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Review

Effect of micronutrient supplementation on IVF outcomes: a systematic review of the literature

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KEY MESSAGE

This review of the current literature found that micronutrient supplementation alone or in combination may influence the main clinical outcomes of IVF treatment. Robust evidence for the clinical use of micronutrients to improve outcomes in IVF therapy needs to be further established from larger clinical studies.

ABSTRACT

There is accumulating evidence on the importance of micronutrients in improving fertility in couples undergoing IVF therapy. Despite this, studies reporting the relevant clinical outcomes of IVF, such as pregnancy and live birth rates, are very scarce. This review aimed to systematically summarize clinical evidence on the effect of micronutrients on primary outcome parameters of IVF treatment. The literature was searched up to February 2017 through Embase and PubMed databases for relevant studies. The quality of eligible studies was assessed with the Downs and Black checklist. A total of five studies qualified for inclusion. These studies reported outcomes on 467 participants administered micronutrient supplements alone or combined with other nutrients as part of IVF therapy. There was significant heterogeneity among the interventions and study designs. However, all the studies reported a positive impact of micronutrient supplementation on clinical outcomes of IVF therapy in terms of pregnancy rate and/or live birth rate. Within the limits of this review, micronutrients appear to influence positive outcomes in couples undergoing fertility treatment. Larger clinical studies are needed to strengthen these findings so that the benefit of micronutrients can be extended to subjects undergoing IVF therapy.

Introduction

Despite significant technological advances and developments in the treatment of infertility by IVF, only about 29% of treatments have resulted in live births after the first complete cycle (McLernon et al., 2016). Most couples have now turned to alternative or adjunctive therapies to improve their success rate with IVF therapy, including acupuncture (Qian et al., 2016) and, increasingly, nutritional supplementation (Kermack and Macklon, 2015).

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Several lifestyle-related factors have been shown to negatively impact the outcomes for patients undergoing IVF, specifically higher body mass index (BMI) and nutrition, including micronutrient deficiencies (Collins and Rossi, 2015). In a recent study, the pregnancy rate in women with higher BMI consistent with being overweight or obese was found to be significantly lower than women with normal BMI undergoing IVF treatment (Comstock et al., 2015).

Accumulating evidence on the significance of nutrition in fertility is emerging from human studies, in particular dietary supplementation with micronutrients such as multivitamins and minerals (Agrawal et al., 2012; Cetin et al., 2010; Gaskins et al., 2012; Özkaya and Nazıroğlu, 2010; Özkaya et al., 2011; Wong et al., 2002). The importance of nutrition at a molecular level is well established as numerous processes in DNA synthesis are dependent on minerals such as zinc, copper and selenium, as well as vitamin B, folate and other antioxidants (Ebisch et al., 2007).

Several clinical trials and systematic reviews have investigated this and found that micronutrients, in particular antioxidants, significantly decrease sperm oxidative damage in men with fertility problems, improving sperm count (Ross et al., 2010; Showell et al., 2013b; Wong et al., 2002). However, the results of studies on the role of micronutrients on female fertility are inconsistent and scarce. A previous systematic review concluded that some studies showed a positive effect of micronutrients such as vitamin B6 and vitamin C on female fertility (Grajecki et al., 2012). On the other hand, a more recent systematic review found no evidence that micronutrients (in particular antioxidants) resulted in improved fertility in treated women compared with the control group (Showell et al., 2013a). The effect of maternal or paternal micronutrient supplementation on IVF outcome may therefore be contingent upon the characteristics of the trial design and study population.

While previous systematic reviews have mainly examined the influence of micronutrient supplementations on infertility in men or women or reviewed a single micronutrient (Giahi et al., 2015; Grajecki et al., 2012; Hosseini and Eslamian, 2015; Lerchbaum and Obermayer-Pietsch, 2012; Ross et al., 2010; Zhou et al., 2007), to date there are no reports on the influence of micronutrients on IVF outcomes and patient follow-up to understand the effects on clinical outcomes.

Therefore, the main focus of this review is to examine human research evidence on the role of micronutrient supplementation during IVF therapy. In addition, the effect of micronutrients will be further determined on the primary outcomes of IVF treatment in couples, and male or female individuals.

Methods and materials

Literature search, study selection and data extraction

The strategy was built up through PICO (P: patient, problem or population; I: intervention; C: comparison, control or comparator; O: outcome) methodology. Embase and PubMed databases were searched for studies describing the clinical outcomes of IVF when using micronutrients. Micronutrients were defined as 'essential dietary elements or organic compounds that are required in only small quantities for normal physiologic processes to occur'. All micronutrient foods, beverages and fortified powders were excluded from the definition. The analysis was also limited to micronutrients that are not synthesized in the body and need to be consumed. An in-vitro technique was defined as 'an assisted reproductive technique that includes the direct handling and manipulation of oocytes and sperm to achieve fertilization *in vitro*'. Studies defining micronutrients as a trace element or an antioxidant were also retrieved wherein trace elements were defined as 'a group of chemical elements that are needed in minute quantities for the proper growth, development, and physiology of an organism' and antioxidants were defined as 'naturally occurring or synthetic substances that inhibit or retard oxidation reactions thereby counteracting the damaging effects of oxidation in animal tissues'. The search included all the studies indexed up to 1 February 2017.

For this study, the primary clinical outcomes of interest were fertilization rate (number of fertilized oocytes per number of oocytes injected) and pregnancy rate (presence of a gestational sac on transvaginal ultrasound). Other outcomes of interest were cancellation rate, oocytes/retrieval, embryos transferred or replaced, implantation rate, spontaneous pregnancy rate, miscarriage rate and live births.

The following keywords were used: '*in vitro* fertilization' (entry terms: *In vitro* Fertilization; *In vitro* Fertilizations; Test-Tube Fertilization; Fertilization, Test-Tube; Fertilizations, Test-Tube; Test Tube Fertilization; Test-Tube Fertilizations; Fertilizations *in vitro*; Test-Tube Babies; Babies, Test-Tube; Baby, Test-Tube; Test Tube Babies; Test-Tube Baby) including sub-keywords 'Mitochondrial Replacement Therapy' (entry terms: Mitochondrial Replacement Therapies; Replacement Therapies, Mitochondrial; Replacement Therapy, Mitochondrial; Therapies, Mitochondrial Replacement; Therapy, Mitochondrial Replacement; Pronuclear Transfer Technique; Pronuclear Transfer Techniques; Technique, Pronuclear Transfer; Techniques, Pronuclear Transfer; Transfer Technique, Pronuclear; Transfer Techniques, Pronuclear; Spindle Transfer Technique; Spindle Transfer Techniques; Technique, Spindle Transfer; Techniques, Spindle Transfer; Transfer Technique, Spindle; Transfer Techniques, Spindle) and 'Sperm Injections, Intracytoplasmic' (entry terms: Injection, Intracytoplasmic Sperm; Injections, Intracytoplasmic Sperm; Intracytoplasmic Sperm Injection; Sperm Injection, Intracytoplasmic; Intracytoplasmic Sperm Injections; ICSI; Injections, Sperm, Intracytoplasmic), 'micronutrients' (entry terms: micronutrient) including sub-keywords 'Trace Elements' (entry terms: Trace Element; Element, Trace; Elements, Trace; Biometals; Biometal; Trace Minerals; Trace Mineral; Mineral, Trace; Minerals, Trace) and 'vitamins' including sub-keywords 'Provitamins' and 'Vitamin B Complex'.

Restrictions applied to the searches were language (English) and species (humans). Screening was conducted in three stages and involved: screening of the titles and abstracts; screening of potential full texts; and manual screening of the reference lists of the potential full texts to identify further suitable articles. Studies published as abstracts/case reports/case series or not providing necessary clinical outcomes data were excluded.

Data on study characteristics, patient profiles, intervention and outcome features were extracted into a customized Excel sheet.

Quality assessment

The quality of the included studies was assessed with the Downs and Black checklist (Downs and Black, 1998). This is one of the six best quality assessment tools for systematic reviews, especially when both randomized and non-randomized trials are included

(Deeks et al., 2003). This 27-point checklist assesses various methodological qualities such as reporting, external validity, internal validity (bias and confounding) and power. A study can score from 0 to 28, with a higher score indicating better quality. A rule of thumb for categorizing the studies is poor (≤14), fair (15–19), good (20–25) and excellent (26–28). Further, if meta-analysis is going to be performed, studies scoring <14 will be excluded.

The report was prepared as per the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Results

The database and manual search generated 241 articles (**Figure 1**). Of these, 64 were not full texts, 72 were duplicates and 91 had irrelevant objectives, provided insufficient data or were based on animal studies. After this initial screening, 14 full-text articles were retrieved for final screening (Dattilo et al., 2014; Fatemi et al., 2017; Geva et al., 1996; Gulino et al., 2016; Ménézo et al., 2007; Özkaya and Nazıroğlu, 2010; Özkaya et al., 2011; Pacchiarotti et al., 2016; Tremellen et al., 2007; Twigt et al., 2010, 2015; Wirleitner et al., 2012; Wun et al., 1994; Youssef et al., 2015). Nine of these articles did not qualify because the primary outcomes were not provided (Gulino et al., 2016; Ménézo et al., 2007; Özkaya and Nazıroğlu, 2010; Özkaya et al., 2011; Pacchiarotti et al., 2016; Twigt et al., 2010, 2015; Wirleitner et al., 2012; Wun et al., 1994). These articles studied the influence of micronutrients on couples, men or women undergoing IVF, but the analyses were limited to the effect on gametes or other in-vitro examinations. These studies did not focus on following up the patients to understand the effects on clinical outcomes. Eventually, five studies involving 467 participants were included for this review (Dattilo et al., 2014; Fatemi et al., 2017; Geva et al., 1996; Tremellen et al., 2007; Youssef et al., 2015).

Characteristics of the included studies, participants and interventions are outlined in **Tables 1 to 3**. Three studies were prospectively randomized controlled trials (RCTs) (Fatemi et al., 2017; Tremellen et al., 2007; Youssef et al., 2015). Two other studies employed single-arm observational exploratory design (Dattilo et al., 2014; Geva et al., 1996). The studies were spread across the world with one study each from Israel, Australia, Egypt, France and Iran. The very first study on this topic was published in 1996, with the second study published 9 years later and the last three included studies published in 2014 and thereafter. Four of the studies enrolled couples with the male partner having normal semen analysis, whereas one study enrolled severely infertile men (Tremellen et al., 2007). Three studies focused on treating men, one each with low fertilization rate (Geva et al., 1996), severe infertility coupled with seminal oxidative stress and sperm DNA fragmentation (Tremellen et al., 2007) or sperm chromatin integrity loss (Dattilo et al., 2014). The Youssef et al. (2015) study reported on treated women failing three previous intrauterine inseminations and Fatemi et al. (2017) reported on treated women with polycystic ovary syndrome (PCOS). Both the observational studies scored 'poor' whereas the RCTs were scored 'good' on the Downs and Black scale (**Table 1**, **Supplementary Tables S1**). The characteristics of the participants are presented in **Table 2**.

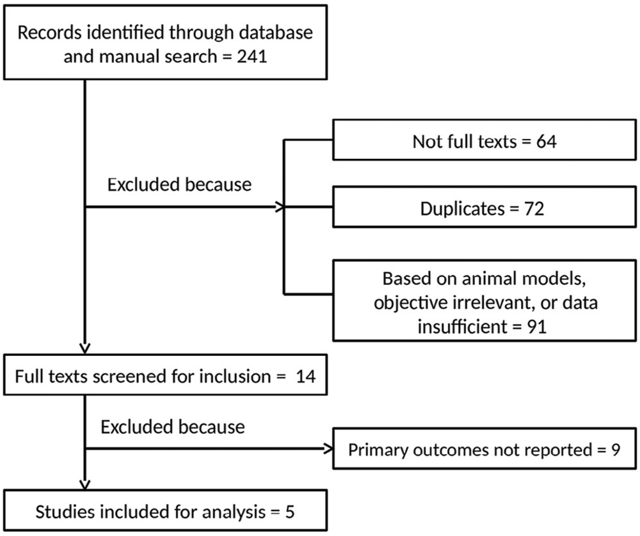

Figure 1 – PRISMA flow diagram for the selection of studies.

The interventions were highly heterogeneous among the included studies (**Table 3**). Geva et al. (1996) tested vitamin E, given at a dose of 200 mg/day for 90 days in 15 male volunteers with a low fertilization record. Tremellen et al. (2007) tested a multivitamin combination (Menevit) developed specifically for enhancing male fertility. The product description suggested that Menevit contains a combination of antioxidants that are thought to support sperm health for couples planning pregnancy. Forty severely infertile men were given one capsule of Menevit daily while 20 men were given placebo for 90 days (Tremellen et al., 2007). Four participants were lost during follow-up in both of the groups. Youssef et al. (2015) tested a multivitamin and trace elements formulation, Octatron (one capsule per day) in 112 women combined with folic acid (2.5 mg/day) given for 58 days; over the same period 106 controls were given folic acid (2.5 mg/day) only. The Octatron product description claims that it is a combination of eight powerful antioxidants comprised of minerals and chelated amino acids, with all vitamins included from natural sources. This product is prescribed for general use as an antioxidant in maintaining health and recovering from complex disorders such as infertility. Dattilo et al. (2014) tested a fig extract that delivered tailored amounts of micronutrients at a dose of 100 mg/day, given for 130 days to 84 men with normal semen profile but with evidence of DNA damage (Dattilo et al., 2014). Fatemi et al. (2017) tested a combination of vitamin E (400 mg/day) and vitamin D3 (50,000 IU once in 2 weeks) given to 52 women with PCOS and a placebo given to 53 women for 56 days (Fatemi et al., 2017).

Outcomes

Four studies reported fertilization rates ranging from 29% to 73% for intervention and 19% to 71% for controls (**Table 4**). Youssef et al. (2015) found that the control group had a higher fertilization rate than the intervention group. Three other studies reported a higher fertilization rate in the intervention group, with just one study finding the rate significantly higher in the treatment group (Geva et al., 1996). It must be noted here that Geva et al. (1996) had no control group and conducted a comparison of pre-treatment and post-treatment values.

Four studies reported clinical pregnancy rates (**Table 4**). Pregnancy rates were higher in the intervention groups in all the RCTs, with one study reporting a statistically significant outcome (Fatemi et al., 2017). In the study by Tremellen et al. (2007), the test agent

Table 1 – Characteristics of the studies included in the systematic review.

Author, year	Location	Study period	Study design	Inclusion criteria	Exclusion criteria	Downs and Black score
Geva et al., 1996	Israel	NR	Exploratory	Men with normal semen profile with low fertilization rate during previous IVF	NR	10
Tremellen et al., 2007	Australia	December 2004 to May 2006	RCT	Men exhibiting both likely oxidative stress (poor sperm morphology, motility or low membrane integrity) and a significant level of sperm DNA fragmentation (>25% TUNEL positive)	Female partners with diminished ovarian reserve (fewer than five oocytes in a prior IVF cycle or elevated early follicular phase FSH result) or those >39 years of age	21
Youssef et al., 2015	Egypt	February 2011 to March 2013	RCT	Failed at least three previous IUI cycles; women <40 years with normal ovulatory cycles, normal baseline; FSH ≤12 IU/l; normal TSH and PRL levels; normal transvaginal ultrasound scan; tubal patency; presence of both ovaries; normal laparoscopy; male partners with normal semen analysis	Couples receiving any vitamin supplement during last 3 months	20
Dattilo et al., 2014	France	August 2010 to March 2013	Exploratory	Male partners of couples with at least two previous assisted reproductive technique failures and showing sperm chromatin integrity loss	Men with organic causes of infertility	12
Fatemi et al., 2017	Iran	November 2014 to June 2015	RCT	18–38 years with PCOS and eligible for ICSI	Patients with heart disease, liver or kidney deficiencies, endometriosis, uterine anomaly or hydrosalpinx, retinitis pigmentosa, and vitamin K deficiency; using vitamin and antioxidant supplementations during past 3 months; and male factor infertility	23

ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; NR = not reported; PCOS = polycystic ovarian disease; PRL = prolactin; RCT = randomized controlled trial; TSH = thyroid-stimulating hormone; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labelling.

Table 2 – Characteristics of the participants.

Author, year	Age, female (years, mean ± SD)	Age, male (years, mean ± SD)	Semen quality	Female factor (%)	Duration of infertility (treated/control; years, mean ± SD)
Geva et al., 1996	–	36.8 ± 5.3	Normal	NR	NR
Tremellen et al., 2007	34.6 ± 3.4/33.6 ± 3.9	37.1 ± 5.1/35.5 ± 4.3	Normospermic with DNA damage and seminal oxidative stress	–	4.2 ± 2.7/3.4 ± 2.1
Youssef et al., 2015	30.9 ± 5.7/30.6 ± 5.4	NR	Normal	NR	6.4 ± 4.6/5.4 ± 3.8
Dattilo et al., 2014	35.0 ± 4.4	37.0 ± 5.5	Normospermic: 23%; oligoasthenospermic: 61%; asthenospermic: 17%	33	NR
Fatemi et al., 2017	28.07 ± 4.21/28.13 ± 3.73	–	NR	100	5.08/5.54

NR = not reported.

resulted in strikingly higher pregnancy rate, but this was not statistically significant, most likely due to a smaller sample size.

Secondary outcomes

Other outcomes were reported to be similar between the groups with one study each reporting a significantly higher implantation rate (Fatemi et al., 2017) and live birth rates (Tremellen et al., 2007) in intervention groups.

Discussion

This systematic review investigated the influence of micronutrient supplementation on IVF outcomes and highlights the paucity of published studies on couples undergoing IVF treatment with subsequent follow-up to understand the effects on clinical outcomes. While the five studies that met the inclusion criteria exhibited great clinical disparity and variability in methodology, making meta-analysis impractical, this review has, however, demonstrated that there is currently a lack

Table 3 – Characteristics of the intervention.

Author, year	Test agent, dose, duration (days)	Composition of test agent (in case of a combined formulation)	Control agent	Number of subjects	
				Test	Control
Geva et al., 1996	Vitamin E, 200 mg/day, 90	–	None	15	–
Tremellen et al., 2007	Menevit, 1 cap/day, 90	Lycopene 6 mg, vitamin E 400 IU, vitamin C 100 mg, zinc 25 mg, selenium 26 µg, folate 0.5 mg, garlic 1000 mg, palm oil (vehicle)	Placebo, 90 days	40 (36 analysed)	20 (16 analysed)
Youssef et al., 2015	Folic acid (2.5 mg/day) + Octatron (1 cap/day), 58	Vitamin A 3000 IU; d-alpha tocopheryl acid; [vitamin E] 15 IU; ascorbic acid [vitamin C] 90 mg; zinc [amino acid chelated] 11 mg; molybdenum [amino acid chelated] 45 µg; selenium [amino acid chelated] 55 µg, biotin 10 µg and mixed bioflavonoid 100 mg	Folic acid, 2.5 mg/day, NR	112	106
Dattilo et al., 2014	Figure extract, 100 mg/day, 130	Proprietary extract of opuntia fig fruits (100 mg) delivering tailored amounts of quercetin (0.05 mg) and betalain (0.001 mg) plus a mix of Group B vitamins: B2 (1.4 mg), B3 (16 mg), B6 (1.4 mg), B9 (400 µg), B12 (2.5 µg). Also contained zinc (12.5 mg) and small doses of N-acetylcysteine (250 mg) and vitamin E (12 mg) (Condensyl™)	–	84	–
Fatemi et al., 2017	Vitamin E (400 mg/day) + vitamin D3 (50,000 IU/2 weeks), 56	–	Placebo, 56 days	52 (44 analysed)	53 (46 analysed)

NR = not reported.

of quality evidence on the association between micronutrients and IVF outcomes, especially for women undergoing fertility treatment. Furthermore, these results concur with findings of earlier systematic reviews that more robust study designs with larger sample size are required to draw conclusions (Giahi et al., 2015; Ross et al., 2010; Showell et al., 2013b).

Previously, the most studied dietary micronutrient supplements in assisted reproductive techniques were found to be antioxidants that include vitamins A, B, C, D, E and coenzyme Q10 (Imamovic Kumalic and Pinter, 2014). In males, antioxidants have been shown to reduce the number of reactive oxygen species, protecting semen from oxidative damage and improving sperm parameters such as motility (Imamovic Kumalic and Pinter, 2014; Zareba et al., 2013), while clinical evidence on the role of antioxidants in female infertility is largely lacking.

Previous systematic reviews found that evidence from six RCTs indicated oral antioxidant supplementation was associated with a considerable improvement in assisted conception pregnancy rates by improving male fertility (Ross et al., 2010). However, due to inconsistencies in other reported effects and heterogeneity in treatment regimens, the authors concluded that the results should be interpreted with caution. They suggested that the effect of standardized dosage and combination of antioxidants on assisted conception rates needs to be examined in large randomized controlled studies before antioxidant therapy can be initiated in a clinical setting (Ross et al., 2010).

Only one study administered vitamin D as an intervention, at a very high dosage combined with vitamin E for 2 months (Fatemi et al., 2017). Incidentally, this study was also the only one with a statistically significant improved outcome of pregnancy rate in females. Recent systematic review findings on the role of vitamin D in fertility revealed evidence that vitamin D may have a positive impact on IVF outcomes such as improved pregnancy rate in females and semen quality in males (Lerchbaum and Obermayer-Pietsch, 2012). Higher vitamin D levels have been associated with increased clinical pregnancy rate following IVF therapy in one study (Ozkan et al., 2010), while in another study more than two-thirds of infertile women were found to be vitamin D-deficient compared with the general population (Li et al., 2012). In addition, vitamin D-deficient women were found to have significantly lower clinical pregnancy rates (Paffoni et al., 2014). However, other studies have not confirmed an association between vitamin D and IVF outcomes (Aleyasin et al., 2011; Anifandis et al., 2010; Franasiak et al., 2015). Collectively, these studies indicate that more robust clinical data is required to assess the effect of vitamin D in women undergoing IVF therapy (Lerchbaum and Obermayer-Pietsch, 2012).

The micronutrient common to all five studies was vitamin E, administered as a single dose or in formulation with a dose of 10–400 mg/day. The study with the highest dose of vitamin E showed significantly higher pregnancy rates compared with other studies (Fatemi et al., 2017). Vitamin E supplementation in both women and men has been shown to impact IVF outcomes not only by reducing the time to achieve pregnancy in women, but also vitamin E administration in men has been found to improve sperm motility and reduce associated oxidative damage (Kefer et al., 2009).

Three included studies administered micronutrient combinations containing zinc at a dose of 11–25 mg/day (Dattilo et al., 2014; Tremellen et al., 2007; Youssef et al., 2015), while two of these studies included selenium at doses of 26–55 µg/day (Tremellen et al., 2007; Youssef et al., 2015). The study with highest zinc content also had the highest live birth rate in the intervention group (Tremellen et al., 2007). While a recent study has demonstrated that zinc and selenium levels were considerably lower in IVF patients than controls (Özkaya et al., 2011), most studies have been performed in animal models. More RCTs are required to investigate the supplementation effect of zinc and selenium on IVF outcomes.

Two of the studies included folate acid in the micronutrient formulation at 0.5 and 2.5 mg/day, respectively (Tremellen et al., 2007; Youssef et al., 2015). The study with the lower folate dose showed a higher implantation rate in the intervention group, but neither study results were statistically significant. This could be due to difference in ethnicity, intervention dosage or formulation and/or the study design. Supplementing the diet with high levels of folate and vitamin B12 in women has been linked to improved IVF outcomes such as significantly increased pregnancy and live birth rates (Boxmeer et al., 2009; Gaskins et al., 2014). A recent study has also demonstrated a link between inadequate folate and B12 levels in women undergoing IVF treatment (La Vecchia et al., 2017).

Although in recent years increasing numbers of studies have been published on the effects of micronutrient supplementation on IVF, the inconsistencies, together with the lack of supportive studies on female IVF, precludes robust conclusions for the use of micronutrients in clinical practice. In addition, no information is available as to which group would benefit more from supplementation. While there may be some benefits from micronutrient supplementations, current evidence is insufficient to substantiate this claim. Therefore, large clinical trials using micronutrient supplementation alone or in combination are necessary in order to investigate their potential effects on clinical outcomes in couples undergoing IVF therapy.

Dietary and lifestyle modifications have been the first line of approach for achieving natural conception in idiopathic infertility (Collins and Rossi, 2015). While cessation of smoking (Kovac et al., 2015) and management of obesity (Talmor and Dunphy, 2015) significantly increase natural conception, micronutrient supplementation has been controversial. Vitamin and antioxidant supplementation improves semen quality but women tend to show varying outcomes (Collins and Rossi, 2015). However, based on our results, we recommend that micronutrients could be beneficial in men as well as women.

This study further supports the increasing body of evidence on the use of micronutrients (especially antioxidant therapy) to improve outcomes for couples undergoing IVF treatment. Furthermore, multiple micronutrient supplementations for IVF couples, men or women may prove to be a promising approach to improving IVF clinical outcomes.

Table 4 – Summary of the intervention outcomes.

Author, year	Cancellation rate[a]	Oocytes/retrieval[a]	Embryos transferred	Fertilization rate[a]	Implantation rate	Clinical pregnancy rate (%)	Spontaneous pregnancy rate (%)	Miscarriage (%)	Live births (%)
Geva et al., 1996	NR/NR	NR/NR	NR/NR	29.1 ± 22.2/19.3 ± 23.3[b]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Tremellen et al., 2007	NR/NR	11.4 ± 4.44/9.6 ± 3.9	1.39 ± 0.6/1.56 ± 0.5	68.8/63	46.2/24	63.9/37.5	NR/NR	2 (n)/2 (n)[c]	38.5/16
Youssef et al., 2015	NR/NR	12.7 ± 9.4/13.2 ± 8.6	3.5 ± 1.3/3.5 ± 1.3	64.8 ± 25.9/68.1 ± 24.5	NR/NR	38/34	NR/NR	4/3	NR/NR
Dattilo et al., 2014	NR/–	NR/–	NR/–	NR/–	NR/–	47.6/–	21/–	4/–	39.3/–
Fatemi et al., 2017	NR/NR	18.59 ± 8.58/18.3 ± 19.86	NR/NR	73.31 ± 19.09/70.92 ± 20.10	35.05/8.6	62/22.6	NR/NR	NR/NR	100/87.5

NR = not reported.

Values are presented as treated/control group, except for Geva et al. (1996) for which the values represent post-treatment/pre-treatment measurements for a single group. Dattilo et al. (2014) did not include a control group.

[a] Mean ± SD.

[b] Before treatment.

[c] Actual number.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2017.08.018.

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REFERENCES

Agrawal, R., Burt, E., Gallagher, A.M., Butler, L., Venkatakrishnan, R., Peitsidis, P., 2012. Prospective randomized trial of multiple micronutrients in subfertile women undergoing ovulation induction: a pilot study. Reprod. Biomed. Online 24, 54–60.

Aleyasin, A., Hosseini, M.A., Mahdavi, A., Safdarian, L., Fallahi, P., Mohajeri, M.R., Abbasi, M., Esfahani, F., 2011. Predictive value of the level of vitamin d in follicular fluid on the outcome of assisted reproductive technology. Eur. J. Obstet. Gynecol. Reprod. Biol. 159, 132–137.

Anifandis, G.M., Dafopoulos, K., Messini, C.I., Chalvatzas, N., Liakos, N., Pournaras, S., Messinis, I.E., 2010. Prognostic value of follicular fluid 25-oh vitamin d and glucose levels in the ivf outcome. Reprod. Biol. Endocrinol. 8, 91.

Boxmeer, J.C., Macklon, N.S., Lindemans, J., Beckers, N.G., Eijkemans, M.J., Laven, J.S., Steegers, E.A., Steegers-Theunissen, R.P., 2009. Ivf outcomes are associated with biomarkers of the homocysteine pathway in monofollicular fluid. Hum. Reprod. 24, 1059–1066.

Cetin, I., Berti, C., Calabrese, S., 2010. Role of micronutrients in the periconceptional period. Hum. Reprod. Update 16, 80–95.

Collins, G.G., Rossi, B.V., 2015. The impact of lifestyle modifications, diet, and vitamin supplementation on natural fertility. Fertility Research and Practice 1, 11.

Comstock, I.A., Kim, S., Behr, B., Lathi, R.B., 2015. Increased body mass index negatively impacts blastocyst formation rate in normal responders undergoing *in vitro* fertilization. J. Assist. Reprod. Genet. 32, 1299–1304.

Dattilo, M., Cornet, D., Amar, E., Cohen, M., Menezo, Y., 2014. The importance of the one carbon cycle nutritional support in human male fertility: a preliminary clinical report. Reprod. Biol. Endocrinol. 12, 71.

Deeks, J., Dinnes, J., D'amico, R., Sowden, A., Sakarovitch, C., Song, F., Petticrew, M., Altman, D., 2003. Evaluating non-randomized intervention studies. Health Technol. Assess. 7, iii–x, 1–173.

Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. J. Epidemiol. Community Health 52, 377–384.

Ebisch, I., Thomas, C., Peters, W., Braat, D., Steegers-Theunissen, R., 2007. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Hum. Reprod. Update 13, 163–174.

Fatemi, F., Mohammadzadeh, A., Sadeghi, M.R., Akhondi, M.M., Mohammadmoradi, S., Kamali, K., Lackpour, N., Jouhari, S., Zafadoust, S., Mokhtar, S., 2017. Role of vitamin e and d 3 supplementation in intra-cytoplasmic sperm injection outcomes of women with polycystic ovarian syndrome: a double blinded randomized placebo-controlled trial. Clinical Nutrition ESPEN.

Franasiak, J.M., Molinaro, T.A., Dubell, E.K., Scott, K.L., Ruiz, A.R., Forman, E.J., Werner, M.D., Hong, K.H., Scott, R.T., 2015. Vitamin d levels do not affect ivf outcomes following the transfer of euploid blastocysts. Am. J. Obstet. Gynecol. 212, 315, e311–315. e316.

Gaskins, A.J., Colaci, D.S., Mendiola, J., Swan, S.H., Chavarro, J.E., 2012. Dietary patterns and semen quality in young men. Hum. Reprod. 27, 2899–2907.

Gaskins, A.J., Afeiche, M., Wright, D.L., Toth, T.L., Williams, P.L., Gillman, M.W., Hauser, R., Chavarro, J.E., 2014. Dietary folate and reproductive success among women undergoing assisted reproduction. Obstet. Gynecol. 124, 801.

Geva, E., Bartoov, B., Zabludovsky, N., Lessing, J.B., Lerner-Geva, L., Amit, A., 1996. The effect of antioxidant treatment on human spermatozoa and fertilization rate in an *in vitro* fertilization program. Fertil. Steril. 66, 430–434.

Giahi, L., Mohammadmoradi, S., Javidan, A., Sadeghi, M.R., 2015. Nutritional modifications in male infertility: a systematic review covering 2 decades. Nutr. Rev. nuv059.

Grajecki, D., Zyriax, B.-C., Buhling, K.J., 2012. The effect of micronutrient supplements on female fertility: a systematic review. Arch. Gynecol. Obstet. 285, 1463–1471.

Gulino, F.A., Leonardi, E., Marilli, I., Musmeci, G., Vitale, S.G., Leanza, V., Palumbo, M.A., 2016. Effect of treatment with myo-inositol on semen parameters of patients undergoing an ivf cycle: *in vivo* study. Gynecol. Endocrinol. 32, 65–68.

Hosseini, B., Eslamian, G., 2015. Association of micronutrient intakes with female infertility: review of recent evidence. Thrita 4.

Imamovic Kumalic, S., Pinter, B., 2014. Review of clinical trials on effects of oral antioxidants on basic semen and other parameters in idiopathic oligoasthenoteratozoospermia. Biomed Res. Int. 2014.

Kefer, J.C., Agarwal, A., Sabanegh, E., 2009. Role of antioxidants in the treatment of male infertility. Int. J. Urol. 16, 449–457.

Kermack, A.J., Macklon, N., 2015. Nutritional supplementation and artificial reproductive technique (art) outcomes. Reprod. Fertil. Dev. 27, 677–683.

Kovac, J.R., Khanna, A., Lipshultz, L.I., 2015. The effects of cigarette smoking on male fertility. Postgrad. Med. 127, 338–341.

La Vecchia, I., Paffoni, A., Castiglioni, M., Ferrari, S., Bortolus, R., Ferraris Fusarini, C., Bettinardi, N., Somigliana, E., Parazzini, F., 2017. Folate, homocysteine and selected vitamins and minerals status in infertile women. Eur. J. Contracept. Reprod. Health Care 22, 70–75.

Lerchbaum, E., Obermayer-Pietsch, B., 2012. Mechanisms in endocrinology: vitamin d and fertility: a systematic review. Eur. J. Endocrinol. 166, 765–778.

Li, L., Schriock, E., Dougall, K., Givens, C., 2012. Prevalence and risk factors of vitamin d deficiency in women with infertility. Fertil. Steril. 97, S26.

McLernon, D.J., Steyerberg, E.W., Te Velde, E.R., Lee, A.J., Bhattacharya, S., 2016. Predicting the chances of a live birth after one or more complete cycles of *in vitro* fertilization: population based study of linked cycle data from 113 873 women. BMJ 355, i5735.

Ménézo, Y.J., Hazout, A., Panteix, G., Robert, F., Rollet, J., Cohen-Bacrie, P., Chapuis, F., Clément, P., Benkhalifa, M., 2007. Antioxidants to reduce sperm DNA fragmentation: an unexpected adverse effect. Reprod. Biomed. Online 14, 418–421.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. PLoS Med. 6, e1000097.

Ozkan, S., Jindal, S., Greenseid, K., Shu, J., Zeitlian, G., Hickmon, C., Pal, L., 2010. Replete vitamin d stores predict reproductive success following *in vitro* fertilization. Fertil. Steril. 94, 1314–1319.

Özkaya, M.O., Nazıroğlu, M., 2010. Multivitamin and mineral supplementation modulates oxidative stress and antioxidant vitamin levels in serum and follicular fluid of women undergoing *in vitro* fertilization. Fertil. Steril. 94, 2465–2466.

Özkaya, M.O., Nazıroğlu, M., Barak, C., Berkkanoglu, M., 2011. Effects of multivitamin/mineral supplementation on trace element levels in serum and follicular fluid of women undergoing *in vitro* fertilization (ivf). Biol. Trace Elem. Res. 139, 1–9.

Pacchiarotti, A., Carlomagno, G., Antonini, G., Pacchiarotti, A., 2016. Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving *in vitro* fertilization ofpatients with polycystic ovarian syndrome. Gynecol. Endocrinol. 32, 69–73.

Paffoni, A., Ferrari, S., Viganò, P., Pagliardini, L., Papaleo, E., Candiani, M., Tirelli, A., Fedele, L., Somigliana, E., 2014. Vitamin d deficiency and infertility: insights from *in vitro* fertilization cycles. J. Clin. Endocrinol. Metab. 99, E2372–E2376.

Qian, Y., Xia, X.-R., Ochin, H., Huang, C., Gao, C., Gao, L., Cui, Y.-G., Liu, J.-Y., Meng, Y., 2016. Therapeutic effect of acupuncture on the outcomes of *in vitro* fertilization: a systematic review and meta-analysis. Arch. Gynecol. Obstet. 295, 543–558.

Ross, C., Morriss, A., Khairy, M., Khalaf, Y., Braude, P., Coomarasamy, A., El-Toukhy, T., 2010. A systematic review of the effect of oral antioxidants on male infertility. Reprod. Biomed. Online 20, 711–723.

Showell, M.G., Brown, J., Clarke, J., Hart, R.J., 2013a. Antioxidants for female subfertility. The Cochrane Library.

Showell, M.G., Mackenzie-Proctor, R., Brown, J., Yazdani, A., Stankiewicz, M.T., Hart, R.J., 2013b. Antioxidants for male subfertility.

Talmor, A., Dunphy, B., 2015. Female obesity and infertility. Best Pract. Res. Clin. Obstet. Gynaecol. 29, 498–506.

Tremellen, K., Miari, G., Froiland, D., Thompson, J., 2007. A randomized control trial examining the effect of an antioxidant (menevit) on pregnancy outcome during ivf-icsi treatment. Aust. N. Z. J. Obstet. Gynaecol. 47, 216–221.

Twigt, J.M., Hammiche, F., Sinclair, K.D., Beckers, N.G., Visser, J.A., Lindemans, J., De Jong, F.H., Laven, J.S., Steegers-Theunissen, R.P., 2010. Preconception folic acid use modulates oestradiol and follicular responses to ovarian stimulation. J. Clin. Endocrinol. Metab. 96, E322–E329.

Twigt, J.M., Bezstarosti, K., Demmers, J., Lindemans, J., Laven, J.S., Steegers-Theunissen, R.P., 2015. Preconception folic acid use influences the follicle fluid proteome. Eur. J. Clin. Invest. 45, 833–841.

Wirleitner, B., Vanderzwalmen, P., Stecher, A., Spitzer, D., Schuff, M., Schwerda, D., Bach, M., Schechinger, B., Herbert Zech, N., 2012. Dietary supplementation of antioxidants improves semen quality of ivf patients in terms of motility, sperm count, and nuclear vacuolization. Int. J. Vitam. Nutr. Res. 82, 391–398.

Wong, W.Y., Merkus, H.M., Thomas, C.M., Menkveld, R., Zielhuis, G.A., Steegers-Theunissen, R.P., 2002. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. Fertil. Steril. 77, 491–498.

Wun, W.-S.A., Cisneros, P., Dunn, R., Grunert, G.M., 1994. Vitamin supplements improve the fertility potential of a subfertile male with macrocytic anemia – a case study. J. Assist. Reprod. Genet. 11, 375–378.

Youssef, M.A., Abdelmoty, H.I., Elashmwi, H.A., Abduljawad, E.M., Elghamary, N., Magdy, A., Mohesen, M.N., Abdella, R.M., Bar, M.A., Gouda, H.M., Ali, A.M.S., 2015. Oral antioxidants supplementation for women with unexplained infertility undergoing ICSI/IVF: randomized controlled trial. Hum. Fertil. 18, 38–42.

Zareba, P., Colaci, D.S., Afeiche, M., Gaskins, A.J., Jørgensen, N., Mendiola, J., Swan, S.H., Chavarro, J.E., 2013. Semen quality in relation to antioxidant intake in a healthy male population. Fertil. Steril. 100, 1572–1579.

Zhou, X., Liu, F., Zhai, S.-D., 2007. Effect of l-carnitine and/or l-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. Asia Pac. J. Clin. Nutr. 16, 383–390.