, T.D, C.K, H.T, Z.K, Y.Y, A.J, S.M
Acquisition of data: M.O, R.P, B.K, M.B, Y.Y
Analysis and interpretation of data: M.O, R.P, B.K, M.B
Drafting of the manuscript: M.O, R.P, B.K, S.M
Critical revision of the manuscript for important intellectual content: M.O, R.P, S.M
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Supervision: M.O, A.J, S.M

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- Ferring Arzneimittel GmbH

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P	**Population**	**Inclusion criteria:** • Male patients aged ≥18 with idiopathic male factor infertility • Couple infertility as defined by the WHO and altered semen parameters according to the WHO manual used at the time of publication of the paper: oligozoospermia / asthenozoospermia / teratozoospermia / azoospermia AND Idiopathic defined as exclusion of all known causes of impaired spermatogenesis (as defined by authors) - if defined by the authors different than above, the study is retained and the results presented as a subgroup analysis **Exclusion criteria:** • Idiopathic hypoganodatrophic hypogonadism • Genetic alterations (e.g. Kallmann syndrome, Klinefelter's syndrome)
I	**Intervention**	• Nutritional therapy including: trace elements (zinc, copper), vitamin C, vitamin E, anti-oxidants, coenzyme Q10, herbal therapy, aminoacides (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, gonadotrophins, 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 of idiopathic male infertility on the live birth rate / pregnancy rate. **Secondary outcome:** • Effectiveness of therapy on routine and functional semen parameters and the development of treatment related adverse outcomes or side effects

Table 1: PICO Search strategy

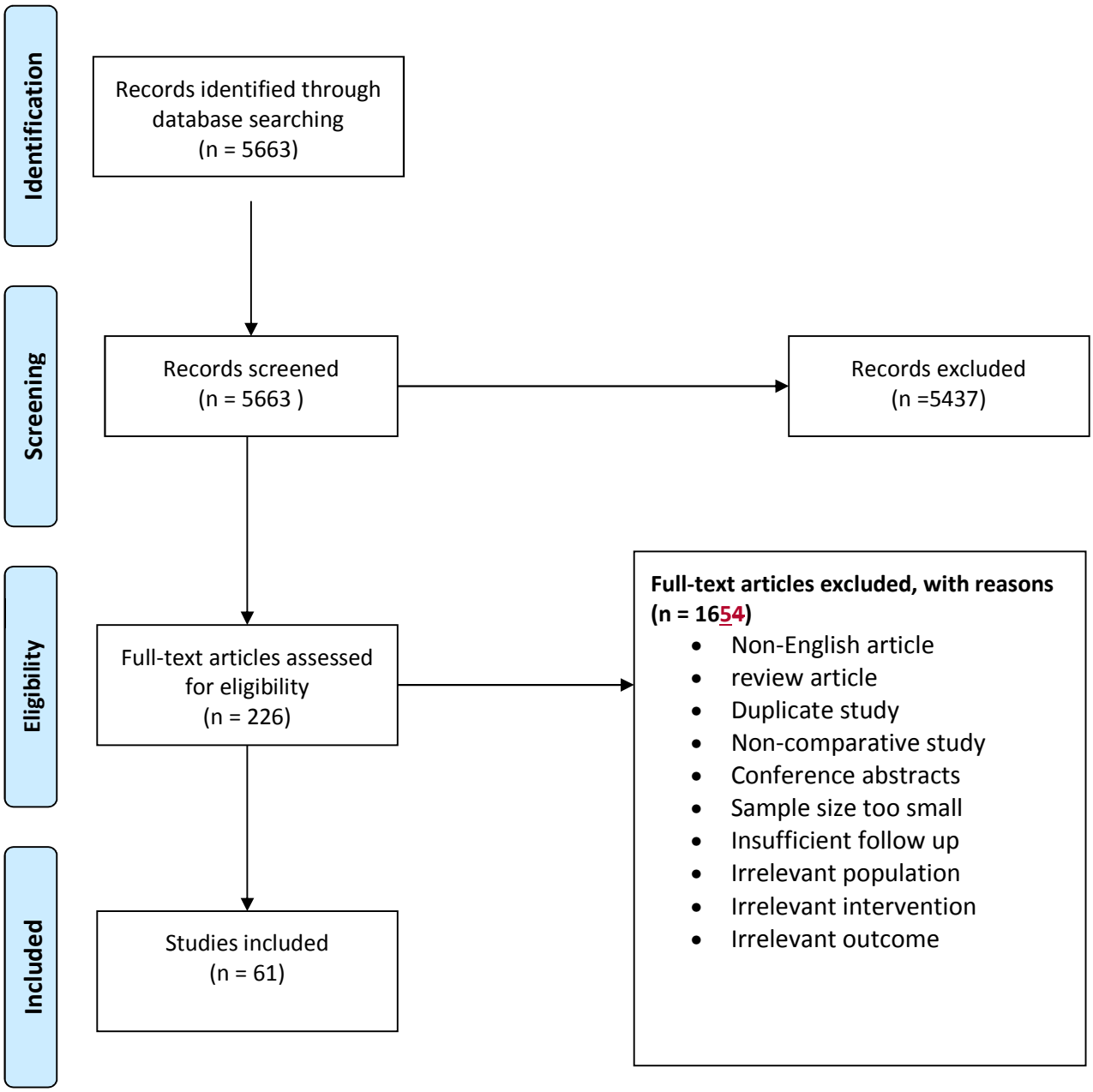
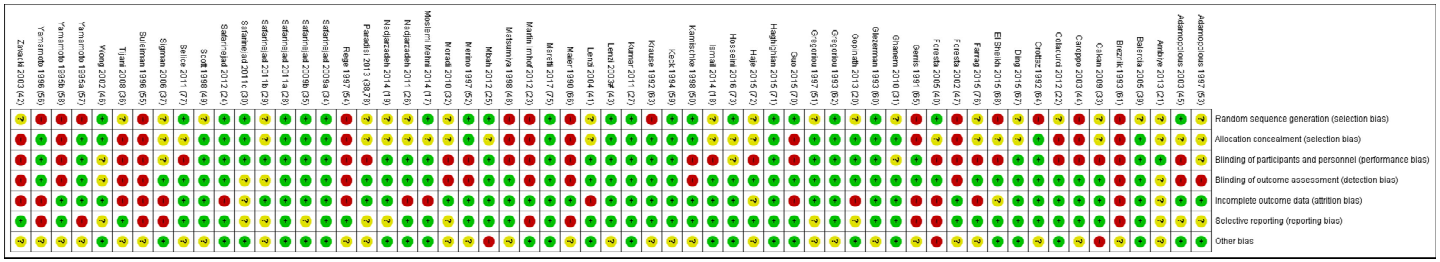
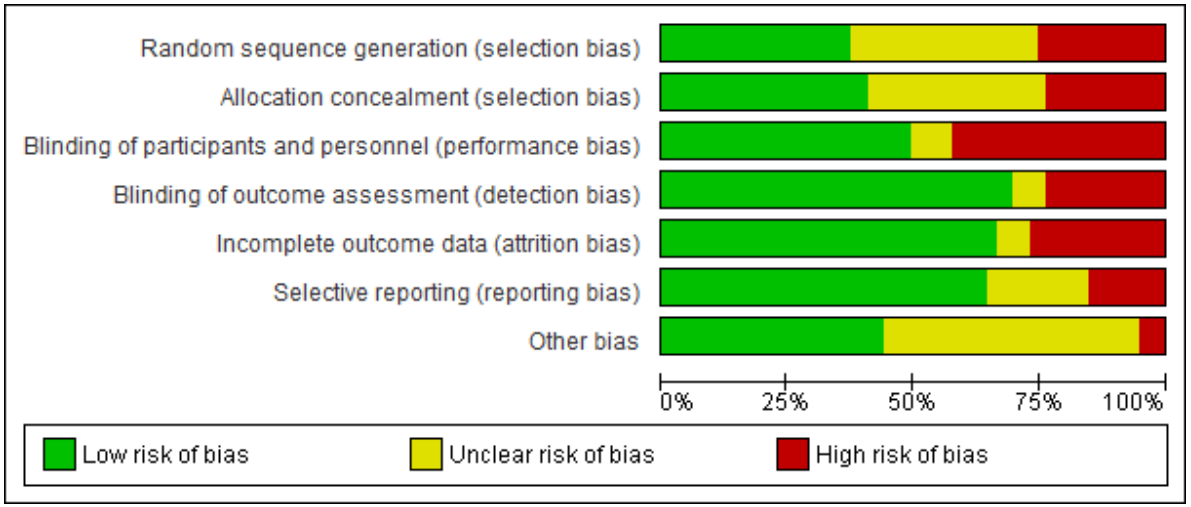


Figure 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.



(a) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. The number within brackets next to the study identification corresponds to the reference number.



(b) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 2: Risk of bias assessment (Red: “High” risk of bias; Yellow: “Unclear” risk of bias; Green: Low” risk of bias

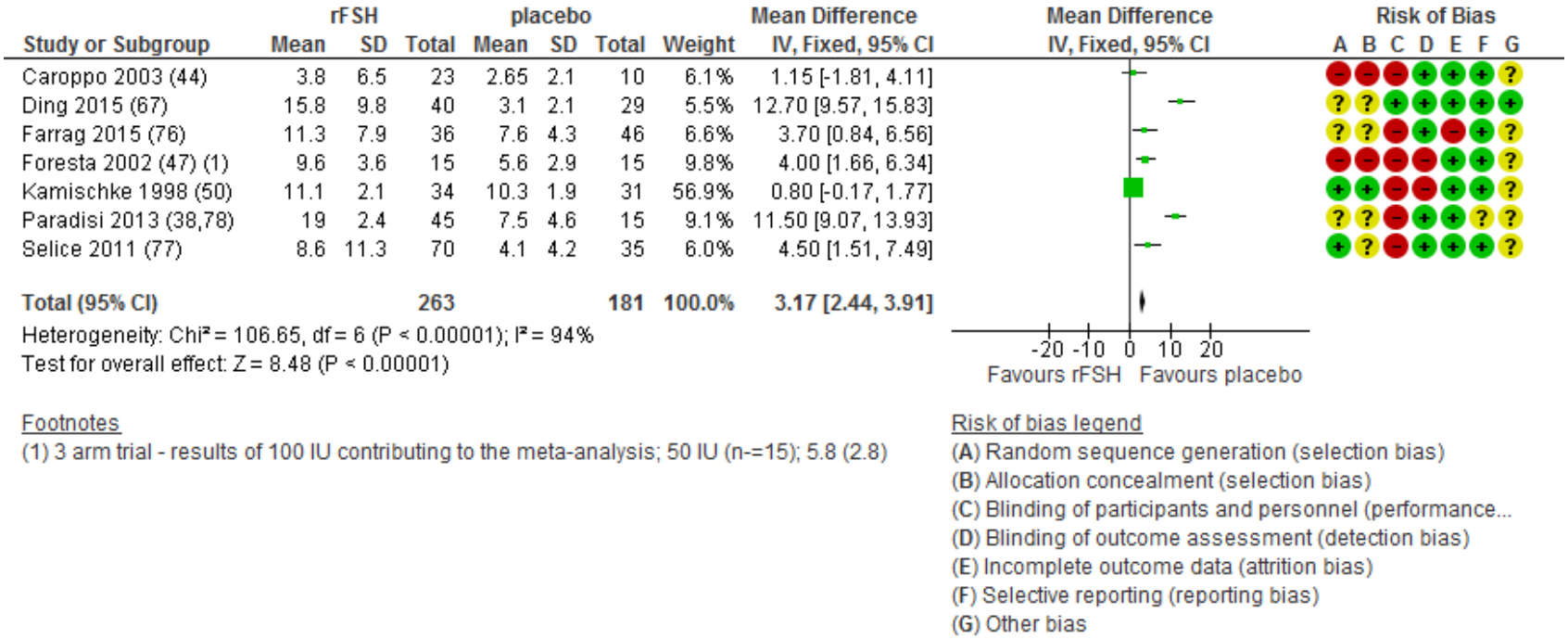
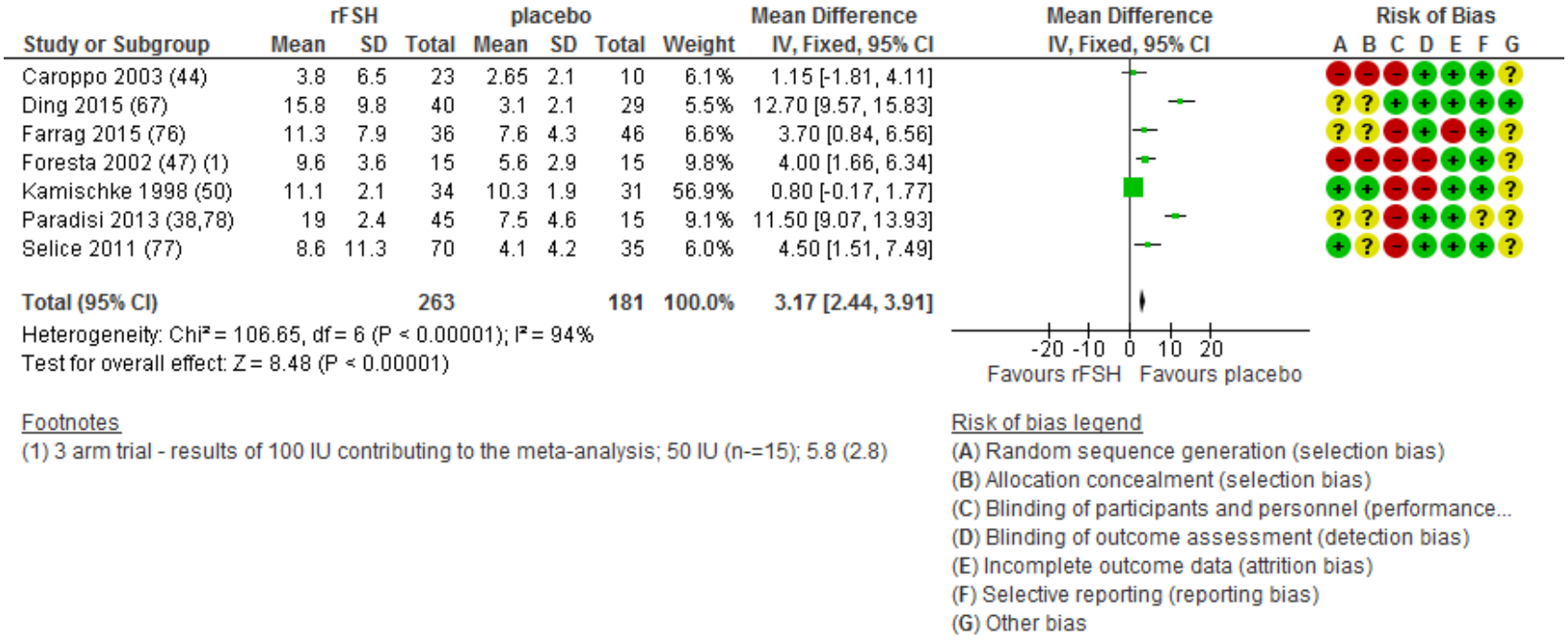


Figure 3: FSH versus placebo; effect on sperm concentration



Footnotes

(1) 3 arm trial - results of 100 IU contributing to the meta-analysis; 50 IU (n-=15); 5.8 (2.8)

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4: FSH versus placebo; effect on sperm morphology

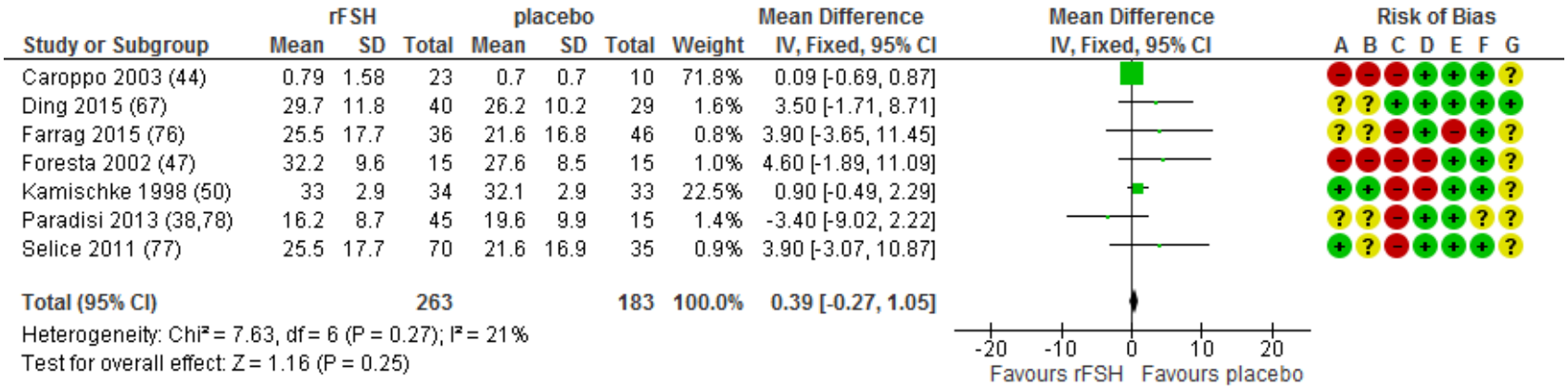


Figure 5: FSH versus placebo; effect on sperm motility

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