National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[S] Sperm DNA fragmentation

NICE guideline NG257

Evidence reviews underpinning recommendations 1.17.6, 1.24.6 and 1.27.1 in the NICE guideline

March 2026

Final

Developed by NICE

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Contents

Sperm DNA fragmentation

Review question

What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Introduction

There is research interest in associations between elevated sperm DNA fragmentation and pregnancy outcomes (such as miscarriage and recurrent pregnancy loss), and in interventions (including antioxidants) that might reduce sperm DNA fragmentation and improve clinical outcomes. DNA fragmentation testing is increasingly offered (and can be costly) but it is unclear whether acting on the finding of the test makes any difference to the outcome for the individual involved. This review aims to examine the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes, and subsequently whether testing is worthwhile.

Summary of the protocol

Table 1: Summary of the protocol (PICO table)

Population	Inclusion: • People with a fertility problem (pregnancy not achieved after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination) that may be associated with sperm DNA fragmentation (above threshold levels of DNA fragmentation identified by DNA assays of ejaculated sperm) Exclusion: • Management of recurrent miscarriage
Intervention	• Antioxidants (individual or combined, including vitamins C and E, carnitine, CoQ10, zinc, folic acid, N-acetyl cysteine and selenium) • Lifestyle advice promoting the following healthy behaviours (alone or in combination): o weight loss o healthy diet o exercise o smoking cessation o reducing alcohol intake o reducing environmental and occupational exposure to toxicants o serial ejaculate • Varicocele treatment (radiological and surgical interventions) • Testicular sperm retrieval and Intracytoplasmic sperm injection (ICSI) • ICSI (with ejaculated sperm) • Physiological ICSI (PICSI)
Comparison	• Placebo • Head to head comparisons of different interventions
Outcome	**Critical** • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate) **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Pregnancy loss (accounting for placental abruption) and stillbirth • Embryo quality/grading (as defined by study [criteria for defining high quality will be extracted], including high quality cleavage stage, blastocyst stage and embryo formation rate) • Percentage of DNA fragmentation in sperm samples

CoQ10: coenzyme Q10; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; PICSI: physiological intracytoplasmic sperm injection.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](). Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness

Included studies

Eighteen randomised controlled trials (RCTs) were included for this review (Abbasi 2021; Abbasi 2020; Barekat 2016; Dadgar 2023; Greco 2005; Habibi 2022; Hosseini 2016; Hozyen 2022; Kumalic 2020; Kumar 2011; Lahimer 2023; Maghsoumi-Norouzabad 2022; Martínez-Soto 2016; Mathieu d'Argent 2021; Micic 2019; Patki 2023; Steiner 2020; Stenqvist 2018).

The included studies are summarised in Table 2.

Fifteen studies compared an antioxidant to placebo (Abbasi 2021; Dadgar 2023; Greco 2005; Habibi 2022; Hosseini 2016; Kumalic 2020; Kumar 2011; Lahimer 2023; Maghsoumi-Norouzabad 2022; Martínez-Soto 2016; Mathieu d'Argent 2021; Micic 2019; Patki 2023; Steiner 2020; Stenqvist 2018). The antioxidants included were:

- probiotic and prebiotic in 1 study (Abbasi 2021)
- zinc in 1 study (Dadgar 2023)
- vitamin C and E in 1 study (Greco 2005)
- alpha-lipoic acid in 1 study (Habibi 2022)
- ginger in 1 study (Hosseini 2016)
- astaxanthin in 1 study (Kumalic 2020)
- herbo-mineral supplement in 1 study (Kumar 2011)
- vitamin D3 in 1 study (Maghsoumi-Norouzabad 2022)
- docosahexaenoic acid (DHA) in 1 study (Martínez-Soto 2016)
- folic acid in 1 study (Mathieu d'Argent 2021), and
- a combination of antioxidants, including coenzyme Q10, L-carnitine, vitamin C and vitamin E, in 5 studies (Lahimer 2023; Micic 2019; Patki 2023; Steiner 2020; Stenqvist 2018).

One study compared post-varicocelectomy antioxidant to post-varicocelectomy placebo (Abbasi 2020), and 1 study compared post-varicocelectomy antioxidant to no post-varicocelectomy treatment (Barekat 2016). One of these studies used alpha-lipoic acid (Abbasi 2020), and the other study used N-acetyl-L-cysteine (Barekat 2016).

One study compared testicular sperm retrieval and intracytoplasmic sperm injection (ICSI) to ICSI with ejaculated sperm (Hozyen 2022). This study also compared testicular sperm retrieval and ICSI to PICSI (physiological intracytoplasmic sperm injection) and compared PICSI to ICSI with ejaculated sperm (Hozyen 2022).

Two studies reported live birth (Lahimer 2023; Steiner 2020), 7 studies reported clinical pregnancy (Barekat 2016; Habibi 2022; Hozyen 2022; Lahimer 2023; Mathieu d'Argent 2021; Steiner 2020; Stenqvist 2018), 3 studies reported miscarriage (Hozyen 2022; Mathieu d'Argent 2021; Steiner 2020), 1 study reported stillbirth (Steiner 2020), 2 studies reported embryo quality/grading (Hozyen 2022; Lahimer 2023), and 16 studies reported percentage of DNA fragmentation in sperm samples (Abbasi 2021; Abbasi 2020; Barekat 2016; Dadgar 2023; Greco 2005; Habibi 2022; Hosseini 2016; Kumalic 2020; Kumar 2011; Norouzabad 2022; Martínez-Soto 2016; Mathieu d'Argent 2021; Micic 2019; Patki 2023; Steiner 2020; Stenqvist 2018).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Abbasi 2021 RCT Iran	N=56 Male age in years, mean (SD): Probiotic and prebiotic: 34.5 (NR) Placebo: 33.8 (NR) Duration of infertility: at least 1 year Male factor infertility, N (%): 56 (100%) Female factor infertility: NR	<u>Antioxidant</u> Probiotic and prebiotic 500 mg once daily for 80 days	<u>Placebo</u> Once daily for 80 days	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: NR
Abbasi 2020 RCT Iran	N=60 Male age in years, mean (SD): Post-varicocelectomy alpha-lipoic acid: 31.14 (5.54) Post-varicocelectomy placebo: 31.89 (5.06) Duration of infertility: NR Male factor infertility, N (%): 60 (100%)	<u>Post-varicocelectomy antioxidant</u> Alpha-lipoic acid 600 mg for 80 days, immediately after varicocelectomy	<u>Post-varicocelectomy placebo</u> Placebo for 80 days, immediately after varicocelectomy	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: TUNEL and SCSA Threshold for defining sperm DNA fragmentation: NR

Study	Population	Intervention	Comparison	Outcomes	Comments
	Female factor infertility: NR				
Barekat 2016 RCT Iran	N=40 Male age in years, mean (SD): Post-varicocelectomy N-acetyl-L-cysteine: 30.73 (1.4) No post-varicocelectomy treatment: 29.64 (0.74) Duration of infertility in months; mean (SD): 2.1 (0.2) Male factor infertility, N (%): 35 (100%)* Female factor infertility: NR *n=35 were included in analysis as n=5 were not compliance with intervention	Post-varicocelectomy antioxidant N-acetyl-L-cysteine 200 mg daily for 3 months	No post-varicocelectomy treatment No drug after varicocelectomy	• Clinical pregnancy • Percentage of DNA integrity in sperm samples	Sperm DNA integrity tests: TUNEL Threshold for defining sperm DNA fragmentation: NR Method used to confirm clinical pregnancy: NR
Dadgar 2023 RCT Iran	N=70 Male age in years (range): 25-43 Duration of infertility: at least 1 year Male factor infertility, N (%): 70 (100%) Female factor infertility: NR	Antioxidant Zinc 15 mg once daily for 3 months	Placebo Placebo tablets twice daily for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation test: SDFA kit Threshold for defining sperm DNA fragmentation: NR

Study	Population	Intervention	Comparison	Outcomes	Comments
Greco 2005 RCT Spain	N=64 Male age in years: NR Duration of infertility: NR Male factor infertility, N (%): 64 (100%) Female factor infertility: NR	Antioxidant Vitamin C and E 500 mg twice daily for 2 months	Placebo Placebo for 2 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation test: TUNEL Threshold for defining sperm DNA fragmentation: ≥15%
Habibi 2022 RCT Iran	N=70 Male age in years: NR Duration of infertility: NR Male factor infertility, N (%): 70 (100%) Female factor infertility, N (%): 0 (0%)	Antioxidant Alpha-lipoic acid 600 mg daily for 80 days	Placebo Placebo 600 mg daily for 80 days	• Clinical pregnancy • Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: TUNEL and SCSA Threshold for defining sperm DNA fragmentation assessed with TUNEL: >15% Threshold for defining sperm DNA fragmentation assessed with SCSA: >30 % Method used to confirm clinical pregnancy: ultrasound
Hosseini 2016 RCT Iran	N=106 Male age in years, mean (SD): Ginger: 33.27 (5.38) Placebo: 32.05 (3.99) Duration of infertility: >2 years Male factor infertility, N	Antioxidant Ginger capsule 250 mg twice daily for 3 months	Placebo Placebo capsule for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation test: TUNEL Threshold for defining sperm DNA fragmentation: ≥15%

Study	Population	Intervention	Comparison	Outcomes	Comments
	(%): 100 (100%)* Female factor infertility: NR *N=100 included in final analysis				
Hozyen 2022 RCT Egypt	N=223 Male age in years, mean (SD): PICSI: 36.0 (5.5) Testicular sperm retrieval and ICSI: 36.5 (7.9) ICSI (with ejaculated sperm): 36.1 (7.1) Duration of infertility: NR Male factor infertility, N (%): 223 (100%) Female factor infertility: NR	Testicular sperm retrieval and ICSI PICSI	ICSI (with ejaculated sperm)	• Clinical pregnancy • Miscarriage • Embryo quality/grading	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: ≥20.3% Method to confirm clinical pregnancy: presence of fetal heartbeats on ultrasound at 6-7 weeks of gestation Method to confirm miscarriage: loss of baby within 20 weeks of gestation Method to confirm high quality blastocyst: graded >3BB
Kumalic 2020 RCT Slovenia	N=80 Male age in years, mean (SD): Astaxanthin: 35.0 (5.2) Placebo: 36.4 (5.5) Duration of infertility in months: at	Antioxidant Oral astaxanthin 16 mg daily from 3 months	Placebo Placebo capsules for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR

Study	Population	Intervention	Comparison	Outcomes	Comments
	least 12 months Male factor infertility, N (%): 80 (100%) Female factor infertility: NR				
Kumar 2011 RCT India	N=50 Male age in years, mean (SD): Herbo-mineral supplement: 32 (5.09) Placebo: 29.6 (2.88) Duration of infertility: at least 1 year Male factor infertility, N (%): 50 (100%) Female factor infertility: NR	<u>Antioxidant</u> Herbo-mineral supplement 2 capsules twice a day for 3 months	<u>Placebo</u> Identical placebo 2 capsules twice a day for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: NR
Lahimer 2023 RCT Tunisia	N=263 Male age in years, mean (SD): 38.94 (5.8) Duration of infertility: NR Male factor infertility, N (%): 263 (100%)	<u>Antioxidant</u> Micronutrients and l-carnitine 2 capsules twice daily for 3 months	<u>Placebo</u> Placebo 2 capsules twice daily for 3 months	• Live birth • Clinical pregnancy • Embryo quality/grading	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR Method used to confirm live birth: NR Method used to confirm clinical pregnancy: ultrasound imaging Embryonic quality assessment:

Study	Population	Intervention	Comparison	Outcomes	Comments
					maturation rate
Maghsoumi-Norouzabad 2022 RCT Iran	N=86 Male age in years, mean (SD): Vit D3: 35.13 (5.51) Placebo: 34.44 (5.07) Duration of infertility in months, mean (SD): Vit D3: 2.75 (2.25) Placebo: 3.27 (1.97) Male factor infertility, N (%): 86 (100%) Female factor infertility, N (%): 0 (0%)	Antioxidant Vitamin D3 (cholecalciferol) 4000 IU daily 3 months	Placebo Identical placebo for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCD test Threshold for defining sperm DNA fragmentation: NR
Martínez-Soto 2016 RCT Spain	N=74 Male age in years, mean (SE): DHA: 35 (0.8) Placebo: 35.6 (1.0) Duration of infertility: NR Male factor infertility, N (%): 74 (100%) Female factor infertility: NR	Antioxidant DHA 1500 mg (500 mg 3 capsules) daily for 10 weeks	Placebo Placebo capsules for 10 weeks	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR
Mathieu d'Argent 2021 RCT France	N=162 Male age in years, mean (SD): Folic acid: 37.1 (6.7)	Antioxidant Folic acid 15 mg (5 mg 3 tablets) daily for 3-4 months	Placebo Identical placebo (3 tablets) daily for 3-4 months	• Clinical pregnancy • Miscarriage • Percentage of DNA fragmentation	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA

Study	Population	Intervention	Comparison	Outcomes	Comments
	Placebo: 36.5 (6.2) Duration of infertility: NR Male factor infertility, N (%): Folic acid: 65 (78.3%) Placebo: 61 (77.2%) Mixed infertility, N (%): Folic acid: 18 (21.7%) Placebo: 17 (21.5%)			in sperm samples	fragmentation: NR Method used to confirm clinical pregnancy: presence of a gestational sac with at least one foetal heart rate on ultrasound at the 7 weeks of gestation Miscarriage: undefined
Micic 2019 RCT Serbia	N=175 Male age in years, mean (range): 31.5 (19-44) Duration of infertility in years: at least 1 year Male factor infertility, N (%): 175 (100%) Female factor infertility: NR	Antioxidants L-carnitine, L-acetylcarnitine, and micronutrients 2 times a day for 6 months	Placebo Placebo two times a day for 6 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCD test Threshold for defining sperm DNA fragmentation: NR
Patki 2023 RCT India	N=300 Male age in years, mean (SD): Antioxidants: 35 (5.1) Placebo: 34 (5.0) Duration of infertility: NR Male factor infertility, N	Antioxidant Combined antioxidant blend tablet once daily for 3 months	Placebo Identical placebo tablet once daily for 3 months	• Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: >20%

Study	Population	Intervention	Comparison	Outcomes	Comments
	(%): 300 (100%) Female factor infertility, N (%): 0 (0%)				
Steiner 2020 RCT USA	N=171 Male age in years, median (IQR): Antioxidants: 34.0 (30.0-38.0) Placebo: 34.0 (30.0-37.0) Duration of infertility in months, median (IQR): Antioxidants: 24.0 (18.0-48.0) Placebo: 24.0 (15.0-36.0) Male factor infertility, N (%): 171 (100%) Female factor infertility: NR	Antioxidant Combined antioxidant formulation daily for 3-6 months	Placebo Placebo daily for 3-6 months	• Live birth • Clinical pregnancy • Miscarriage • Stillbirth • Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: ≥25% Method used to confirm live birth: a delivery of a live infant after 20 weeks of gestation Method used to confirm clinical pregnancy: NR Method used to confirm pregnancy: positive home pregnancy test
Stenqvist 2018 RCT Sweden	N=79 Male age in years, mean (SD): Antioxidants: 38.0 (5.2) Placebo: 37.3 (4.9) Duration of infertility: ≥1 year Male factor infertility, N (%): 77 (100%)*	Antioxidant Combined antioxidant treatment twice daily for 6 months	Placebo Placebo twice daily for 6 months	• Clinical pregnancy • Percentage of DNA fragmentation in sperm samples	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: ≥25%

Study	Population	Intervention	Comparison	Outcomes	Comments
	Female factor infertility: NR *n=2 were lost to follow up, so N=77 were included in final analysis				

DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IQR: interquartile range; NR: not reported; RCT: randomised controlled trial; SCD: sperm chromatin dispersion test; SCSA: sperm chromatin structure assay; SD: standard deviation; SDFA: sperm DNA fragmentation assay kit; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Antioxidants

There was evidence from 2 RCTs for antioxidants compared to placebo for the live birth outcome. However, because of very serious heterogeneity, these estimates could not be pooled. Very low quality evidence from 1 RCT showed a higher live birth rate for participants receiving an antioxidant relative to those receiving placebo, but the other RCT showed no clinically important difference in live birth rate between antioxidant and placebo (low quality evidence).

Low quality evidence from 5 RCTs showed no clinically important difference in clinical pregnancy rate between those receiving antioxidants and those receiving placebo.

Low quality evidence from 2 RCTs showed no clinically important difference in the rate of miscarriage between antioxidants and placebo. Low quality evidence from 1 of these RCTs also showed no clinically important difference for stillbirth.

Low to moderate quality evidence from 1 RCT showed no clinically important difference between antioxidants and placebo on embryo quality/grading as defined by maturation rate, fertilisation rate, cleavage rate, or blastocyst rate.

The analysis of the evidence for the percentage of sperm DNA fragmentation was stratified by the DNA fragmentation test. Low quality evidence from 4 RCTs showed no clinically important difference between antioxidants and placebo in the percentage of DNA fragmentation in the sperm samples as assessed by sperm chromatin structure assay (SCSA).

There was evidence from 6 RCTs for the percentage of sperm DNA fragmentation assessed by terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay (TUNEL). However, because of very serious heterogeneity these estimates could not be pooled. Very low to high quality evidence from 4 of these RCTs showed a lower percentage of sperm DNA fragmentation for those receiving antioxidants (vitamin C and E in 1 study, alpha-lipoic acid in 1 study, ginger in 1 study, and DHA in 1 study) relative to placebo, but very low and moderate quality evidence from 2 of these RCTs showed no clinically important difference in DNA fragmentation percentage between antioxidant and placebo.

Low quality evidence from 1 RCT showed no clinically important difference between antioxidant and placebo on the percentage of sperm DNA fragmentation as assessed by the sperm chromatin dispersion test (SCD).

Low quality evidence from 1 RCT showed a lower percentage of sperm DNA fragmentation in those receiving antioxidant (zinc) relative to placebo as assessed by the sperm DNA fragmentation assay kit (SDFA).

Post-varicocelectomy antioxidants

Low quality evidence from 1 RCT comparing post-varicocelectomy antioxidant and post-varicocelectomy placebo showed no clinically important difference for percentage of sperm DNA fragmentation assessed by SCSA or TUNEL.

Very low quality evidence from 1 RCT comparing post-varicocelectomy antioxidant with no post-varicocelectomy treatment, showed no clinically important difference for clinical pregnancy. Low quality evidence from the same RCT showed a higher percentage of DNA integrity in sperm samples as assessed by TUNEL.

Testicular sperm retrieval and intracytoplasmic sperm injection (ICSI)

Low to very low quality evidence from 1 RCT showed no clinically important difference in clinical pregnancy or miscarriage rates between testicular sperm retrieval and intracytoplasmic sperm injection (ICSI) relative to ICSI with ejaculated sperm for those with abnormal sperm DNA fragmentation. Low quality evidence from the same RCT showed a lower percentage of high-quality blastocysts in those receiving ICSI with testicular extracted sperm relative to ICSI with ejaculated sperm, but this difference was below the threshold for a minimally important difference.

Low to very low quality evidence from the same RCT showed no clinically important difference in clinical pregnancy, miscarriage, or embryo quality between testicular sperm retrieval and ICSI and sperm selection using physiological ICSI (PICSI, with ejaculated sperm) in those with sperm DNA fragmentation.

Sperm selection with physiological ICSI (PICSI)

Low quality evidence from 1 RCT showed a higher clinical pregnancy rate for those with abnormal sperm DNA fragmentation where sperm were selected using PICSI compared to ICSI where sperm were selected based on density gradient centrifugation. Very low to moderate quality evidence from the same RCT showed no clinically important difference between PICSI and ICSI for miscarriage rate or the percentage of high-quality blastocysts.

No evidence was found that reported on lifestyle advice and varicocele treatment (radiological and surgical interventions). The outcome of pregnancy loss was not reported by any studies.

See appendix F for full GRADE tables.

Economic evidence

A total of 272 studies were identified in the health economic literature search for this review question. After duplicates were removed, 184 studies were screened on title and abstract, of which all were excluded at this stage.

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix B and the economic study selection flow chart in appendix G.

Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

Economic model

This area was not prioritised for new cost-effectiveness analysis as it was not anticipated that recommendations would have a significant resource impact.

Unit costs

Unit costs for the interventions listed in the protocol are presented in Table 3.

Table 3: Unit costs

Resource	Unit costs	Source
Antioxidants		
Vitamin C	Tablets likely to be independently purchased by person requiring antioxidant	
Vitamin E	Tablets likely to be independently purchased by person requiring antioxidant	
Carnitine	Tablets likely to be purchased by person requiring antioxidant • NHS indicative price for 125, 250mg capsules: £17.04 – BNF, date accessed 31.01.2025	
Zinc	Tablets likely to be independently purchased by person requiring antioxidant • NHS drug tariff price for 90, 125mg effervescent tables £17.72 – BNF, date accessed 31.01.2025	
Folic acid	Tablets likely to be purchased by person requiring antioxidant	
N-acetyl cysteine	Tablets likely to be independently purchased by person requiring antioxidant • NHS indicative price for 20, 600mg capsules: £65.20 – BNF, date accessed 31.01.2025 • NHS drug tariff price for solution for infusion: £2.13 per unit – BNF, date accessed 31.01.2025	
Selenium	Tablets likely to be independently purchased by person requiring antioxidant • NHS drug tariff price for 120, 200mcg capsules: £6.00 – BNF, date accessed 31.01.2025	

Resource	Unit costs	Source
	• NHS indicative price for solution for injection: £3.00 per unit (100mcg/2ml) & £9.00 per unit (500mcg/10ml) – BNF, date accessed 31.01.2025	
Lifestyle advice		
Nurse time[a] Band 6 Band 7	 £58 per hour £69 per hour	The unit costs of health and social care 2022/23 *Cost to the NHS will be less than the hourly unit cost presented*
Doctors time[a] Registrar Associate specialist Medical consultant	 £72 per hour £122 per hour £143 per hour	The unit costs of health and social care 2022/23 *Cost to the NHS will be less than the hourly unit cost presented*
Varicocele treatment		
Varicocelectomy	£532	Minor, Scrotum, Testis or Vas Deferens Procedures, 19 years and over, National schedule of NHS costs 2023/24, Currency code: LB54A, outpatient procedures Day case cost - £2,436
Percutaneous embolization	£176	Varicocele Embolisation, National schedule of NHS costs 2023/24, Currency code: YR56Z, outpatient procedures Day case - £1,398
Testicular sperm retrieval and Intracytoplasmic sperm injection (ICSI)		
Surgical extraction of sperm	£3,386	National schedule of NHS costs 2023/24; MC20Z day case unit cost
ICSI	£4,120	2023-25 NHS Payment Scheme (amended) (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2)[b, b]
ICSI (with ejaculated sperm)		
ICSI	£4,120	2023-25 NHS Payment Scheme (amended) (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2)[b]
Collection of sperm	£398	National schedule of NHS costs 2023/24; MC21Z outpatient procedure unit cost
Physiological ICSI (PICSI)		
PICSI[(b)]	£4,510	2023-25 NHS Payment Scheme (amended) (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2) and the estimated additional cost of PICSI obtained by calculating the difference in between the PICSI and ICSI cost (£1,690 - £1,300) from a private clinic and adding this difference to the NHS cost for ICSI.
Collection of sperm	£398	National schedule of NHS costs 2023/24; MC21Z outpatient procedure unit cost
Surgical extraction of sperm	£3,386	National schedule of NHS costs 2023/24; MC20Z day case unit cost

(a) Hospital based staff, Including qualification costs
(b) Price to include 1 fresh and 1 frozen cycle

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Live birth and clinical pregnancy were prioritised as critical outcomes by the committee. They were selected as the best indicators of effectiveness of fertility treatment and were specified in the core outcome set for fertility research (Duffy 2020).

Miscarriage, pregnancy loss and stillbirth were prioritised as important outcomes as they provide meaningful information about the success of a pregnancy and can have a significant impact on psychological and physical health. The percentage of sperm DNA fragmentation was also selected as an important outcome given that this is a direct measure of the primary target of interventions aimed at treating DNA fragmentation. The committee were aware of evidence suggesting an association between sperm DNA fragmentation and poor embryo quality (Borges 2019; Li 2024), and embryo quality/grading was therefore considered an important outcome.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The quality of evidence ranged from very low to high quality. The main reasons for downgrading were risk of bias (arising from uncertainties around allocation concealment, failure to use an intention-to-treat analysis, and missing outcome data) and imprecision (95% confidence intervals crossing decision making thresholds or low event rates or small sample sizes).

Benefits and harms

The committee discussed the heterogeneity of sperm DNA fragmentation tests and noted that all modalities of testing were included in this review, such as terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay (TUNEL), sperm chromatin structure assay (SCSA), sperm DNA fragmentation assay (SDFA), and sperm chromatin dispersion test (SCD). The committee highlighted that these tests assess different aspects of sperm DNA damage and can also be highly variable in terms of point estimates and confidence intervals. For example, compared to TUNEL, SCSA can be associated with a point estimate with a more precise confidence interval. The committee also noted variability in the different interventions used to treat sperm DNA fragmentation and acknowledged that some of the interventions reviewed were very poorly specified.

The committee considered the evidence showing no important differences between antioxidants and placebo for clinical pregnancy, miscarriage, stillbirth, and embryo quality/grading. The committee also discussed the inconsistent and non-pooled evidence for live birth and the percentage of sperm DNA fragmentation. The committee noted that the single RCT showing a potential benefit for antioxidants on live birth included live births from spontaneous conception and following assisted reproductive technologies (ART) treatment. The committee discussed the equivocal effects of antioxidants on the percentage of sperm DNA fragmentation and agreed that the heterogeneity in results was not necessarily surprising given the different types, doses, and combinations of antioxidants across studies. The committee acknowledged that the evidence was very low quality and from a very heterogeneous population. Based on the lack of a consistent benefit in the evidence reviewed the committee recommended that supplements, antioxidants and medical treatments should not be offered to improve sperm DNA integrity. The committee discussed the need for further research in order to identify and validate the best assay that should be used and define a threshold for high DNA fragmentation, establish a link between elevated DNA fragmentation and subfertility, and develop a standardised antioxidant and vitamin treatment and dose (particularly given the potential for unexpected adverse effects, as in Ménézo 2007). The committee agreed that given all these unknowns, it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results about the potential benefits of supplements and antioxidants for improving sperm DNA integrity and improving the chances of live birth.

The committee considered the evidence on post-varicocelectomy antioxidants and noted that no important benefit was shown for clinical pregnancy, and effects on the percentage of sperm DNA fragmentation were mixed. The committee discussed that the evidence for this comparison is difficult to interpret given that it is a combination of two different treatments. The committee agreed that it was not appropriate to make a specific recommendation for post-varicocelectomy antioxidants.

The committee discussed the limited evidence identified for testicular sperm retrieval as an intervention for abnormal sperm DNA fragmentation. One RCT compared testicular sperm retrieval and intracytoplasmic sperm injection (ICSI) with ICSI using ejaculated sperm and found no important differences in clinical pregnancy or miscarriage rates. This RCT showed a small benefit in favour of ICSI with ejaculated sperm on the percentage of high-quality blastocysts, but this difference was below the threshold for a minimally important difference.

The same RCT also compared testicular sperm extraction with ICSI to sperm selection using physiological ICSI (PICSI, on ejaculated sperm) and showed no important differences for clinical pregnancy, miscarriage or embryo quality. Based on this evidence the committee recommended that surgical sperm retrieval should not be offered as a way of improving outcomes for non-azoospermic people with reduced sperm DNA integrity (elevated fragmentation levels). The committee acknowledged the wider evidence base of observational studies that suggest that testicular extracted sperm may be less fragmented than ejaculated sperm. However, limitations of the evidence identified were discussed, namely a single RCT where methods of sperm selection and preparation were potential confounders for the comparison of ICSI using testicular extraction relative to ejaculated sperm. Based on this limited evidence for benefit, considered in the context of the more general uncertainties about testing and treatment for high levels of DNA fragmentation (discussed above), the committee agreed that it was not appropriate to make a research recommendation on surgical sperm retrieval for people with reduced sperm DNA integrity.

The committee also considered evidence from this RCT for the comparison focusing on sperm selection using PICSI (on ejaculated sperm) relative to sperm selection using density gradient centrifugation (on ejaculated sperm). There was some evidence for a potential benefit of PICSI on clinical pregnancy for those with elevated sperm DNA fragmentation. However, no important difference was observed for other outcomes. The committee agreed that given that this was an isolated clinically important difference across a number of comparisons from this RCT, and that the study did not report the primary outcome of live birth, there was insufficient evidence to justify recommending sperm selection with PICSI for people with male factor fertility problems and elevated sperm DNA fragmentation.

The committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. The committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee recommended that testing for sperm DNA integrity (fragmentation) should not be carried out.

Cost effectiveness and resource use

No health economic evidence was identified for this review question, therefore the committee qualitatively assessed cost-effectiveness.

Based on the clinical evidence, which failed to demonstrate the effectiveness of treating sperm DNA fragmentation, the committee concluded that testing for sperm DNA integrity (fragmentation) should not be carried out. This reflects current NHS practice and therefore the committee's recommendation is not expected to result in a significant resource impact.

The committee discussed the use of antioxidants and vitamins, noting that the cost of these would typically be incurred by an individual. However, despite the minimal costs to the NHS, the committee concluded there was insufficient clinical evidence to recommend the use of antioxidants or vitamins.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.17.6, 1.24.6 and 1.27.1.

References – included studies

Effectiveness

Abbasi 2021

Abbasi, Behzad; Abbasi, Homayoun; Niroumand, Hassan (2021) Synbiotic (FamiLact) administration in idiopathic male infertility enhances sperm quality, DNA integrity, and chromatin status: A triple-blinded randomized clinical trial. International journal of reproductive biomedicine 19(3): 235-244

Abbasi 2020

Abbasi, Behzad, Molavi, Newsha, Tavalaee, Marziyeh et al. (2020) Alpha-lipoic acid improves sperm motility in infertile men after varicocelectomy: a triple-blind randomized controlled trial. Reproductive biomedicine online 41(6): 1084-1091

Barekat 2016

Barekat, Foroogh, Tavalaee, Marziyeh, Deemeh, Mohammad Reza et al. (2016) A Preliminary Study: N-acetyl-L-cysteine Improves Semen Quality following Varicocelectomy. International journal of fertility & sterility 10(1): 120-6

Dadgar 2023

Dadgar, Zeynab, Shariatzadeh, Seyed Mohammad Ali, Mehranjani, Malek Soleimani et al. (2023) The therapeutic effect of co-administration of pentoxifylline and zinc in men with idiopathic infertility. Irish journal of medical science 192(1): 431-439

Greco 2005

Greco, Ermanno, Iacobelli, Marcello, Rienzi, Laura et al. (2005) Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. Journal of andrology 26(3): 349-53

Habibi 2022

Habibi, Masoud, Abbasi, Behzad, Fakhari Zavareh, Zohreh et al. (2022) Alpha-Lipoic Acid Ameliorates Sperm DNA Damage and Chromatin Integrity in Men with High DNA Damage: A Triple Blind Randomized Clinical Trial. Cell journal 24(10): 603-611

Hosseini 2016

Hosseini, Jalil, Mardi Mamaghani, Azar, Hosseinifar, Hani et al. (2016) The influence of ginger (Zingiber officinale) on human sperm quality and DNA fragmentation: A double-blind randomized clinical trial. International journal of reproductive biomedicine 14(8): 533-40

Hozyen 2022

Hozyen, Manar, Hasanen, Eman, Elqusi, Khaled et al. (2022) Reproductive Outcomes of Different Sperm Selection Techniques for ICSI Patients with Abnormal Sperm DNA Fragmentation: a Randomized Controlled Trial. Reproductive sciences (Thousand Oaks, Calif.) 29(1): 220-228

Kumalic 2020

Kumalic, Senka Imamovic, Klun, Irma Virant, Bokal, Eda Vrtacnik et al. (2020) Effect of the oral intake of astaxanthin on semen parameters in patients with oligo-astheno-teratozoospermia: a randomized double-blind placebo-controlled trial. Radiology and oncology 55(1): 97-105

Kumar 2011

Kumar, Rajeev, Saxena, Vaibhav, Shamsi, Monis Bilal et al. (2011) Herbo-mineral supplementation in men with idiopathic oligoasthenoteratospermia: A double blind randomized placebo-controlled trial. Indian journal of urology: IJU: journal of the Urological Society of India 27(3): 357-62

Lahimer 2023

Lahimer, Marwa, Gherissi, Oumaima, Ben Salem, Nesrine et al. (2023) Effect of Micronutrients and L-Carnitine as Antioxidant on Sperm Parameters, Genome Integrity, and ICSI Outcomes: Randomized, Double-Blind, and Placebo-Controlled Clinical Trial. Antioxidants (Basel, Switzerland) 12(11)

Maghsoumi-Norouzabad 2022

Maghsoumi-Norouzabad, Leila, Zare Javid, Ahmad, Mansoori, Anahita et al. (2022) Vitamin D3 Supplementation Effects on Spermatogram and Oxidative Stress Biomarkers in Asthenozoospermia Infertile Men: a Randomized, Triple-Blind, Placebo-Controlled Clinical Trial. Reproductive sciences (Thousand Oaks, Calif.) 29(3): 823-835

Martínez-Soto 2016

Martínez-Soto, Juan Carlos, Domingo, Juan Carlos, Cordobilla, Begoña, Nicolás, María et al. (2016). Dietary supplementation with docosahexaenoic acid (DHA) improves seminal antioxidant status and decreases sperm DNA fragmentation. Systems Biology in Reproductive Medicine, 62(6), 387–395.

Mathieu d'Argent 2021

Mathieu d'Argent, Emmanuelle, Ravel, Celia, Rousseau, Alexandra et al. (2021) High-Dose Supplementation of Folic Acid in Infertile Men Improves IVF-ICSI Outcomes: A Randomized Controlled Trial (FOLFIV Trial). Journal of clinical medicine 10(9)

Micic 2019

Micic, Sava, Lalic, Natasa, Djordjevic, Dejan et al. (2019) Double-blind, randomised, placebo-controlled trial on the effect of L-carnitine and L-acetylcarnitine on sperm parameters in men with idiopathic oligoasthenozoospermia. Andrologia 51(6): e13267

Patki 2023

Patki, Ameet, Shelatkar, Rohit, Singh, Monica et al. (2023) Impact of antioxidants in improving semen parameters like count, motility and DNA fragmentation in sub-fertile males: a randomized, double-blind, placebo-controlled clinical trial. Translational and clinical pharmacology 31(1): 28-39

Steiner 2020

Steiner, Anne Z, Hansen, Karl R, Barnhart, Kurt T et al. (2020) The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. Fertility and sterility 113(3): 552-560e3

Stenqvist 2018

Stenqvist, A, Oleszczuk, K, Leijonhufvud, I et al. (2018) Impact of antioxidant treatment on DNA fragmentation index: a double-blind placebo-controlled randomized trial. Andrology 6(6): 811-816

Economic

None.

Other

Borges 2019

Borges, E Jr, Zanetti BF, Setti AS, Braga DPAF, Provenza RR, Iaconelli A Jr. Sperm DNA fragmentation is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in reproductive cycles of non-male factor infertility. Fertil Steril. 2019 Sep;112(3):483-490.

Duffy 2020

Duffy, J.M., AlAhwany, H., Bhattacharya, S., Collura, B., Curtis, C., Evers, J.L., Farquharson R.G., Franik, S., Giudice, L.C., Khalaf, Y., Knijnenburg, J.M., Developing a core outcome set for future infertility research: an international consensus development study, Human Reproduction, 35(12), 2725-2734, 2020

Li 2024

Li, F., Duan, X., Li, M. et al. Sperm DNA fragmentation index affect pregnancy outcomes and offspring safety in assisted reproductive technology. Sci Rep 14, 356 (2024).

Ménézo 2007

Ménézo YJ, 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. Reproductive Biomedicine Online. 14(4): 418-421.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42023467979
Review title	Clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems
Review question	What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?
Objective	To determine the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) for male factor fertility problems. This will also inform decisions about investigations of sperm DNA.
Searches	The following databases will be searched (with no date restriction): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by: • English language

Field	Content
	• Human studies The guideline committee will decide whether and when to re-run the searches to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Treatments for sperm DNA fragmentation in males with fertility problems, to inform investigations for male factor fertility problems
Population	Inclusion: • People with a fertility problem (pregnancy not achieved after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination) that may be associated with sperm DNA fragmentation (above threshold levels of DNA fragmentation identified by DNA assays of ejaculated sperm) Exclusion: • Management of recurrent miscarriage
Intervention	• Antioxidants (individual or combined, including vitamins C and E, carnitine, CoQ10, zinc, folic acid, N-acetyl cysteine and selenium) • Lifestyle advice promoting the following healthy behaviours (alone or in combination): o weight loss o healthy diet o exercise o smoking cessation o reducing alcohol intake o reducing environmental and occupational exposure to toxicants o serial ejaculate • Varicocele treatment (radiological and surgical interventions) • Testicular sperm retrieval and Intracytoplasmic sperm injection (ICSI) • ICSI (with ejaculated sperm)

Field	Content
	• Physiological ICSI (PICSI)
Comparator	• Placebo • Head to head comparisons of different interventions
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) If no RCT evidence: • Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with matched comparison or another method of controlling for confounding variables)
Other exclusion criteria	Other exclusion criteria: • Language limitations: non-English-language papers will be excluded • Conference abstracts, dissertations and unpublished data will not be included
Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
Primary outcomes (critical outcomes)	• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate)
Secondary outcomes (important outcomes)	• Miscarriage (loss of a baby before 24 weeks gestational age) • Pregnancy loss (accounting for placental abruption) and stillbirth • Embryo quality/grading (as defined by study [criteria for defining high quality will be extracted], including high quality cleavage stage, blastocyst stage and embryo formation rate) • Percentage of DNA fragmentation in sperm samples
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.

Field	Content
	Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details (reference, country where study was carried out, and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions, follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (dichotomous outcomes) and mean differences or standardised mean differences (continuous outcomes). It is considered likely that a random-effects model will be used for meta-analyses (based on assumptions about methodological diversity of studies). Funnel plot asymmetry (relationship between the magnitude of the effect estimate and study size) will be considered (for meta-analyses that include at least 10 studies), and where asymmetry is indicated a fixed-effects model will be conducted (and both random-effects and fixed-effects analyses will be presented) or sensitivity analyses excluding small studies will be considered. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses.

Field	Content
	The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all other relative dichotomous outcomes • Continuous outcomes (where published MIDs are not available): +/- 0.5x control group SD

Analysis of sub-groups	Evidence will be stratified by:
	• Sperm DNA fragmentation test:
	  ○ Sperm chromatin structure assay (SCSA)
	  ○ Terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling (TUNEL) assay
	  ○ Sperm chromatin dispersion (SCD) test
	  ○ Single cell gel electrophoresis (Comet) assay
	
	Evidence will be sub-grouped by the following:
	• Threshold for defining sperm DNA fragmentation (as defined by study)
	• Female factor fertility:
	  ○ No female factor fertility problems
	  ○ Female factor fertility problems
	  ○ Female factor fertility not specified
	
	Evidence will be sub-grouped by the following only if there is significant heterogeneity in outcomes:
	• Male age (based on the mean age in the study):
	  ○ <45 years
	  ○ ≥45 years
	• Female age (based on the mean age in the study)

<table>
<tr><th>Field</th><th colspan="3">Content</th></tr>
<tr><td></td><td colspan="3">
<35 years
35-39 years
>39 years
Previous implantation failure:
Screening sperm DNA fragmentation prior to 1st embryo transfer (treatment)
Screening sperm DNA fragmentation after previous treatment failure
Where evidence is stratified or sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.</td></tr>
<tr><td rowspan="7">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify) Proportional (single-arm) meta-analysis</td></tr>
<tr><td>Language</td><td colspan="3">English</td></tr>
<tr><td>Country</td><td colspan="3">England</td></tr>
<tr><td>Anticipated or actual start date</td><td colspan="3">August 2023</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">November 2024</td></tr>
<tr><td rowspan="3">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
</table>

Field	Content		
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: Guideline development team A Named contact e-mail: FertilityProblems@nice.org.uk Organisational affiliation of the review: Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
Review team members	• Senior Technical Analyst • Technical Analyst		
Funding sources/sponsor	This systematic review is being completed by NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263		

Field	Content	
Other registration details	None	
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=467979	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Male factor fertility problems, infertility, DNA fragmentation, DNA assays, DNA damage, antioxidants	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CoQ10: coenzyme Q10; DNA: deoxyribonucleic acid; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; ICSI: intracytoplasmic sperm injection; NICE: National Institute for Health and Care Excellence; PICSI: physiological intracytoplasmic sperm injection; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SCD: sperm chromatin dispersion test; SCSA: sperm chromatin structure assay; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Database: Ovid MEDLINE(R) ALL <1946 to June 07, 2024>

Date of last search: 10/06/2024

#	Searches
1	Infertility/ or exp infertility, male/
2	fertility/
3	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*).tw.
4	or/1-3
5	(exp Spermatozoa/ or Semen/ or exp Semen Analysis/) and (dna damage/ or dna fragmentation/ or Oxidative Stress/)
6	((sperm* or semen* or seminal plasma*) and ((deoxyribonucleic acid* or dna or oxidative) adj3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))).tw,kf.
7	or/5-6
8	4 and 7
9	sdf.tw,kf.
10	8 or 9
11	exp Antioxidants/
12	(antioxid* or anti oxid*).tw,kf.
13	exp Vitamins/
14	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).tw,kf.
15	dietary supplements/ or probiotics/
16	((diet* or nutrition*) adj2 supplement*).tw,kf.
17	(probiotic* or lactobacill* or bifidobacteri*).tw,kf.
18	((good or benefi*) adj2 (bacteria* or yeast* or microorganism* or micro organism*)).tw,kf.
19	(ascorb* or dehydroascorbic acid*).tw,kf.
20	(abortosan* or "antioxidans e-hevert*" or "aquasol e*" or "austrovit e*" or "auxina e*" or "bio e*" or biopto-e* or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate*" or "dagravit e*" or dalfatol* or "dal e*" or davitamon* or dermorelle* or detulin* or "dumovit e*" or "e mulsin*" or "e vicotrat*" or "e ferol*" or ecoro* or "elex verla*" or embial* or "e perle*" or "e perte*" or "e recordati*" or "e toplex*" or "e vicotrat*" or "e vimin*" or "e vita*" or "e viterbin*" or ecoferol* or efer* or eferol* or "enoulan forte*" or ephynal* or eplonat* or eprolin* or "eps?lan m*" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e*" or eusovit* or "godabion e*" or gonavit* or "hanobakor hydrovit e*" or "ido e*" or juvel? or lasar* or livingpherol* or "malton e*" or "micorvit e*" or "mulsal e*" or natopherol* or "optovit e*" or phytoferol* or pletocol* or "puncto e*" or "richtavit e*" or "sanavitan s*" or socopherol* or spondyvit* or "toco 500*" or tocoferol* or "tocoferolo bioglan*" or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e*" or uno-vit* or vedrop* or vibolex* or "vi dom e*" or "vi e caps*" or "vi ea*" or "vi etal*" or "vidom e*" or viea* or vietal* or viprimol* or viteolin? or "wandervit e*" or "vita e*" or "vita-plus e*" or vitazell* or tocotrienol* or "alpha* e*" or e-tabs* or e-caps* or nutra-e* or liqua-e*).tw,kf.
21	Carnitine/
22	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnit?n? or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or "gamma butyro beta hydroxybetaine*" or "l cartin*" or "l carn*" or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*).tw,kf.
23	Ubiquinone/
24	("coenzyme Q*" or "coenzyme Q10*" or "coenzyme CoQ*" or CoQ10* or CoQ* or "Q 10*" or ubiquinone*).tw,kf.
25	Zinc/
26	zinc*.tw,kf.
27	Folic Acid/
28	(folic acid* or folate* or folacin* or pteroylglutamic acid* or folvite*).tw,kf.
29	Acetylcysteine/

#	Searches
30	(acetylcystein? or "acetyl cystein?" or (acetyl adj l adj cystein?) or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or (dampo adj mucopect*) or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or (mercapturic adj acid*) or muciteran* or (muco adj sanigen*) or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or (optipect adj hustengetrank*) or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A-CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*).tw,kf.
31	Selenium/
32	(selenium or selenoPrecise* or 200-SEL* or abselen* or selenase* or radioselenium* or selenicum*).tw,kf.
33	exp Life Style/
34	(life style* or lifestyle*).tw,kf.
35	"diet, food, and nutrition"/ or exp food/ or exp diet/ or eating/ or feeding behavior/ or food preferences/
36	Nutritional Status/
37	((food* or feed* or diet* or eat*) adj3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)).tw,kf.
38	nutriti*.tw,kf.
39	Weight Loss/
40	overweight/ or obesity/ or obesity, morbid/
41	body mass index/
42	((weight* or obes* or overweight or BMI or body mass or body fat or quetelet index) adj3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)).tw,kf.
43	exp Exercise/
44	recreation/ or exp sports/
45	(exercis* or sport* or fitness or physical* activ*).tw,kf.
46	(recreation* adj2 (activ* or physical*)).tw,kf.
47	exp Smoking/ or exp "tobacco use"/
48	exp Smoking Devices/
49	Nicotine/
50	health behavior/ or smoking cessation/ or "tobacco use cessation"/
51	((health* or drink*) adj2 behavio*).tw,kf.
52	(smok* or tobacco* or nicotine* or e-cig* or ecig* or electronic cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or "water pipe*" or waterpipe*).tw,kf.
53	drinking behavior/ or alcohol drinking/
54	(alcohol* or wine or beer or spirits or liquor or intoxicant*).tw,kf.
55	exp Environmental Pollution/
56	exp Environmental Pollutants/
57	exp Hazardous Substances/
58	exp Pesticides/
59	((pollut* or hazard* or contaminat* or chemical*) adj4 (environment* or air* or water* or occupation* or expos*)).tw,kf.
60	(toxin* or toxic*).tw,kf.
61	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*).tw,kf.
62	Endocrine Disruptors/
63	(endocrine adj2 disrupt*).tw,kf.
64	Ejaculation/
65	(ejaculat* adj2 (serial or frequen*)).tw,kf.
66	Varicocele/
67	(Varicocele? or Varicocoele?).tw,kf.
68	((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf.
69	((varicos* or dilat* or enlarg* or tortuos*) adj4 ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))).tw,kf.
70	or/66-69
71	Radiology, Interventional/
72	radiolog*.tw,kf.
73	Embolization, Therapeutic/

#	Searches
74	(embol* or coil* or balloon* or plug*).tw,kf.
75	Sclerotherapy/ or exp Sclerosing Solutions/
76	(sclero* or anti-varicos* or antivari*).tw,kf.
77	Urologic Surgical Procedures, Male/
78	microsurgery/ or minimally invasive surgical procedures/ or surgery, computer-assisted/ or robotic surgical procedures/
79	(surg* or microsurg* or microscop* or magnif*).tw,kf.
80	ligation/
81	(ligat* or constrict*).tw,kf.
82	Laparoscopy/
83	(laparoscop* or laparoendoscop*).tw,kf.
84	or/71-83
85	70 and 84
86	Varicocele/su, th
87	(varicocelectom* or varicocoelectom*).tw,kf.
88	((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf.
89	Sperm Retrieval/
90	"Tissue and Organ Harvesting"/
91	((sperm* or testi* or testes* or needle* or epididym*) adj3 (retriev* or aspirat* or extract* or procur* or harvest*)).tw.
92	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA).tw.
93	Sperm Injections, Intracytoplasmic/
94	(((intra-cytoplasmic or intracytoplasmic) adj2 sperm*) or ICSI or PICSI).tw,kf.
95	or/11-65,85-94
96	10 and 95
97	letter/
98	editorial/
99	news/
100	exp historical article/
101	Anecdotes as topic/
102	comment/
103	case reports/
104	(letter or comment*).ti.
105	or/97-104
106	randomized controlled trial/ or random*.ti,ab.
107	105 not 106
108	animals/ not humans/
109	exp Animals, Laboratory/
110	exp Animal Experimentation/
111	exp Models, Animal/
112	exp Rodentia/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/107-113
115	96 not 114
116	limit 115 to English language
117	randomized controlled trial.pt.
118	controlled clinical trial.pt.
119	pragmatic clinical trial.pt.
120	randomi#ed.ab.
121	placebo.ab.
122	drug therapy.fs.
123	randomly.ab.

#	Searches
124	trial.ab.
125	groups.ab.
126	or/117-125
127	meta-analysis/
128	meta-analysis as topic/
129	(meta analy* or metanaly* or metaanaly*).ti,ab.
130	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
131	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
132	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
133	(search* adj4 literature).ab.
134	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
135	cochrane.jw.
136	or/127-135
137	116 and (126 or 136)

Database: Embase <1974 to 2024 June 07>

Date of last search: 10/06/2024

#	Searches
1	exp male infertility/ or semen abnormality/
2	infertility/ or subfertility/
3	fertility/
4	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*).tw.
5	or/1-4
6	exp sperm/
7	spermatogonium/
8	semen analysis/
9	exp semen parameters/
10	or/6-9
11	dna damage/ or dna fragmentation/
12	oxidative stress/
13	11 or 12
14	10 and 13
15	((sperm* or semen* or seminal plasma*) and ((deoxyribonucleic acid* or dna or oxidative) adj3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))).tw,kf.
16	14 or 15
17	5 and 16
18	sdf.tw,kf.
19	or/17-18
20	exp antioxidant/
21	(antioxid* or anti oxid*).tw,kf.
22	exp vitamin/
23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).tw,kf.
24	dietary supplement/
25	exp probiotic agent/
26	((diet* or nutrition*) adj2 supplement*).tw,kf.
27	(probiotic* or lactobacill* or bifidobacteri*).tw,kf.
28	((good or benefi*) adj2 (bacteria* or yeast* or microorganism* or micro organism*)).tw,kf.
29	(ascorb* or dehydroascorbic acid*).tw,kf.
30	(abortosan* or "antioxidans e-hevert*" or "aquasol e*" or "austrovit e*" or "auxina e*" or "bio e*" or biopto-e* or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate*" or "dagravit e*" or dalfatol* or "dal e*" or davitamon* or dermorelle* or detulin* or "dumovit e*" or "e mulsin*" or "e vicotrat*" or "e ferol*" or ecoro* or "elex verla*" or

#	Searches
	embial* or "e perle*" or "e perte*" or "e recordati*" or "e toplex*" or "e vicotrat*" or "e vimin*" or "e vita*" or "e viterbin*" or ecoferol* or efer* or eferol* or "enoulan forte*" or ephynal* or eplonat* or eprolin* or "eps?lan m*" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e*" or eusovit* or "godabion e*" or gonavit* or "hanobakor hydrovit e*" or "ido e*" or juvel? or lasar* or livingpherol* or "malton e*" or "micorvit e*" or "mulsal e*" or natopherol* or "optovit e*" or phytoferol* or pletocol* or "puncto e*" or "richtavit e*" or "sanavitan s*" or socopherol* or spondyvit* or "toco 500*" or tocoferol* or "tocoferolo bioglan*" or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e*" or uno-vit* or vedrop* or vibolex* or "vi dom e*" or "vi e caps*" or "vi ea*" or "vi etal*" or "vidom e*" or viea* or vietal* or viprimol* or viteolin? or "wandervit e*" or "vita e*" or "vita-plus e*" or vitazell* or tocotrienol* or "alpha* e*" or e-tabs* or e-caps* or nutra-e* or liqua-e*).tw,kf.
31	carnitine/
32	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnit?n? or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or "gamma butyro beta hydroxybetaine*" or "l cartin*" or "l carn*" or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*).tw,kf.
33	ubiquinone/
34	("coenzyme Q*" or "coenzyme Q10*" or "coenzyme CoQ*" or CoQ10* or CoQ* or "Q 10*" or ubiquinone*).tw,kf.
35	zinc/
36	zinc*.tw,kf.
37	folic acid/
38	(folic acid* or folate* or folacin* or pteroylglutamic acid* or folvite*).tw,kf.
39	acetylcysteine/
40	(acetylcystein? or "acetyl cystein?" or (acetyl adj l adj cystein?) or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or (dampo adj mucopect*) or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or (mercapturic adj acid*) or muciteran* or (muco adj sanigen*) or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or (optipect adj hustengetrank*) or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A-CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*).tw,kf.
41	selenium/
42	(selenium or selenoPrecise* or 200-SEL* or abselen* or selenase* or radioselenium* or selenicum*).tw,kf.
43	exp lifestyle/
44	(life style* or lifestyle*).tw,kf.
45	nutrition/ or exp diet/ or exp dietary intake/ or dietary pattern/ or feeding behavior/ or food preference/ or eating habit/ or exp food/ or eating/
46	nutritional status/
47	((food* or feed* or diet* or eat*) adj3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)).tw,kf.
48	nutriti*.tw,kf.
49	body weight loss/
50	obesity/ or morbid obesity/
51	body mass/
52	((weight* or obes* or overweight or BMI or body mass or body fat or quetelet index) adj3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)).tw,kf.
53	exp exercise/
54	recreation/
55	exp sport/
56	(exercis* or sport* or fitness or physical* activ*).tw,kf.
57	(recreation* adj2 (activ* or physical*)).tw,kf.
58	exp "tobacco use"/
59	exp smoking device/
60	nicotine/
61	health behavior/ or drinking behavior/ or smoking cessation/ or smoking reduction/
62	((health* or drink*) adj2 behavio*).tw,kf.
63	(smok* or tobacco* or nicotine* or e-cig* or ecig* or electronic cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or "water pipe*" or waterpipe*).tw,kf.
64	(alcohol* or wine or beer or spirits or liquor or intoxicant*).tw,kf.
65	exp pollution/
66	exp pollutant/

#	Searches
67	hazard/ or dangerous goods/ or exp hazardous waste/ or exp health hazard/ or exp occupational exposure/ or occupational hazard/ or radiation hazard/
68	exp "environmental, industrial and domestic chemicals"/
69	((pollut* or hazard* or contaminat* or chemical*) adj4 (environment* or air* or water* or occupation* or expos*)).tw,kf.
70	(toxin* or toxic*).tw,kf.
71	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*).tw,kf.
72	endocrine disruptor/
73	(endocrine adj2 disrupt*).tw,kf.
74	ejaculation/
75	(ejaculat* adj2 (serial or frequen*)).tw,kf.
76	exp varicocele/
77	(Varicocele? or Varicocoele?).tw,kf.
78	((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf.
79	((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf.
80	or/76-79
81	interventional radiology/
82	radiolog*.tw,kf.
83	artificial embolization/ or balloon embolization/ or coil embolization/
84	(embol* or coil* or balloon* or plug*).tw,kf.
85	exp sclerotherapy/ or exp sclerosing agent/
86	(sclero* or anti-varicos* or antivari*).tw,kf.
87	male genital system surgery/
88	microsurgery/ or robot assisted microsurgery/
89	minimally invasive surgery/ or minimally invasive procedure/
90	(surg* or microsurg* or microscop* or magnif*).tw,kf.
91	ligation/ or vein ligation/
92	(ligat* or constrict*).tw,kf.
93	exp laparoscopy/
94	(laparoscop* or laparoendoscop*).tw,kf.
95	or/81-94
96	80 and 95
97	exp varicocelectomy/
98	exp varicocele/su, th
99	(varicocelectom* or varicocoelectom*).tw,kf.
100	((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf.
101	exp sperm retrieval/
102	graft harvesting/
103	((sperm* or testi* or testes* or needle* or epididym*) adj3 (retriev* or aspirat* or extract* or procur* or harvest*)).tw.
104	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA).tw.
105	intracytoplasmic sperm injection/
106	(((intra-cytoplasmic or intracytoplasmic) adj2 sperm*) or ICSI or PICSI).tw,kf.
107	or/20-75,96-106
108	19 and 107
109	letter.pt. or letter/
110	note.pt.
111	editorial.pt.
112	case report/ or case study/
113	(letter or comment*).ti.
114	or/109-113
115	randomized controlled trial/ or random*.ti,ab.

#	Searches
116	114 not 115
117	animal/ not human/
118	nonhuman/
119	exp Animal Experiment/
120	exp Experimental Animal/
121	animal model/
122	exp Rodent/
123	(rat or rats or rodent* or mouse or mice).ti.
124	or/116-123
125	108 not 124
126	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
127	125 not 126
128	limit 127 to English language
129	random*.ti,ab.
130	factorial*.ti,ab.
131	(crossover* or cross over*).ti,ab.
132	((doubl* or singl*) adj blind*).ti,ab.
133	(assign* or allocat* or volunteer* or placebo*).ti,ab.
134	crossover procedure/
135	single blind procedure/
136	randomized controlled trial/
137	double blind procedure/
138	or/129-137
139	systematic review/
140	meta-analysis/
141	(meta analy* or metanaly* or metaanaly*).ti,ab.
142	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
143	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
144	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
145	(search* adj4 literature).ab.
146	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
147	((pool* or combined) adj2 (data or trials or studies or results)).ab.
148	cochrane.jw.
149	or/139-148
150	128 and (138 or 149)

Database: Cochrane Database of Systematic Reviews Issue 6 of 12, June 2024

Date of last search: 10/06/2024

#	Searches
#1	MeSH descriptor: [Infertility] this term only
#2	MeSH descriptor: [Infertility, Male] explode all trees
#3	MeSH descriptor: [Fertility] this term only
#4	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*):ti,ab,kw
#5	{OR #1-#4}
#6	MeSH descriptor: [Spermatozoa] explode all trees
#7	MeSH descriptor: [Semen] this term only
#8	MeSH descriptor: [Semen Analysis] explode all trees
#9	{OR #6-#8}
#10	MeSH descriptor: [DNA Damage] this term only
#11	MeSH descriptor: [DNA Fragmentation] this term only
#12	MeSH descriptor: [Oxidative Stress] this term only

#	Searches
#13	{OR #10-#12}
#14	#9 AND #13
#15	((sperm* or semen* or seminal NEXT plasma*) and ((deoxyribonucleic NEXT acid* or dna or oxidative) NEAR/3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))):ti,ab,kw
#16	#14 OR #15
#17	#5 AND #16
#18	sdf:ti,ab,kw
#19	#17 OR #18
#20	MeSH descriptor: [Antioxidants] explode all trees
#21	(antioxid* or anti NEXT oxid*):ti,ab,kw
#22	MeSH descriptor: [Vitamins] explode all trees
#23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* NEXT micronutrient*):ti,ab,kw
#24	MeSH descriptor: [Dietary Supplements] this term only
#25	MeSH descriptor: [Probiotics] this term only
#26	((diet* or nutrition*) NEAR/2 supplement*):ti,ab,kw
#27	(probiotic* or lactobacill* or bifidobacteri*):ti,ab,kw
#28	((good or benefi*) NEAR/2 (bacteria* or yeast* or microorganism* or micro organism*)):ti,ab,kw
#29	(ascorb* or dehydroascorbic NEXT acid*):ti,ab,kw
#30	(abortosan* or antioxidans NEXT e NEXT hevert* or "aquasol e" or "austrovit e" or "auxina e" or "bio e" or "biopto e" or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate" or "dagravit e" or dalfatol* or "dal e" or davitamon* or dermorelle* or detulin* or "dumovit e" or e NEXT mulsin* or e NEXT vicotrat* or e NEXT ferol* or ecoro* or elex NEXT verla* or embial* or e NEXT perle* or e NEXT perte* or e NEXT recordati* or e NEXT toplex* or e NEXT vicotrat* or e NEXT vimin* or e NEXT vita* or e NEXT viterbin* or ecoferol* or efer* or eferol* or enoulan NEXT forte* or ephynal* or eplonat* or eprolin* or "epsilan m" or "epsylan m" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e" or eusovit* or "godabion e" or gonavit* or "hanobakor hydrovit e" or "ido e" or juvela or juvele or lasar* or livingpherol* or "malton e" or "micorvit e" or "mulsal e" or natopherol* or "optovit e" or phytoferol* or pletocol* or "puncto e" or "richtavit e" or "sanavitan s" or socopherol* or spondyvit* or "toco 500" or tocoferol* or tocoferolo NEXT bioglan* or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e" or uno NEXT vit* or vedrop* or vibolex* or "vi dom e" or vi NEXT e NEXT caps* or vi NEXT ea* or vi NEXT etal* or "vidom e" or viea* or vietal* or viprimol* or viteolin or viteoline or "wandervit e" or "vita e" or "vita plus e" or vitazell* or tocotrienol* or alpha* NEXT e or e NEXT tabs* or e NEXT caps* or "nutra e" or "liqua e"):ti,ab,kw
#31	MeSH descriptor: [Carnitine] this term only
#32	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnitin or carnitene or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or gamma NEXT butyro NEXT beta NEXT hydroxybetaine* or l NEXT cartin* or l NEXT carn* or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*):ti,ab,kw
#33	MeSH descriptor: [Ubiquinone] this term only
#34	("coenzyme Q" or "coenzyme Q10" or "coenzyme CoQ" or CoQ10* or CoQ* or "Q 10" or ubiquinone*):ti,ab,kw
#35	MeSH descriptor: [Zinc] this term only
#36	zinc*:ti,ab,kw
#37	MeSH descriptor: [Folic Acid] this term only
#38	(folic NEXT acid* or folate* or folacin* or pteroylglutamic NEXT acid* or folvite*):ti,ab,kw
#39	MeSH descriptor: [Acetylcysteine] this term only
#40	(acetylcystein or acetylcysteine or "acetyl cystein" or "acetyl cysteine" or "acetyl l cysteine" or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or dampo NEXT mucopect* or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or mercapturic NEXT acid* or muciteran* or muco NEXT sanigen* or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or optipect NEXT hustengetrank* or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A NEXT CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*):ti,ab,kw
#41	MeSH descriptor: [Selenium] this term only
#42	(selenium or selenoPrecise* or 200 NEXT SEL* or abselen* or selenase* or radioselenium* or selenicum*):ti,ab,kw
#43	MeSH descriptor: [Life Style] explode all trees
#44	(life NEXT style* or lifestyle*):ti,ab,kw
#45	MeSH descriptor: [Diet, Food, and Nutrition] this term only
#46	MeSH descriptor: [Food] explode all trees
#47	MeSH descriptor: [Diet] explode all trees

#	Searches
#48	MeSH descriptor: [Eating] this term only
#49	MeSH descriptor: [Feeding Behavior] this term only
#50	MeSH descriptor: [Food Preferences] this term only
#51	MeSH descriptor: [Nutritional Status] this term only
#52	((food* or feed* or diet* or eat*) NEAR/3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)):ti,ab,kw
#53	nutriti*:ti,ab,kw
#54	MeSH descriptor: [Weight Loss] this term only
#55	MeSH descriptor: [Overweight] this term only
#56	MeSH descriptor: [Obesity] this term only
#57	MeSH descriptor: [Obesity, Morbid] this term only
#58	MeSH descriptor: [Body Mass Index] this term only
#59	((weight* or obes* or overweight or BMI or "body mass" or "body fat" or "quetelet index") NEAR/3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)):ti,ab,kw
#60	MeSH descriptor: [Exercise] explode all trees
#61	MeSH descriptor: [Recreation] this term only
#62	MeSH descriptor: [Sports] explode all trees
#63	(exercis* or sport* or fitness or physical* activ*):ti,ab,kw
#64	(recreation* NEAR/2 (activ* or physical*)):ti,ab,kw
#65	MeSH descriptor: [Smoking] explode all trees
#66	MeSH descriptor: [Tobacco Use] explode all trees
#67	MeSH descriptor: [Smoking Devices] explode all trees
#68	MeSH descriptor: [Nicotine] this term only
#69	MeSH descriptor: [Health Behavior] this term only
#70	MeSH descriptor: [Smoking Cessation] this term only
#71	MeSH descriptor: [Tobacco Use Cessation] this term only
#72	((health* or drink*) NEAR/2 behavio*):ti,ab,kw
#73	(smok* or tobacco* or nicotine* or e NEXT cig* or ecig* or electronic NEXT cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or water NEXT pipe* or waterpipe*):ti,ab,kw
#74	MeSH descriptor: [Drinking Behavior] this term only
#75	MeSH descriptor: [Alcohol Drinking] this term only
#76	(alcohol* or wine or beer or spirits or liquor or intoxicant*):ti,ab,kw
#77	MeSH descriptor: [Environmental Pollution] explode all trees
#78	MeSH descriptor: [Environmental Pollutants] explode all trees
#79	MeSH descriptor: [Hazardous Substances] explode all trees
#80	MeSH descriptor: [Pesticides] explode all trees
#81	((pollut* or hazard* or contaminat* or chemical*) NEAR/4 (environment* or air* or water* or occupation* or expos*)):ti,ab,kw
#82	(toxin* or toxic*):ti,ab,kw
#83	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*):ti,ab,kw
#84	MeSH descriptor: [Endocrine Disruptors] this term only
#85	(endocrine NEAR/2 disrupt*):ti,ab,kw
#86	MeSH descriptor: [Ejaculation] this term only
#87	(ejaculat* NEAR/2 (serial or frequen*)):ti,ab,kw
#88	MeSH descriptor: [Varicocele] this term only
#89	(Varicocele or varicoceles or varicocoele or varicocoeles):ti,ab,kw
#90	((varicos* or dilat* or enlarg* or tortuos*) NEAR/4 (pampiniform NEAR/2 plexus)):ti,ab,kw
#91	((varicos* or dilat* or enlarg* or tortuos*) NEAR/4 ((sperm* or scrot* or testic* or testis or testes or gonad*) NEAR/3 (vein* or cord* or vessel* or tract* or duct*))):ti,ab,kw
#92	{OR #88-#91}
#93	MeSH descriptor: [Radiology, Interventional] this term only
#94	radiolog*:ti,ab,kw
#95	MeSH descriptor: [Embolization, Therapeutic] this term only
#96	(embol* or coil* or balloon* or plug*):ti,ab,kw

#	Searches
#97	MeSH descriptor: [Sclerotherapy] this term only
#98	MeSH descriptor: [Sclerosing Solutions] explode all trees
#99	(sclero* or anti NEXT varicos* or antivari*):ti,ab,kw
#100	MeSH descriptor: [Urologic Surgical Procedures, Male] this term only
#101	MeSH descriptor: [Microsurgery] this term only
#102	MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only
#103	MeSH descriptor: [Surgery, Computer-Assisted] this term only
#104	MeSH descriptor: [Robotic Surgical Procedures] this term only
#105	(surg* or microsurg* or microscop* or magnif*):ti,ab,kw
#106	MeSH descriptor: [Ligation] this term only
#107	(ligat* or constrict*):ti,ab,kw
#108	MeSH descriptor: [Laparoscopy] this term only
#109	(laparoscop* or laparoendoscop*):ti,ab,kw
#110	{OR #93-#109}
#111	#92 AND #110
#112	MeSH descriptor: [Varicocele] this term only and with qualifier(s): [surgery - SU, therapy - TH]
#113	(varicocelectom* or varicocoelectom*):ti,ab,kw
#114	((Varicocele or varicoceles or varicocoele or varicocoeles or (pampiniform NEAR/2 plexus) or ((sperm* or scrot* or testic* or testis or testes or gonad*) NEAR/3 (vein* or cord* or vessel* or tract* or duct*))) NEAR/5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)):ti,ab,kw
#115	MeSH descriptor: [Sperm Retrieval] this term only
#116	MeSH descriptor: [Tissue and Organ Harvesting] this term only
#117	((sperm* or testi* or testes* or needle* or epididym*) NEAR/3 (retriev* or aspirat* or extract* or procur* or harvest*)):ti,ab,kw
#118	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA):ti,ab,kw
#119	MeSH descriptor: [Sperm Injections, Intracytoplasmic] this term only
#120	(((intra-cytoplasmic or intracytoplasmic) NEAR/2 sperm*) or ICSI or PICSI):ti,ab,kw
#121	{OR #20-#87, #111-#120}
#122	#19 AND #121
#123	conference:pt or (clinicaltrials or trialsearch):so
#124	#122 NOT #123 in Cochrane Reviews

Database: Cochrane Central Register of Controlled Trials Issue 5 of 12, May 2024

Date of last search: 10/06/2024

#	Searches
#1	MeSH descriptor: [Infertility] this term only
#2	MeSH descriptor: [Infertility, Male] explode all trees
#3	MeSH descriptor: [Fertility] this term only
#4	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*):ti,ab,kw
#5	{OR #1-#4}
#6	MeSH descriptor: [Spermatozoa] explode all trees
#7	MeSH descriptor: [Semen] this term only
#8	MeSH descriptor: [Semen Analysis] explode all trees
#9	{OR #6-#8}
#10	MeSH descriptor: [DNA Damage] this term only
#11	MeSH descriptor: [DNA Fragmentation] this term only
#12	MeSH descriptor: [Oxidative Stress] this term only
#13	{OR #10-#12}
#14	#9 AND #13
#15	((sperm* or semen* or seminal NEXT plasma*) and ((deoxyribonucleic NEXT acid* or dna or oxidative) NEAR/3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))):ti,ab,kw
#16	#14 OR #15
#17	#5 AND #16

#	Searches
#18	sdf:ti,ab,kw
#19	#17 OR #18
#20	MeSH descriptor: [Antioxidants] explode all trees
#21	(antioxid* or anti NEXT oxid*):ti,ab,kw
#22	MeSH descriptor: [Vitamins] explode all trees
#23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* NEXT micronutrient*):ti,ab,kw
#24	MeSH descriptor: [Dietary Supplements] this term only
#25	MeSH descriptor: [Probiotics] this term only
#26	((diet* or nutrition*) NEAR/2 supplement*):ti,ab,kw
#27	(probiotic* or lactobacill* or bifidobacteri*):ti,ab,kw
#28	((good or benefi*) NEAR/2 (bacteria* or yeast* or microorganism* or micro organism*)):ti,ab,kw
#29	(ascorb* or dehydroascorbic NEXT acid*):ti,ab,kw
#30	(abortosan* or antioxidans NEXT e NEXT hevert* or "aquasol e" or "austrovit e" or "auxina e" or "bio e" or "biopto e" or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate" or "dagravit e" or dalfatol* or "dal e" or davitamon* or dermorelle* or detulin* or "dumovit e" or e NEXT mulsin* or e NEXT vicotrat* or e NEXT ferol* or ecoro* or elex NEXT verla* or embial* or e NEXT perle* or e NEXT perte* or e NEXT recordati* or e NEXT toplex* or e NEXT vicotrat* or e NEXT vimin* or e NEXT vita* or e NEXT viterbin* or ecoferol* or efer* or eferol* or enoulan NEXT forte* or ephynal* or eplonat* or eprolin* or "epsilan m" or "epsylan m" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e" or eusovit* or "godabion e" or gonavit* or "hanobakor hydrovit e" or "ido e" or juvela or juvele or lasar* or livingpherol* or "malton e" or "micorvit e" or "mulsal e" or natopherol* or "optovit e" or phytoferol* or pletocol* or "puncto e" or "richtavit e" or "sanavitan s" or socopherol* or spondyvit* or "toco 500" or tocoferol* or tocoferolo NEXT bioglan* or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e" or uno NEXT vit* or vedrop* or vibolex* or "vi dom e" or vi NEXT e NEXT caps* or vi NEXT ea* or vi NEXT etal* or "vidom e" or viea* or vietal* or viprimol* or viteolin or viteoline or "wandervit e" or "vita e" or "vita plus e" or vitazell* or tocotrienol* or alpha* NEXT e or e NEXT tabs* or e NEXT caps* or "nutra e" or "liqua e"):ti,ab,kw
#31	MeSH descriptor: [Carnitine] this term only
#32	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnitin or carnitene or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or gamma NEXT butyro NEXT beta NEXT hydroxybetaine* or l NEXT cartin* or l NEXT carn* or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*):ti,ab,kw
#33	MeSH descriptor: [Ubiquinone] this term only
#34	("coenzyme Q" or "coenzyme Q10" or "coenzyme CoQ" or CoQ10* or CoQ* or "Q 10" or ubiquinone*):ti,ab,kw
#35	MeSH descriptor: [Zinc] this term only
#36	zinc*:ti,ab,kw
#37	MeSH descriptor: [Folic Acid] this term only
#38	(folic NEXT acid* or folate* or folacin* or pteroylglutamic NEXT acid* or folvite*):ti,ab,kw
#39	MeSH descriptor: [Acetylcysteine] this term only
#40	(acetylcystein or acetylcysteine or "acetyl cystein" or "acetyl cysteine" or "acetyl l cysteine" or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or dampo NEXT mucopect* or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or mercapturic NEXT acid* or muciteran* or muco NEXT sanigen* or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or optipect NEXT hustengetrank* or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A NEXT CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*):ti,ab,kw
#41	MeSH descriptor: [Selenium] this term only
#42	(selenium or selenoPrecise* or 200 NEXT SEL* or abselen* or selenase* or radioselenium* or selenicum*):ti,ab,kw
#43	MeSH descriptor: [Life Style] explode all trees
#44	(life NEXT style* or lifestyle*):ti,ab,kw
#45	MeSH descriptor: [Diet, Food, and Nutrition] this term only
#46	MeSH descriptor: [Food] explode all trees
#47	MeSH descriptor: [Diet] explode all trees
#48	MeSH descriptor: [Eating] this term only
#49	MeSH descriptor: [Feeding Behavior] this term only
#50	MeSH descriptor: [Food Preferences] this term only
#51	MeSH descriptor: [Nutritional Status] this term only
#52	((food* or feed* or diet* or eat*) NEAR/3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)):ti,ab,kw

#	Searches
#53	nutriti*:ti,ab,kw
#54	MeSH descriptor: [Weight Loss] this term only
#55	MeSH descriptor: [Overweight] this term only
#56	MeSH descriptor: [Obesity] this term only
#57	MeSH descriptor: [Obesity, Morbid] this term only
#58	MeSH descriptor: [Body Mass Index] this term only
#59	((weight* or obes* or overweight or BMI or "body mass" or "body fat" or "quetelet index") NEAR/3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)):ti,ab,kw
#60	MeSH descriptor: [Exercise] explode all trees
#61	MeSH descriptor: [Recreation] this term only
#62	MeSH descriptor: [Sports] explode all trees
#63	(exercis* or sport* or fitness or physical* activ*):ti,ab,kw
#64	(recreation* NEAR/2 (activ* or physical*)):ti,ab,kw
#65	MeSH descriptor: [Smoking] explode all trees
#66	MeSH descriptor: [Tobacco Use] explode all trees
#67	MeSH descriptor: [Smoking Devices] explode all trees
#68	MeSH descriptor: [Nicotine] this term only
#69	MeSH descriptor: [Health Behavior] this term only
#70	MeSH descriptor: [Smoking Cessation] this term only
#71	MeSH descriptor: [Tobacco Use Cessation] this term only
#72	((health* or drink*) NEAR/2 behavio*):ti,ab,kw
#73	(smok* or tobacco* or nicotine* or e NEXT cig* or ecig* or electronic NEXT cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or water NEXT pipe* or waterpipe*):ti,ab,kw
#74	MeSH descriptor: [Drinking Behavior] this term only
#75	MeSH descriptor: [Alcohol Drinking] this term only
#76	(alcohol* or wine or beer or spirits or liquor or intoxicant*):ti,ab,kw
#77	MeSH descriptor: [Environmental Pollution] explode all trees
#78	MeSH descriptor: [Environmental Pollutants] explode all trees
#79	MeSH descriptor: [Hazardous Substances] explode all trees
#80	MeSH descriptor: [Pesticides] explode all trees
#81	((pollut* or hazard* or contaminat* or chemical*) NEAR/4 (environment* or air* or water* or occupation* or expos*)):ti,ab,kw
#82	(toxin* or toxic*):ti,ab,kw
#83	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*):ti,ab,kw
#84	MeSH descriptor: [Endocrine Disruptors] this term only
#85	(endocrine NEAR/2 disrupt*):ti,ab,kw
#86	MeSH descriptor: [Ejaculation] this term only
#87	(ejaculat* NEAR/2 (serial or frequen*)):ti,ab,kw
#88	MeSH descriptor: [Varicocele] this term only
#89	(Varicocele or varicoceles or varicocoele or varicocoeles):ti,ab,kw
#90	((varicos* or dilat* or enlarg* or tortuos*) NEAR/4 (pampiniform NEAR/2 plexus)):ti,ab,kw
#91	((varicos* or dilat* or enlarg* or tortuos*) NEAR/4 ((sperm* or scrot* or testic* or testis or testes or gonad*) NEAR/3 (vein* or cord* or vessel* or tract* or duct*))):ti,ab,kw
#92	{OR #88-#91}
#93	MeSH descriptor: [Radiology, Interventional] this term only
#94	radiolog*:ti,ab,kw
#95	MeSH descriptor: [Embolization, Therapeutic] this term only
#96	(embol* or coil* or balloon* or plug*):ti,ab,kw
#97	MeSH descriptor: [Sclerotherapy] this term only
#98	MeSH descriptor: [Sclerosing Solutions] explode all trees
#99	(sclero* or anti NEXT varicos* or antivari*):ti,ab,kw
#100	MeSH descriptor: [Urologic Surgical Procedures, Male] this term only
#101	MeSH descriptor: [Microsurgery] this term only

#	Searches
#102	MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only
#103	MeSH descriptor: [Surgery, Computer-Assisted] this term only
#104	MeSH descriptor: [Robotic Surgical Procedures] this term only
#105	(surg* or microsurg* or microscop* or magnif*):ti,ab,kw
#106	MeSH descriptor: [Ligation] this term only
#107	(ligat* or constrict*):ti,ab,kw
#108	MeSH descriptor: [Laparoscopy] this term only
#109	(laparoscop* or laparoendoscop*):ti,ab,kw
#110	{OR #93-#109}
#111	#92 AND #110
#112	MeSH descriptor: [Varicocele] this term only and with qualifier(s): [surgery - SU, therapy - TH]
#113	(varicocelectom* or varicocoelectom*):ti,ab,kw
#114	((Varicocele or varicoceles or varicocoele or varicocoeles or (pampiniform NEAR/2 plexus) or ((sperm* or scrot* or testic* or testis or testes or gonad*) NEAR/3 (vein* or cord* or vessel* or tract* or duct*))) NEAR/5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)):ti,ab,kw
#115	MeSH descriptor: [Sperm Retrieval] this term only
#116	MeSH descriptor: [Tissue and Organ Harvesting] this term only
#117	((sperm* or testi* or testes* or needle* or epididym*) NEAR/3 (retriev* or aspirat* or extract* or procur* or harvest*)):ti,ab,kw
#118	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA):ti,ab,kw
#119	MeSH descriptor: [Sperm Injections, Intracytoplasmic] this term only
#120	(((intra-cytoplasmic or intracytoplasmic) NEAR/2 sperm*) or ICSI or PICSI):ti,ab,kw
#121	{OR #20-#87, #111-#120}
#122	#19 AND #121
#123	conference:pt or (clinicaltrials or trialsearch):so
#124	#122 NOT #123 in Trials

Database: Epistemonikos

Date of last search: 10/06/2024

#	Searches
1	(sperm* OR semen* OR seminal plasma*)
2	((deoxyribonucleic acid* OR dna OR oxidative) AND (fragment* OR degrad* OR cleav* OR damag* OR stress* OR injur* OR integrity OR quality))
3	1 and 2 [Filters: protocol=no, classification=systematic-review, cochrane=missing]

Health economic literature searches

Database: Ovid MEDLINE(R) ALL <1946 to June 07, 2024>

Date of last search: 10/06/2024

#	Searches
1	Infertility/ or exp infertility, male/
2	fertility/
3	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*).tw.
4	or/1-3
5	(exp Spermatozoa/ or Semen/ or exp Semen Analysis/) and (dna damage/ or dna fragmentation/ or Oxidative Stress/)
6	((sperm* or semen* or seminal plasma*) and ((deoxyribonucleic acid* or dna or oxidative) adj3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))).tw,kf.
7	or/5-6
8	4 and 7
9	sdf.tw,kf.
10	8 or 9
11	exp Antioxidants/

#	Searches
12	(antioxid* or anti oxid*).tw,kf.
13	exp Vitamins/
14	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).tw,kf.
15	dietary supplements/ or probiotics/
16	((diet* or nutrition*) adj2 supplement*).tw,kf.
17	(probiotic* or lactobacill* or bifidobacteri*).tw,kf.
18	((good or benefi*) adj2 (bacteria* or yeast* or microorganism* or micro organism*)).tw,kf.
19	(ascorb* or dehydroascorbic acid*).tw,kf.
20	(abortosan* or "antioxidans e-hevert*" or "aquasol e*" or "austrovit e*" or "auxina e*" or "bio e*" or biopto-e* or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate*" or "dagravit e*" or dalfatol* or "dal e*" or davitamon* or dermorelle* or detulin* or "dumovit e*" or "e mulsin*" or "e vicotrat*" or "e ferol*" or ecoro* or "elex verla*" or embial* or "e perle*" or "e perte*" or "e recordati*" or "e toplex*" or "e vicotrat*" or "e vimin*" or "e vita*" or "e viterbin*" or ecoferol* or efer* or eferol* or "enoulan forte*" or ephynal* or eplonat* or eprolin* or "eps?lan m*" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e*" or eusovit* or "godabion e*" or gonavit* or "hanobakor hydrovit e*" or "ido e*" or juvel? or lasar* or livingpherol* or "malton e*" or "micorvit e*" or "mulsal e*" or natopherol* or "optovit e*" or phytoferol* or pletocol* or "puncto e*" or "richtavit e*" or "sanavitan s*" or socopherol* or spondyvit* or "toco 500*" or tocoferol* or "tocoferolo bioglan*" or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e*" or uno-vit* or vedrop* or vibolex* or "vi dom e*" or "vi e caps*" or "vi ea*" or "vi etal*" or "vidom e*" or viea* or vietal* or viprimol* or viteolin? or "wandervit e*" or "vita e*" or "vita-plus e*" or vitazell* or tocotrienol* or "alpha* e*" or e-tabs* or e-caps* or nutra-e* or liqua-e*).tw,kf.
21	Carnitine/
22	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnit?n? or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or "gamma butyro beta hydroxybetaine*" or "l cartin*" or "l carn*" or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*).tw,kf.
23	Ubiquinone/
24	("coenzyme Q*" or "coenzyme Q10*" or "coenzyme CoQ*" or CoQ10* or CoQ* or "Q 10*" or ubiquinone*).tw,kf.
25	Zinc/
26	zinc*.tw,kf.
27	Folic Acid/
28	(folic acid* or folate* or folacin* or pteroylglutamic acid* or folvite*).tw,kf.
29	Acetylcysteine/
30	(acetylcystein? or "acetyl cystein?" or (acetyl adj l adj cystein?) or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or (dampo adj mucopect*) or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or (mercapturic adj acid*) or muciteran* or (muco adj sanigen*) or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or (optipect adj hustengetrank*) or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A-CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*).tw,kf.
31	Selenium/
32	(selenium or selenoPrecise* or 200-SEL* or abselen* or selenase* or radioselenium* or selenicum*).tw,kf.
33	exp Life Style/
34	(life style* or lifestyle*).tw,kf.
35	"diet, food, and nutrition"/ or exp food/ or exp diet/ or eating/ or feeding behavior/ or food preferences/
36	Nutritional Status/
37	((food* or feed* or diet* or eat*) adj3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)).tw,kf.
38	nutriti*.tw,kf.
39	Weight Loss/
40	overweight/ or obesity/ or obesity, morbid/
41	body mass index/
42	((weight* or obes* or overweight or BMI or body mass or body fat or quetelet index) adj3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)).tw,kf.
43	exp Exercise/
44	recreation/ or exp sports/
45	(exercis* or sport* or fitness or physical* activ*).tw,kf.
46	(recreation* adj2 (activ* or physical*)).tw,kf.

#	Searches
47	exp Smoking/ or exp "tobacco use"/
48	exp Smoking Devices/
49	Nicotine/
50	health behavior/ or smoking cessation/ or "tobacco use cessation"/
51	((health* or drink*) adj2 behavio*).tw,kf.
52	(smok* or tobacco* or nicotine* or e-cig* or ecig* or electronic cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or "water pipe*" or waterpipe*).tw,kf.
53	drinking behavior/ or alcohol drinking/
54	(alcohol* or wine or beer or spirits or liquor or intoxicant*).tw,kf.
55	exp Environmental Pollution/
56	exp Environmental Pollutants/
57	exp Hazardous Substances/
58	exp Pesticides/
59	((pollut* or hazard* or contaminat* or chemical*) adj4 (environment* or air* or water* or occupation* or expos*)).tw,kf.
60	(toxin* or toxic*).tw,kf.
61	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*).tw,kf.
62	Endocrine Disruptors/
63	(endocrine adj2 disrupt*).tw,kf.
64	Ejaculation/
65	(ejaculat* adj2 (serial or frequen*)).tw,kf.
66	Varicocele/
67	(Varicocele? or Varicocoele?).tw,kf.
68	((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf.
69	((varicos* or dilat* or enlarg* or tortuos*) adj4 ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))).tw,kf.
70	or/66-69
71	Radiology, Interventional/
72	radiolog*.tw,kf.
73	Embolization, Therapeutic/
74	(embol* or coil* or balloon* or plug*).tw,kf.
75	Sclerotherapy/ or exp Sclerosing Solutions/
76	(sclero* or anti-varicos* or antivari*).tw,kf.
77	Urologic Surgical Procedures, Male/
78	microsurgery/ or minimally invasive surgical procedures/ or surgery, computer-assisted/ or robotic surgical procedures/
79	(surg* or microsurg* or microscop* or magnif*).tw,kf.
80	ligation/
81	(ligat* or constrict*).tw,kf.
82	Laparoscopy/
83	(laparoscop* or laparoendoscop*).tw,kf.
84	or/71-83
85	70 and 84
86	Varicocele/su, th
87	(varicocelectom* or varicocoelectom*).tw,kf.
88	((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf.
89	Sperm Retrieval/
90	"Tissue and Organ Harvesting"/
91	((sperm* or testi* or testes* or needle* or epididym*) adj3 (retriev* or aspirat* or extract* or procur* or harvest*)).tw.
92	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA).tw.
93	Sperm Injections, Intracytoplasmic/
94	(((intra-cytoplasmic or intracytoplasmic) adj2 sperm*) or ICSI or PICSI).tw,kf.
95	or/11-65,85-94

#	Searches
96	10 and 95
97	letter/
98	editorial/
99	news/
100	exp historical article/
101	Anecdotes as topic/
102	comment/
103	case reports/
104	(letter or comment*).ti.
105	or/97-104
106	randomized controlled trial/ or random*.ti,ab.
107	105 not 106
108	animals/ not humans/
109	exp Animals, Laboratory/
110	exp Animal Experimentation/
111	exp Models, Animal/
112	exp Rodentia/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/107-113
115	96 not 114
116	limit 115 to English language
117	Economics/
118	Value of life/
119	exp "Costs and Cost Analysis"/
120	exp Economics, Hospital/
121	exp Economics, Medical/
122	exp Resource Allocation/
123	Economics, Nursing/
124	Economics, Pharmaceutical/
125	exp "Fees and Charges"/
126	exp Budgets/
127	budget*.ti,ab.
128	cost*.ti,ab.
129	(economic* or pharmaco?economic*).ti,ab.
130	(price* or pricing*).ti,ab.
131	(financ* or fee or fees or expenditure* or saving*).ti,ab.
132	(value adj2 (money or monetary)).ti,ab.
133	resourc* allocat*.ti,ab.
134	(fund or funds or funding* or funded).ti,ab.
135	(ration or rations or rationing* or rationed).ti,ab.
136	ec.fs.
137	or/117-136
138	quality-adjusted life years/
139	sickness impact profile/
140	(quality adj2 (wellbeing or well being)).ti,ab.
141	sickness impact profile.ti,ab.
142	disability adjusted life.ti,ab.
143	(qal* or qtime* or qwb* or daly*).ti,ab.
144	(euroqol* or eq5d* or eq 5*).ti,ab.
145	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
146	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
147	(hui or hui1 or hui2 or hui3).ti,ab.

#	Searches
148	(health* year* equivalent* or hye or hyes).ti,ab.
149	discrete choice*.ti,ab.
150	rosser.ti,ab.
151	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
152	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
153	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
154	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
155	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
156	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
157	or/138-156
158	116 and (137 or 157)

Database: Embase <1974 to 2024 June 07>

Date of last search: 10/06/2024

#	Searches
1	exp male infertility/ or semen abnormality/
2	infertility/ or subfertility/
3	fertility/
4	(infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*).tw.
5	or/1-4
6	exp sperm/
7	spermatogonium/
8	semen analysis/
9	exp semen parameters/
10	or/6-9
11	dna damage/ or dna fragmentation/
12	oxidative stress/
13	11 or 12
14	10 and 13
15	((sperm* or semen* or seminal plasma*) and ((deoxyribonucleic acid* or dna or oxidative) adj3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality))).tw,kf.
16	14 or 15
17	5 and 16
18	sdf.tw,kf.
19	or/17-18
20	exp antioxidant/
21	(antioxid* or anti oxid*).tw,kf.
22	exp vitamin/
23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).tw,kf.
24	dietary supplement/
25	exp probiotic agent/
26	((diet* or nutrition*) adj2 supplement*).tw,kf.
27	(probiotic* or lactobacill* or bifidobacteri*).tw,kf.
28	((good or benefi*) adj2 (bacteria* or yeast* or microorganism* or micro organism*)).tw,kf.
29	(ascorb* or dehydroascorbic acid*).tw,kf.
30	(abortosan* or "antioxidans e-hevert*" or "aquasol e*" or "austrovit e*" or "auxina e*" or "bio e*" or biopto-e* or biosan* or bioweyxin* or covitol* or "d alphatocopherylacetate*" or "dagravit e*" or dalfatol* or "dal e*" or davitamon* or dermorelle* or detulin* or "dumovit e*" or "e mulsin*" or "e vicotrat*" or "e ferol*" or ecoro* or "elex verla*" or embial* or "e perle*" or "e perte*" or "e recordati*" or "e toplex*" or "e vicotrat*" or "e vimin*" or "e vita*" or "e viterbin*" or ecoferol* or efer* or eferol* or "enoulan forte*" or ephynal* or eplonat* or eprolin* or "eps?lan m*" or erevit* or esol* or esorb* or eterapion* or eviabit* or evigen* or eviol* or evion* or evit* or "equivit e*" or eusovit* or "godabion e*" or gonavit* or "hanobakor hydrovit e*" or "ido e*" or juvel? or lasar* or livingpherol* or "malton e*" or "micorvit e*" or "mulsal e*" or natopherol* or "optovit e*" or phytoferol* or pletocol* or "puncto e*" or "richtavit e*" or

#	Searches
	"sanavitan s*" or socopherol* or spondyvit* or "toco 500*" or tocoferol* or "tocoferolo bioglan*" or tocolion* or tocopa* or tocomine* or tocopherex* or tocopharm* or tocophrine* or tocovigor* or tocovital* or toferol* or tocopherol* or "unique e*" or uno-vit* or vedrop* or vibolex* or "vi dom e*" or "vi e caps*" or "vi ea*" or "vi etal*" or "vidom e*" or viea* or vietal* or viprimol* or viteolin? or "wandervit e*" or "vita e*" or "vita-plus e*" or vitazell* or tocotrienol* or "alpha* e*" or e-tabs* or e-caps* or nutra-e* or liqua-e*).tw,kf.
31	carnitine/
32	(abedine* or biocarn* or biomux* or cardiogen* or carnicor* or carnil* or carnit?n? or carnitor* or carnovis* or cartin* or bicarnesine* or entomin* or "gamma butyro beta hydroxybetaine*" or "l cartin*" or "l carn*" or lefcar* or levocarnitine* or monocamin* or nefrocarnit* or novain* or vitacarn*).tw,kf.
33	ubiquinone/
34	("coenzyme Q*" or "coenzyme Q10*" or "coenzyme CoQ*" or CoQ10* or CoQ* or "Q 10*" or ubiquinone*).tw,kf.
35	zinc/
36	zinc*.tw,kf.
37	folic acid/
38	(folic acid* or folate* or folacin* or pteroylglutamic acid* or folvite*).tw,kf.
39	acetylcysteine/
40	(acetylcystein? or "acetyl cystein?" or (acetyl adj l adj cystein?) or NAC or acemuc* or acetabs* or acetylin* or acetyst* or airbron* or alveolex* or azubronchin* or bromuc* or broncho-fips* or broncholysin* or broncoclar* or brunac* or codotussyl* or cystamucil* or (dampo adj mucopect*) or eurespiran* or exomuc* or fabrol* or fluimucil* or fluprowit* or frekatuss* or genac* or hoestil* or ilube* or jenacystein* or jenapharm* or lappe* or lantamed* or lindocetyl* or m-Pectil* or (mercapturic adj acid*) or muciteran* or (muco adj sanigen*) or mucomyst* or mucopect* or mucosil* or mucosol* or mucosolvin* or (optipect adj hustengetrank*) or respaire* or siccoral* or siran* or solmucol* or acebraus* or durabronchal* or A-CYS* or aceCil* or acepiro* or aceteff* or NACSYS* or acetadote* or parvolex*).tw,kf.
41	selenium/
42	(selenium or selenoPrecise* or 200-SEL* or abselen* or selenase* or radioselenium* or selenicum*).tw,kf.
43	exp lifestyle/
44	(life style* or lifestyle*).tw,kf.
45	nutrition/ or exp diet/ or exp dietary intake/ or dietary pattern/ or feeding behavior/ or food preference/ or eating habit/ or exp food/ or eating/
46	nutritional status/
47	((food* or feed* or diet* or eat*) adj3 (health* or balance* or pattern* or behavio* or habit* or practi* or prefer* or intake)).tw,kf.
48	nutriti*.tw,kf.
49	body weight loss/
50	obesity/ or morbid obesity/
51	body mass/
52	((weight* or obes* or overweight or BMI or body mass or body fat or quetelet index) adj3 (loss or lost or lose or losing or reduc* or health* or ideal* or optimal*)).tw,kf.
53	exp exercise/
54	recreation/
55	exp sport/
56	(exercis* or sport* or fitness or physical* activ*).tw,kf.
57	(recreation* adj2 (activ* or physical*)).tw,kf.
58	exp "tobacco use"/
59	exp smoking device/
60	nicotine/
61	health behavior/ or drinking behavior/ or smoking cessation/ or smoking reduction/
62	((health* or drink*) adj2 behavio*).tw,kf.
63	(smok* or tobacco* or nicotine* or e-cig* or ecig* or electronic cigarette* or vape or vaping or cigar* or polytobacco* or multitobacco* or "water pipe*" or waterpipe*).tw,kf.
64	(alcohol* or wine or beer or spirits or liquor or intoxicant*).tw,kf.
65	exp pollution/
66	exp pollutant/
67	hazard/ or dangerous goods/ or exp hazardous waste/ or exp health hazard/ or exp occupational exposure/ or occupational hazard/ or radiation hazard/
68	exp "environmental, industrial and domestic chemicals"/
69	((pollut* or hazard* or contaminat* or chemical*) adj4 (environment* or air* or water* or occupation* or expos*)).tw,kf.

#	Searches
70	(toxin* or toxic*).tw,kf.
71	(acaricid* or pesticid* or insecticid* or herbicid* or fungicid* or rodenticid* or chemosterilant*).tw,kf.
72	endocrine disruptor/
73	(endocrine adj2 disrupt*).tw,kf.
74	ejaculation/
75	(ejaculat* adj2 (serial or frequen*)).tw,kf.
76	exp varicocele/
77	(Varicocele? or Varicocoele?).tw,kf.
78	((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf.
79	((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf.
80	or/76-79
81	interventional radiology/
82	radiolog*.tw,kf.
83	artificial embolization/ or balloon embolization/ or coil embolization/
84	(embol* or coil* or balloon* or plug*).tw,kf.
85	exp sclerotherapy/ or exp sclerosing agent/
86	(sclero* or anti-varicos* or antivari*).tw,kf.
87	male genital system surgery/
88	microsurgery/ or robot assisted microsurgery/
89	minimally invasive surgery/ or minimally invasive procedure/
90	(surg* or microsurg* or microscop* or magnif*).tw,kf.
91	ligation/ or vein ligation/
92	(ligat* or constrict*).tw,kf.
93	exp laparoscopy/
94	(laparoscop* or laparoendoscop*).tw,kf.
95	or/81-94
96	80 and 95
97	exp varicocelectomy/
98	exp varicocele/su, th
99	(varicocelectom* or varicocoelectom*).tw,kf.
100	((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf.
101	exp sperm retrieval/
102	graft harvesting/
103	((sperm* or testi* or testes* or needle* or epididym*) adj3 (retriev* or aspirat* or extract* or procur* or harvest*)).tw.
104	(PESA or MESA or TESA or TESE or MicroTESE or mTESE or TEFNA or FNA or FNAC or SSR or OESA).tw.
105	intracytoplasmic sperm injection/
106	(((intra-cytoplasmic or intracytoplasmic) adj2 sperm*) or ICSI or PICSI).tw,kf.
107	or/20-75,96-106
108	19 and 107
109	letter.pt. or letter/
110	note.pt.
111	editorial.pt.
112	case report/ or case study/
113	(letter or comment*).ti.
114	or/109-113
115	randomized controlled trial/ or random*.ti,ab.
116	114 not 115
117	animal/ not human/
118	nonhuman/
119	exp Animal Experiment/

#	Searches
120	exp Experimental Animal/
121	animal model/
122	exp Rodent/
123	(rat or rats or rodent* or mouse or mice).ti.
124	or/116-123
125	108 not 124
126	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
127	125 not 126
128	limit 127 to English language
129	health economics/
130	exp economic evaluation/
131	exp health care cost/
132	exp fee/
133	budget/
134	funding/
135	resource allocation/
136	budget*.ti,ab.
137	cost*.ti,ab.
138	(economic* or pharmaco?economic*).ti,ab.
139	(price* or pricing*).ti,ab.
140	(financ* or fee or fees or expenditure* or saving*).ti,ab.
141	(value adj2 (money or monetary)).ti,ab.
142	resourc* allocat*.ti,ab.
143	(fund or funds or funding* or funded).ti,ab.
144	(ration or rations or rationing* or rationed).ti,ab.
145	or/129-144
146	quality adjusted life year/
147	"quality of life index"/
148	short form 12/ or short form 20/ or short form 36/ or short form 8/
149	sickness impact profile/
150	(quality adj2 (wellbeing or well being)).ti,ab.
151	sickness impact profile.ti,ab.
152	disability adjusted life.ti,ab.
153	(qal* or qtime* or qwb* or daly*).ti,ab.
154	(euroqol* or eq5d* or eq 5*).ti,ab.
155	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
156	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
157	(hui or hui1 or hui2 or hui3).ti,ab.
158	(health* year* equivalent* or hye or hyes).ti,ab.
159	discrete choice*.ti,ab.
160	rosser.ti,ab.
161	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
162	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
163	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
164	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
165	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
166	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
167	or/146-166
168	128 and (145 or 167)

Database: INAHTA

Date of last search: 10/06/2024

#	Searches
1	"Infertility"[mh]
2	"Infertility, Male"[mhe]
3	"Fertility"[mh]
4	((infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))[Title] OR ((infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))[abs]
5	#4 OR #3 OR #2 OR #1
6	"Spermatozoa"[mhe]
7	"Semen"[mh]
8	"Semen Analysis"[mhe]
9	#8 OR #7 OR #6
10	"DNA Damage"[mh]
11	"DNA Fragmentation"[mh]
12	"Occupational Stress"[mh]
13	#12 OR #11 OR #10
14	#13 AND #9
15	((sperm* or semen* or seminal plasma*))[Title] OR ((sperm* or semen* or seminal plasma*))[abs]
16	(((deoxyribonucleic acid* or dna or oxidative) AND (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality)))[Title] OR (((deoxyribonucleic acid* or dna or oxidative) AND (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality)))[abs]
17	#16 AND #15
18	#17 OR #14
19	#18 AND #5
20	(sdf)[Title] OR (sdf)[abs]
21	#20 OR #19

Database: HTA via CRD

Date of last search: 10/06/2024

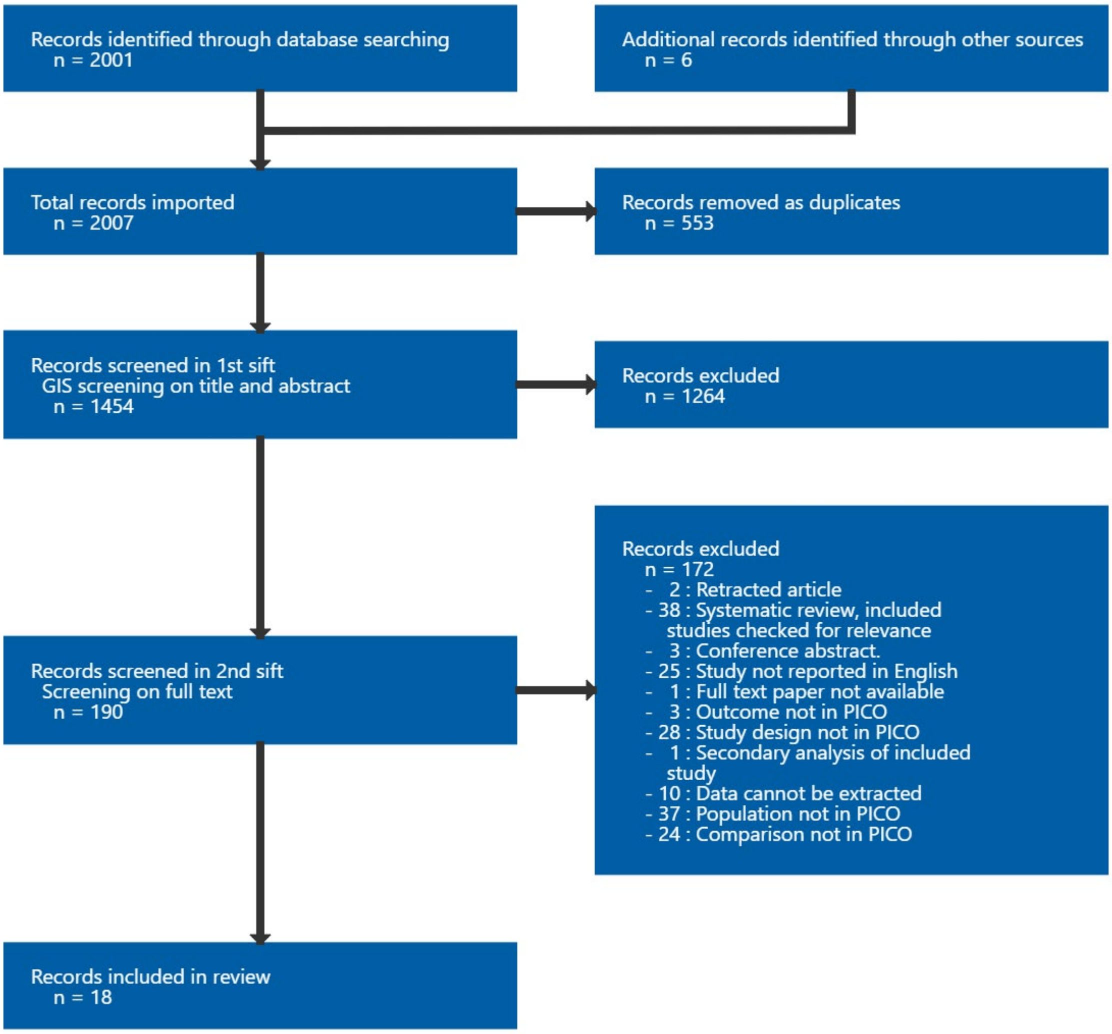
#	Searches
1	MeSH DESCRIPTOR infertility
2	MeSH DESCRIPTOR infertility, male EXPLODE ALL TREES
3	MeSH DESCRIPTOR fertility
4	((infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*))
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Spermatozoa EXPLODE ALL TREES
7	MeSH DESCRIPTOR semen
8	MeSH DESCRIPTOR semen analysis EXPLODE ALL TREES
9	#6 OR #7 OR #8
10	MeSH DESCRIPTOR dna damage
11	MeSH DESCRIPTOR dna fragmentation
12	MeSH DESCRIPTOR oxidative stress
13	#10 OR #11 OR #12
14	#9 AND #13
15	((sperm* or semen* or seminal plasma*))
16	(((deoxyribonucleic acid* or dna or oxidative) adj3 (fragment* or degrad* or cleav* or damag* or stress* or injur* or integrity or quality)))
17	#15 AND #16
18	#14 OR #17
19	#5 AND #18
20	((19):XFU) and (Project record:ZDT OR Full publication record:ZDT) IN HTA

Appendix C Effectiveness evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Clinical search

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Table 5: Evidence tables

Abbasi, 2021

Bibliographic Reference	Abbasi, Behzad; Abbasi, Homayoun; Niroumand, Hassan; Synbiotic (FamiLact) administration in idiopathic male infertility enhances sperm quality, DNA integrity, and chromatin status: A triple-blinded randomized clinical trial.; International journal of reproductive biomedicine; 2021; vol. 19 (no. 3); 235-244

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	November 2019 - May 2020
Inclusion criteria	Men with male factor infertility (failure to establish a pregnancy following 12 months of regular unprotected sex), oligozoospermia, teratozoospermia, and asthenozoospermia
Exclusion criteria	Men with varicocele, cryptorchidism, chromosome abnormalities, epididymal-orchitis, leukocytospermia, prostatitis, genitourinary injury, testicular torsion, history of hormone therapy, history of inguinal/genital surgery, history or ongoing use of immunosuppressants, cytotoxic drugs, anticonvulsants, and androgens, endocrinopathies, and recent sexual transmitted infections
Patient characteristics	Male age in years, mean (SD): Probiotic and prebiotic: 34.5 (NR) Placebo: 33.8 (NR) Female age in years: NR BMI in kg/m^2: NR

	Duration of infertility: at least 1 year Percentage of sperm DNA fragmentation at baseline; mean (SD): Probiotic and prebiotic: 28.81 (13.27) Placebo: 26.75 (10.54) Male factor infertility, N (%): 56 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Probiotic and prebiotic: probiotic and prebiotic 500 mg once daily for 80 days Placebo: identical placebo once daily for 80 days
Duration of follow-up	Semen samples were assessed before and 80 days after the onset of treatments
Sources of funding	Part industry funded - The study was supported by the AJA University of Medical Sciences and the Isfahan Fertility and Infertility Centre
Sample size	N=56 N randomised: Probiotic and prebiotic: 28 Placebo: 28 N included in final analysis: Probiotic and prebiotic: 22 (as n=2 lost contact, n=1 declined consent, n=1 had pregnancy, and n=2 discontinued for unknown reason) Placebo: 25 (as n=3 lost contact)
Other information	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation

Outcomes

Probiotic and prebiotic versus Placebo

Outcome	Probiotic and prebiotic, N = 28	Placebo, N = 28
Percentage of DNA fragmentation in sperm samples (SCSA, at 80 days of treatment) Mean (SD)	25.19 (7.22)	25.32 (6.66)

SCSA: sperm chromatin structure assay; SD: standard deviation

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information of allocation sequence concealment, but no baseline differences between intervention groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and study personnel were not aware of interventions, but per-protocol analysis excluding participants who discontinued interventions was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data were available for only 84% of participants and missing data was greater in intervention group (6/28 in Prebiotic and probiotic vs. 3/28 in Placebo))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported result for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Abbasi, 2020

Bibliographic Reference	Abbasi, Behzad; Molavi, Newsha; Tavalaee, Marziyeh; Abbasi, Homayoun; Nasr-Esfahani, Mohammad H; Alpha-lipoic acid improves sperm motility in infertile men after varicocelectomy: a triple-blind randomized controlled trial.; Reproductive biomedicine online; 2020; vol. 41 (no. 6); 1084-1091

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	2018 - 2019
Inclusion criteria	Men aged 19-45 years who had microsurgical repair of unilateral or bilateral varicocele (grade II and grade III)

Exclusion criteria	Men with azoospermia, a history of mumps, solitary testis, cryptorchidism, endocrinopathies, infections or malignancies, occupational exposure to heat, pesticides, and radiation, Sertoli cell-only syndrome, scrotal trauma, leukocytospermia, high temperature prior to sampling, severe alcoholism, recurrent varicocele, and heavy smoking
Patient characteristics	Male age in years, mean (SD): Post-varicocelectomy alpha-lipoic acid: 31.14 (5.54) Post-varicocelectomy placebo: 31.89 (5.06) Female age in years: NR BMI in kg/m^2, mean (95% CI): Post-varicocelectomy alpha-lipoic acid: 25.39 (23.11-27.67) Post-varicocelectomy placebo: 24.02 (23.08-24.96) Duration of infertility in months: NR Percentage of sperm DNA fragmentation assessed with TUNEL at baseline; mean (SE): Post-varicocelectomy alpha-lipoic acid: 11.25 (0.62) Post-varicocelectomy placebo: 13.65 (2.44) Percentage of sperm DNA fragmentation assessed with SCSA at baseline; mean (SE): Post-varicocelectomy alpha-lipoic acid: 23.22 (1.56) Post-varicocelectomy placebo: 20.47 (2.31) Male factor infertility, N (%): 60 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Post-varicocelectomy alpha-lipoic acid: alpha-lipoic acid 600 mg for 80 days, immediately after varicocelectomy Post-varicocelectomy placebo: identical placebo for 80 days, immediately after varicocelectomy
Duration of follow-up	Semen samples were assessed at baseline and 80 days of treatment

Sources of funding	Part industry funded - The study was supported by Raha company (Iran, Isfahan), Royan Institute, and Isfahan Fertility and Infertility Centre
Sample size	N=60 N randomised: Post-varicocelectomy alpha-lipoic acid: 30 Post-varicocelectomy placebo: 30 N included in final analysis: Post-varicocelectomy alpha-lipoic acid: 19 (as n=11 did not attend final visit) Post-varicocelectomy placebo: 22 (as n=8 did not attend final visit)
Other information	Sperm DNA fragmentation tests: TUNEL and SCSA Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; CI: confidence interval; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Post-varicocelectomy alpha-lipoic acid versus Post-varicocelectomy placebo

Outcome	Post-varicocelectomy alpha-lipoic acid, N = 30	Post-varicocelectomy placebo, N = 30
Percentage of DNA fragmentation in sperm samples (TUNEL, at 80 days of treatment) Mean (SE)	12.26 (1.06)	10.38 (0.99)
Percentage of DNA fragmentation in sperm samples (SCSA, at 80 days of treatment) Mean (SE)	18.37 (1.41)	16.45 (1.28)

DNA: deoxyribonucleic acid; SCSA: sperm chromatin structure assay; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Block randomisation method used, and the allocation sequence was revealed only after the final analysis of the data)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and study personnel were not aware of interventions, but per-protocol analysis excluding participants who discontinued interventions was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data were available for only 68% of participants and missing data was greater in intervention group (11/30 in Alpha-lipoic acid vs. 8/30 in Placebo))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported result for the outcome correspond to intended outcome measurement and analyses)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Barekat, 2016

Bibliographic Reference	Barekat, Foroogh; Tavalaee, Marziyeh; Deemeh, Mohammad Reza; Bahreinian, Mahsa; Azadi, Leila; Abbasi, Homayoun; Rozbahani, Shahla; Nasr-Esfahani, Mohammad Hossein; A Preliminary Study: N-acetyl-L-cysteine Improves Semen Quality following Varicocelectomy.; International journal of fertility & sterility; 2016; vol. 10 (no. 1); 120-6

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	2011 - 2013
Inclusion criteria	Male aged <45 years with primary infertility, and left-sided varicocele grade II and III
Exclusion criteria	Grade I varicocele, recurrent varicocele, azoospermia, leukocytospermia, testicular size discrepancy, urogenital infections, anatomical disorders, abnormal hormonal profile, cancer, fever in previous 90 days, Klinefelter's syndrome, seminal sperm antibodies, excessive alcohol and drug abuse, occupational exposure, and previous history of scrotal surgery or trauma

Patient characteristics	Male age in years, mean (SD): Post-varicocelectomy N-acetyl-L-cysteine: 30.73 (1.4) No post-varicocelectomy treatment: 29.64 (0.74) Female age in years, mean (SD): 26.6 (4.9) BMI in kg/m^2: NR Duration of infertility in months; mean (SD): 2.1 (0.2) Percentage of sperm DNA integrity at baseline, mean (SD): Post-varicocelectomy N-acetyl-L-cysteine: 80.6 (1.8) No post-varicocelectomy treatment: 82.2 (1.7) Male factor infertility, N (%): 35 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Post-varicocelectomy N-acetyl-L-cysteine: N-acetyl-L-cysteine 200 mg daily for 3 months No post-varicocelectomy treatment: no drug after varicocelectomy
Duration of follow-up	Sperm DNA integrity was assessed at baseline and at 3 months of treatment
Sources of funding	Part industry funded - The study was supported by Royan Institute and the Isfahan Fertility and Infertility Centre
Sample size	N=40 N randomised: Post-varicocelectomy N-acetyl-L-cysteine: 20 No post-varicocelectomy treatment: 20 N included in final analysis: Post-varicocelectomy N-acetyl-L-cysteine: 15 (as n=5 not compliance with intervention) No post-varicocelectomy treatment: 20

Other information	Sperm DNA integrity tests: TUNEL Threshold for defining sperm DNA fragmentation: NR Method used to confirm clinical pregnancy: NR In this study, mean was reported but it was unclear whether SD or SE was reported, but we assumed that SD was used.

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Post-varicocelectomy N-acetyl-L-cysteine vs. No post-varicocelectomy treatment

Outcome	Post-varicocelectomy N-acetyl-L-cysteine, N = 20	No post-varicocelectomy treatment, N = 20
Clinical pregnancy (undefined, denominator: N randomised) No of events	5/20	2/20
Percentage of DNA integrity in sperm samples (TUNEL; at 3 months of treatment) Mean (SD)	89.8 (1.4)	85.9 (1.7)

DNA: deoxyribonucleic acid; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment, but no baseline differences between interventions groups)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Per-protocol analysis excluding participants who discontinued intervention was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data were available for only 88% of participants, and number of participants who discontinued intervention was greater in Post-varicocelectomy N-acetyl-L-cysteine compared with control group (5/20 vs. 0/20))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate for DNA integrity, but method used to confirm clinical pregnancy was not provided. No difference in measurement of the outcomes between groups.* *Low: sperm DNA integrity* *Some concerns: clinical pregnancy)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported results for the outcomes do not correspond to intended outcome measurements and analyses)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain for all outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	None

DNA: deoxyribonucleic acid; RoB: risk of bias

Dadgar, 2023

Bibliographic Reference	Dadgar, Zeynab; Shariatzadeh, Seyed Mohammad Ali; Mehranjani, Malek Soleimani; Kheirolahi, Abdolreza; The therapeutic effect of co-administration of pentoxifylline and zinc in men with idiopathic infertility.; Irish journal of medical science; 2023; vol. 192 (no. 1); 431-439

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	NR
Inclusion criteria	Men aged 25-43 years with idiopathic infertility for at least 1 year, no use of contraception, normal reproductive hormones levels and total testicular volume C12 ml
Exclusion criteria	History of diseases, including testicular torsion, orchitis, varicocele, cryptorchidism, sexually transmitted disease, genitourinary infection, hyper-prolactinaemia, and alcohol or substance abuse; history of androgens, chemotherapy, anti-androgens, and tobacco use, and history of renal insufficiency, karyotypic abnormalities, presence of anti-sperm antibodies, and leukocytospermia
Patient characteristics	Male age in years (range): 25-43 Female age in years: NR BMI in kg/m^2, mean (SD): 27.3 (NR)

	Duration of infertility: at least 1 year Percentage of sperm DNA fragmentation at baseline; mean (SD): Zinc: 31.0 (1.5) Placebo: 31.8 (1.7) Male factor infertility, N (%): N=70 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Zinc: zinc 15 mg once daily for 3 months Placebo: placebo tablets twice daily for 3 months
Duration of follow-up	Sperm samples were assessed at baseline and 3 months after treatment
Sources of funding	The study was conducted as part of a PhD project, and supported by a public university and the infertility clinic of a private hospital
Sample size	N=70 (N=140)* N randomised: Zinc: 35 Placebo: 35 N included in final analysis: Zinc: 35 Placebo: 22 (as n=13 discontinued intervention for unknown reason) *This study is a four-arm randomised controlled trial comparing Pentoxifylline vs. Zinc vs. Pentoxifylline plus Zinc vs. Placebo and total sample size was 140, but we only extracted data on Zinc and Placebo groups as other interventions are not relevant to our review.
Other information	Sperm DNA fragmentation test: SDFA kit (sperm DNA fragmentation assay kit)

	Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SDFA: sperm DNA fragmentation assay kit

Outcomes

Zinc versus Placebo

Outcome	**Zinc, N = 35**	**Placebo, N = 35**
Percentage of DNA fragmentation in sperm samples (SDFA, at 3 months of treatment) Mean (SD)	25.5 (1.3)	30.3 (2.7)

SD: standard deviation; SDFA: sperm DNA fragmentation assay kit

Critical appraisal – Cochrane RoB2

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on baseline characteristics and allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Unclear whether participants were aware of interventions, and per-protocol analysis excluding participants who discontinued interventions was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(About 37% of participants from placebo group were lost to follow-up)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and*

Section	Question	Answer
		no difference in measurement of the outcome between intervention groups)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Greco, 2005

Bibliographic Reference	Greco, Ermanno; Iacobelli, Marcello; Rienzi, Laura; Ubaldi, Filippo; Ferrero, Susanna; Tesarik, Jan; Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment.; Journal of andrology; 2005; vol. 26 (no. 3); 349-53

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	NR
Inclusion criteria	Men with unexplained infertility and elevated sperm DNA fragmentation (≥15% of ejaculated spermatozoa)

Exclusion criteria	Presence of genitourinary inflammation, infection, or varicocele, and smokers
Patient characteristics	Male age in years: NR Female age in years: NR Mean BMI in kg/m^2: NR Duration of infertility: NR Percentage of sperm DNA fragmentation at baseline; mean (SD): Vitamin C and E: 22.1 (7.7) Placebo: 22.4 (7.8) Male factor infertility, N (%): 64 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Vitamin C and E: vitamin C and E 500 mg twice daily for 2 months Placebo: placebo for 2 months
Duration of follow-up	Semen samples were assessed at baseline and 2 months of treatment
Sources of funding	NR
Sample size	N=64 N randomised: Vitamin C and E: 32 Placebo: 32 N included in final analysis: Vitamin C and E: 32 Placebo: 32

Other information	Sperm DNA fragmentation test: TUNEL Threshold for defining sperm DNA fragmentation: ≥15%

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Vitamin C and E versus Placebo

Outcome	Vitamin C and E, N = 32	Placebo, N = 32
Percentage of DNA fragmentation in sperm samples (TUNEL, at 2 months of treatment) Mean (SD)	9.1 (7.2)	22.9 (7.9)

DNA: deoxyribonucleic acid; NR: not reported; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and personnel were not aware of intervention. It seems that appropriate analysis was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(It seems that the data were available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate,*

Section	Question	Answer
		and no difference in measurement of the outcome between intervention groups)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Habibi, 2022

Bibliographic Reference	Habibi, Masoud; Abbasi, Behzad; Fakhari Zavareh, Zohreh; Esmaeili, Vahid; Shaverdi, Abdolhossein; Sadighi Gilani, Mohammad Ali; Tavalaee, Marziyeh; Nasr Esfahani, Mohammad Hossein; Alpha-Lipoic Acid Ameliorates Sperm DNA Damage and Chromatin Integrity in Men with High DNA Damage: A Triple Blind Randomized Clinical Trial.; Cell journal; 2022; vol. 24 (no. 10); 603-611

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	July 2018 - June 2020

Inclusion criteria	Men with infertility and high sperm DNA fragmentation (>15% for TUNEL method and >30% for SCSA)
Exclusion criteria	participants with current/ongoing history of varicocele, chemoradiation, leukocytospermia, cytotoxic medication, malignancies, and female factor infertility, such as endometriosis, tubal factor infertility, and polycystic ovary syndrome
Patient characteristics	Male age in years: NR Female age in years: NR Mean BMI in kg/m^2: NR Duration of infertility: NR Percentage of sperm DNA fragmentation assessed with SCSA at baseline; mean (SD): Alpha-lipoic acid: 36.98 (15.67) Placebo: 30.08 (14.24) Percentage of sperm DNA fragmentation assessed with TUNEL at baseline; mean (SD): Alpha-lipoic acid: 18.2 (12.64) Placebo: 16.23 (9.2) Male factor infertility, N (%): 70 (100%) Female factor infertility, N (%): 0 (0%) Previous implantation failure: NR
Intervention(s)/control	Alpha-lipoic acid: alpha-lipoic acid 600 mg daily for 80 days Placebo: placebo 600 mg daily for 80 days
Duration of follow-up	6 months after termination of interventions
Sources of funding	Alpha-lipoic acid and placebo tablets were provided by a private company (Raha)
Sample size	N=70 N randomised:

	Alpha-lipoic acid: 35 Placebo: 35 N included in final analysis: Alpha-lipoic acid: 34 (as n=1 lost to follow-up/lost contact) Placebo: 29 (as n=4 lost contact, and n=2 discontinued)
Other information	Sperm DNA fragmentation tests: TUNEL and SCSA Threshold for defining sperm DNA fragmentation assessed with TUNEL: >15% Threshold for defining sperm DNA fragmentation assessed with SCSA: >30 % Method used to confirm clinical pregnancy: ultrasound The study reported abortion rate (Alpha-lipoic acid 70.37% vs. Placebo 97.06%, P=0.004) and recurrent pregnancy loss (Alpha-lipoic acid 85.29% vs. Placebo 55.56%, P=0.01), however, we were unable to extract the data (i.e., n/N) because we do not know how they calculated abortion and pregnancy loss rates (e.g., we do not know whether denominator was number of participants or total pregnancies).

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Alpha-lipoic acid versus Placebo

Outcome	Alpha-lipoic acid, N = 35	Placebo, N = 35
Clinical pregnancy (natural pregnancy confirmed by ultrasound, denominator: N randomised) No of events	8/35	3/35
Percentage of DNA fragmentation in sperm samples (TUNEL, at 80 days of treatment) Mean (SD)	13.7 (8.58)	20.54 (10.44)
Percentage of DNA fragmentation in sperm samples (SCSA, at 80 days of treatment)	25.38 (14.68)	32.41 (14.62)

Outcome	Alpha-lipoic acid, N = 35	Placebo, N = 35
Mean (SD)		

DNA: deoxyribonucleic acid; NR: not reported; SCSA: sperm chromatin structure assay SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was carried out by independent persons using computer-mediated random digits table)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Per-protocol analysis excluding participants who discontinued interventions was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Loss to follow up and discontinued intervention were greater in placebo group compared with Alpha-lipoic acid for all outcomes (17% vs 2.8%))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcomes correspond to all intended outcome measurements and analyses)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Hosseini, 2016

Bibliographic Reference	Hosseini, Jalil; Mardi Mamaghani, Azar; Hosseinifar, Hani; Sadighi Gilani, Mohammad Ali; Dadkhah, Farid; Sepidarkish, Mahdi; The influence of ginger (Zingiber officinale) on human sperm quality and DNA fragmentation: A double-blind randomized clinical trial.; International journal of reproductive biomedicine; 2016; vol. 14 (no. 8); 533-40

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	May 2013 - November 2014
Inclusion criteria	Participants aged >45 years with idiopathic infertility >2 years, sperm DNA fragmentation ≥15%, and without leukocytospermia, drug or alcohol addiction, occupational chemical exposure, systematic diseases, and no history of warfarin or other anticoagulant or ginger or other herbal medicine use
Exclusion criteria	History of epididymal surgery, post pubertal mumps, radiation therapy, chemotherapy, unilateral or bilateral subclinical or recurrent varicoceles, acute epididymitis, and abnormal hormone levels

Patient characteristics	Male age in years, mean (SD): Ginger: 33.27 (5.38) Placebo: 32.05 (3.99) Female age in years: NR BMI in kg/m^2, mean (SD): Ginger: 25.86 (3.22) Placebo: 26.47 (4.6) Duration of infertility: >2 years Percentage of sperm DNA fragmentation at baseline; mean (SE): Ginger: 53.48 (0.07) Placebo: 56.75 (0.08) Male factor infertility, N (%): 100 (100%) Female factor infertility: NR Previous implantation failure: NR Vitamin use, n (%): Ginger: 10 (20%) Placebo: 14 (28%)
Intervention(s)/control	Ginger: ginger capsule 250 mg twice daily for 3 months Placebo: placebo capsule for 3 months
Duration of follow-up	Semen samples were assessed at baseline and after 3 months of treatment
Sources of funding	The study was supported by Royan Institute for Reproductive Biomedicine, Tehran, Iran.
Sample size	N=106 N randomised:

	Ginger: 53 Placebo: 53 N included in final analysis: Ginger: 50 Placebo: 50
Other information	Sperm DNA fragmentation test: TUNEL Threshold for defining sperm DNA fragmentation: ≥15% Patients were advised to follow a standard diet in order to avoid effects attributable to ginger intake in food. Analysis was adjusted for age, BMI, sperm count, sperm concentration, sperm motility and sperm DNA fragmentation at baseline.

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Ginger versus Placebo

Outcome	Ginger, N = 53	Placebo, N = 53
Percentage of DNA fragmentation in sperm samples (TUNEL, at 3 months of treatment) Mean (SE)	17.77 (0.05)	40.54 (0.08)

DNA: deoxyribonucleic acid; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer-generated random number sequence was produced by independent person. No important differences between groups at baseline.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of intervention allocations. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for nearly all participants (94.3%))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	Low *(The study is judged to be at low risk of bias for all domains)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Hozyen, 2022

Bibliographic Reference	Hozyen, Manar; Hasanen, Eman; Elqusi, Khaled; ElTanbouly, Salma; Gamal, Samar; Hussin, Abdul Ghafar; AlKhader, Hanaa; Zaki, Hosam; Reproductive Outcomes of Different Sperm Selection Techniques for ICSI Patients with Abnormal Sperm DNA Fragmentation: a Randomized Controlled Trial.; Reproductive sciences (Thousand Oaks, Calif.); 2022; vol. 29 (no. 1); 220-228

Study details

Country/ies where study was carried out	Egypt
Study type	Randomised controlled trial (RCT)
Study dates	March 2017 - December 2018
Inclusion criteria	Male participants with abnormal sperm DNA fragmentation (≥20.3%, TUNEL) undergoing ICSI, and female partners aged ≤37 years who had COCs on the trigger day with minimum one mature oocyte developed to a blastocyst with fresh embryo transfer
Exclusion criteria	Couples with endometriosis, recurrent miscarriage, recurrent implantation failure, varicocele, leukocytospermia, cryopreserved semen samples, gestational carrier, sperm or oocytes donation, and sextually transmitted diseases
Patient characteristics	Male age in years, mean (SD): PICSI (with ejaculated sperm): 36.0 (5.5) Testicular sperm retrieval and ICSI: 36.5 (7.9) ICSI (with ejaculated sperm): 36.1 (7.1) Female age in years, mean (SD): PICSI (with ejaculated sperm): 29.7 (4.7) Testicular sperm retrieval and ICSI: 29.9 (4.9) ICSI (with ejaculated sperm): 29.7 (4.5) Male BMI in kg/m^2, mean (SD): NR Female BMI in kg/m^2, mean (SD): PICSI (with ejaculated sperm): 30.2 (6.1) Testicular sperm retrieval and ICSI: 31.0 (5.8) ICSI (with ejaculated sperm): 30.8 (4.3) Duration of infertility: NR Percentage of sperm DNA fragmentation at baseline; mean (SD):

	PICSI (with ejaculated sperm): 28.7 (7.5) Testicular sperm retrieval and ICSI: 28.6 (7.7) ICSI (with ejaculated sperm): 28.5 (6.5) Male factor infertility, N (%): 223 (100%)* Female factor infertility: NR Previous implantation failure: NR** *The study did not clearly state whether all participants had male factor infertility but participants had abnormal DNA fragmentation and were recruited from fertility centre, so we assumed that all participants had male factor infertility. **The study excluded participants with recurrent implantation failure, but unclear whether participants with a single episode of previous implantation failure were included.
Intervention(s)/control	PICSI (with ejaculated sperm) Testicular sperm retrieval and ICSI ICSI (with ejaculated sperm)
Duration of follow-up	NR
Sources of funding	NR
Sample size	N=223*** N randomised: 223 PICSI (with ejaculated sperm): 78 Testicular sperm retrieval and ICSI: 73 ICSI (with ejaculated sperm): 72 N included in final analysis: PICSI (with ejaculated sperm): 78 Testicular sperm retrieval and ICSI: 73 ICSI (with ejaculated sperm): 72

	***This study is a four-arm study with total sample N=302, but we only extracted the data from three arms (ICSI with ejaculated sperm where sperm were selected based on density gradient centrifugation, PICSI with ejaculated sperm, and testicular sperm retrieval and ICSI) because we were not interested in the other arm (i.e., magnetic activated cell sorting).
Other information	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: ≥20.3% Method to confirm clinical pregnancy: presence of fetal heartbeats on ultrasound at 6-7 weeks of gestation Method to confirm miscarriage: loss of baby within 20 weeks of gestation Method to confirm high quality blastocyst: graded >3BB Blastulation rate was calculated as number of blastocysts on day 5 and 6/number of cleaved embryos.

BMI: body mass index; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; NR: not reported; PICSI: physiological intracytoplasmic sperm injection; RCT: randomised controlled trial; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Testicular sperm retrieval and ICSI versus PICSI versus ICSI (with ejaculated sperm)

Outcome	Testicular sperm retrieval and ICSI, N = 73	PICSI (with ejaculated sperm), N = 78	ICSI (with ejaculated sperm), N = 72
Clinical pregnancy (presence of fetal heartbeats on ultrasound, denominator: N randomised) No of events	41/73	54/78	37/72
Miscarriage (loss of baby within 20 weeks of gestation, denominator: clinical pregnancy) No of events	2/41	5/54	4/37

Outcome	Testicular sperm retrieval and ICSI, N = 73	PICSI (with ejaculated sperm), N = 78	ICSI (with ejaculated sperm), N = 72
Embryo quality/grading (high-quality blastocyst rate [graded >3BB]) Mean (SD)	45.9 (32.1)	54.9 (28.3)	60.4 (30.3)

ICSI: intracytoplasmic sperm injection; PICSI: physiological intracytoplasmic sperm injection; SD: standard deviation

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment, but no baseline differences between interventions groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Blinding could not be possible because of the nature of interventions but there was no reason to believe that deviations from the intended intervention arose because of the experimental context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for all or nearly all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Participants and study personnel could be aware of the interventions, but assessment of the outcomes might not be influenced by knowledge of intervention received as they were objective outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the*

Section	Question	Answer
		outcomes correspond to intended outcome measurements and analyses)
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Kumalic, 2020

Bibliographic Reference	Kumalic, Senka Imamovic; Klun, Irma Virant; Bokal, Eda Vrtacnik; Pinter, Bojana; Effect of the oral intake of astaxanthin on semen parameters in patients with oligo-astheno-teratozoospermia: a randomized double-blind placebo-controlled trial.; Radiology and oncology; 2020; vol. 55 (no. 1); 97-105

Study details

Country/ies where study was carried out	Slovenia
Study type	Randomised controlled trial (RCT)
Study dates	November 2014 - January 2019
Inclusion criteria	Men with infertility (unable to conceive for at least 12 months after unprotected sex or after a failed assisted conception intervention) with oligospermia, asthenozoospermia, and teratozoospermia
Exclusion criteria	smoking >20 cigarettes a day, endocrinopathies, infertility problems because of genetic conditions, genital tract infections, systematic diseases, undescended testis, history of testicular cancer, and treatment with food supplements (such as antioxidants) and other drugs during 3 months before enrolling in the study

Patient characteristics	Male age in years, mean (SD): Astaxanthin: 35.0 (5.2) Placebo: 36.4 (5.5) Female age in years: NR BMI in kg/m^2, mean (SD): Astaxanthin: 25.9 (3.8) Placebo: 27.1 (4.6) Duration of infertility in months: at least 12 months Percentage of sperm DNA fragmentation at baseline; mean (SD): Astaxanthin: 50.5 (23.9) Placebo: 45.8 (21.8) Male factor infertility, N (%): 80 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Astaxanthin: oral astaxanthin 16 mg daily from 3 months Placebo: identical placebo capsules for 3 months
Duration of follow-up	Sperm samples were assessed at baseline and 3 months after treatment
Sources of funding	Part industry funded - Astaxanthin and placebo capsules were provided by Sensilab, Ljubljana, Slovenia.
Sample size	N=80 N randomised: Astaxanthin: 40 Placebo: 40 N included in final analysis: Astaxanthin: 37 (as n=3 lost to follow up)

	Placebo: 35 (as n=5 lost to follow up)
Other information	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Astaxanthin versus Placebo

Outcome	Astaxanthin, N = 40	Placebo, N = 40
Percentage of DNA fragmentation in sperm samples (TUNEL; at 3 months of treatment) Mean (SD)	51.2 (17.9)	49.8 (16.9)

SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was carried out by a third party using computerised randomisation table.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of interventions, and appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data were available for only 91% of participants, and it is unlikely that missingness in the outcome dependent on its true value.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were not aware of interventions.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported result for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Kumar, 2011

Bibliographic Reference	Kumar, Rajeev; Saxena, Vaibhav; Shamsi, Monis Bilal; Venkatesh, S; Dada, Rima; Herbo-mineral supplementation in men with idiopathic oligoasthenoteratospermia: A double blind randomized placebo-controlled trial.; Indian journal of urology : IJU : journal of the Urological Society of India; 2011; vol. 27 (no. 3); 357-62

Study details

Country/ies where study was carried out	India
Study type	Randomised controlled trial (RCT)
Study dates	April 2009 - August 2009

Inclusion criteria	Men with infertility (failure to conceive in 1 year), normal semen volume (>2 ml), sperm counts >5 mill/ml, and at least one of the following: sperm counts <20 mill/ml, morphology <50% normal forms, and motility <50% (Type A + B) or 25% (Type A)
Exclusion criteria	Varicocele, cryptorchidism, chemotherapy or radiation, abnormal hormone levels, pelvic or scrotal surgery, and current febrile illness or medication use during the last 3 months
Patient characteristics	Male age in years, mean (SD): Herbo-mineral supplement: 32 (5.09) Placebo: 29.6 (2.88) Female age in years: NR BMI in kg/m^2: NR Duration of infertility: at least 1 year Percentage of sperm DNA fragmentation assessed with SCSA at baseline; mean (SD): Herbo-mineral supplement: 40.8 (9.9) Placebo: 39.9 (10.8) Male factor infertility, N (%): 50 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Herbo-mineral supplement: purnachandrodaya rasa 45 mg, suvarnavang 30 mg, muktashukti bhasma 30 mg, suvarnamakshik bhasma 30 mg, shilajit shuddha 30 mg, abhrak bhasma 15 mg, makardhwaj rasa 15 mg, rasa sindur 5 mg, tribulus terrestris 200 mg, chlorophytum arundinaceum 150 mg, ashtavarga 200 mg, purifi ed Mucuna pruriens 150 mg, tinospora cordifolia 150, withania somnifera 150 mg, emblica offi cinalis 75 mg, sida cordifolia 75 mg, argyreia speciosa 75 mg, asparagus racemosus 75 mg, tacca aspera 30 mg, smilax china 30 mg, ipomoea digitata 30 mg, and eulophia campestris 15 mg two capsules twice a day for 3 months Placebo: identical placebo two capsules twice a day for 3 months
Duration of follow-up	Semen samples were assessed at 3 months of treatment

Sources of funding	Industry funded - The study was supported by M/s Charak Pharmaceuticals, Mumbai, India
Sample size	N=50 N randomised: Herbo-mineral supplement: 25 Placebo: 25 N included in final analysis: Herbo-mineral supplement: 21 Placebo: 23
Other information	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation

Outcomes

Herbo-mineral supplement versus Placebo

Outcome	Herbo-mineral supplement, N = 25	Placebo, N = 25
Percentage of DNA fragmentation in sperm samples (SCSA, at 3 months of treatment) Mean (SD)	41.7 (9)	41.8 (9.5)

DNA: deoxyribonucleic acid; SCSA: sperm chromatin structure assay; SD: standard deviation

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment, but no baseline differences between interventions groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of assigned interventions and appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data were available for only 88% of participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported results for the outcome do not correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Lahimer, 2023

Bibliographic Reference	Lahimer, Marwa; Gherissi, Oumaima; Ben Salem, Nesrine; Ben Mustapha, Henda; Bach, Veronique; Khorsi-Cauet, Hafida; Khairi, Hedi; Ben Ali, Habib; BenKhalifa, Moncef; Ajina, Mounir; Effect of Micronutrients and L-Carnitine as Antioxidant on Sperm Parameters, Genome Integrity, and ICSI Outcomes: Randomized, Double-Blind, and Placebo-Controlled Clinical Trial.; Antioxidants (Basel, Switzerland); 2023; vol. 12 (no. 11)

Study details

Country/ies where study was carried out	Tunisia
Study type	Randomised controlled trial (RCT)
Study dates	April 2020 - December 2022
Inclusion criteria	Male aged 20 years or over consulting for male infertility, oligozoospermia, asthenozoospermia, teratozoospermia, idiopathic infertility, and being candidates for IUI, IVF and/or ICSI.
Exclusion criteria	Lactose intolerance, varicocele, chronic health condition with long-term management (cardiovascular disorders and asthma), aspermia, erectile dysfunction, leukospermia, azoospermia obstructive and non-obstructive, cryptozoospermia, current or recent urogenital infection, currently taking antioxidants, central hypogonadism, hormonal or endocrine disorders, female partner aged over 40, female partner with premature ovarian failure, that is related to the cessation of ovarian function before the age of 40 (defined by a triad of signs: (i) amenorrhea for minimum 4 months, (ii) reduced estradiol serum levels, and (iii) increased follicle-stimulating hormone levels (>40 IU/l in at least two samples a few weeks apart)), female partners who are poor ovarian responders (defined as the presence of minimum two of the following three characteristics: (i) advanced maternal age (≥40 years) or any of the risk factors for poor ovarian responders such as endometrioma, pelvic infection, ovarian surgery, and extensive periovarian adhesions; (ii) a previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol), and (iii) an abnormal ovarian reserve test (antral follicular count of 5–7 follicles or anti-Müllerian hormone of 0.5–1.1 ng/mL); female partner with diminished ovarian reserve (defined as (i) the presence of any of the risk factors for poor ovarian responders and/or (ii) an abnormal ovarian reserve test (antra follicular count of < 5–7 follicles or anti-Müllerian hormone < 0.5–1.1 ng/mL); female partner with thyroid dysfunction or prolactinoma; and female partner who did not want their male partners to take part in the study
Patient characteristics	Male age in years, mean (SD): 38.94 (5.8)

	Female age in years, range: 28.6-37.8 Male BMI in kg/m^2, mean (SD): Antioxidants: 26.14 (4.2) Placebo: 26.27 (3.9) Female BMI in kg/m^2, mean (SD): Antioxidants: 26.18 (4.5) Placebo: 26.15 (4.2) Duration of infertility: NR Percentage of sperm DNA fragmentation assessed with TUNEL at baseline; mean (SD): Antioxidants: 20 (NR) Placebo: 18 (NR) Male factor infertility, N (%): 263 (100%)* Factors that may impact female factor infertility, N (%): Antioxidants: obstructed/absent/ligated right fallopian tube N=5 (3.8%), obstructed/absent/ligated left fallopian tube N=8 (6.1%), ovarian reserve anomaly N=1 (0.8%), endometriosis N=1 (0.8%), uterine pathology N=0 (0%), cervical pathology 1 (0.8%), other pathology 1 (0.8%) Placebo: obstructed/absent/ligated right fallopian tube N=8 (6.1%), obstructed/absent/ligated left fallopian tube N=3 (2.3%), ovarian reserve anomaly N=1 (0.8%), endometriosis N=0 (0%), uterine pathology N=1 (0.8%), cervical pathology 0 (0%), other pathology 0 (0%) Previous implantation failure: NR *This study included participants consulting for male infertility
Intervention(s)/control	Antioxidants: l-carnitine 220 mg, l-arginine 125 mg, vitamin E 60 mg, l-glutathione 40 mg, zinc 20 mg, coenzyme Q10 7.5 mg, folic acid (vitB-9) 0.4 mg, and selenium 0.03 mg two capsules twice daily for 3 months Placebo: two placebo capsules twice daily for 3 months

	Participants had IVF/ICSI after 3 months of treatment. N=57 and N=18 from antioxidants group underwent ICSI and IVF respectively. N=57 and N=13 from placebo group underwent ICSI and IVF, respectively.
Duration of follow-up	Semen samples assessment and pelvic ultrasound were performed at 3 months of treatment, and rate of live birth was assessed at 24 months
Sources of funding	Industry funded - The study was supported by the MEDIS laboratories
Sample size	N=263 N randomised: Antioxidants: 131 Placebo: 132 N included in final analysis: Antioxidants: 131 Placebo: 132
Other information	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR Method used to confirm live birth: NR Method used to confirm clinical pregnancy: ultrasound imaging Embryonic quality assessment: maturation rate ([number of mature oocytes/number of retrieved oocytes] x 100), fertilization rate ([number of zygotes/number of mature oocytes] x 100), cleavage rate ([number of embryos/number of zygotes] x 100), and blastocyst rate ([number of blastocysts/number of embryos] x 100) We did not extract data on DNA fragmentation outcome as the study did not report variance (e.g., SD).

BMI: body mass index; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilisation; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Antioxidants versus Placebo

Outcome	Antioxidants, N = 131	Placebo, N = 132
Live birth (undefined, at 24 months after treatment, denominator: N randomised) No of events	17/131	7/132
Clinical pregnancy (assisted and spontaneous pregnancy confirmed by ultrasound, denominator: N randomised) No of events	26/131	15/132
Embryo quality/grading (defined as maturation rate, ICSI outcome) Mean (SD)	67.8 (38.9)	57.57 (35.8)
Embryo quality/grading (defined as fertilisation rate, ICSI outcome) Mean (SD)	48.13 (45.5)	38.9 (33.7)
Embryo quality/grading (defined as cleavage rate, CISI outcome) Mean (SD)	54.1 (49.9)	44.4 (49)
Embryo quality/grading (defined as blastocyst rate, ICSI outcome) Mean (SD)	15.1 (63.3)	10.5 (31.5)

ICSI: intracytoplasmic sperm injection; SD: standard deviation

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment, but no baseline differences between interventions groups.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of intervention allocations. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for all or nearly all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate for clinical pregnancy and embryo quality/grading, but the study did not define live birth outcome.* *Low: clinical pregnancy, and embryo quality/grading* *Some concerns: live birth)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcomes correspond to all intended outcome measurements and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Maghsoumi-Norouzabad, 2022

Bibliographic Reference	Maghsoumi-Norouzabad, Leila; Zare Javid, Ahmad; Mansoori, Anahita; Dadfar, Mohammadreza; Serajian, Amirarsalan; Vitamin D3 Supplementation Effects on Spermatogram and Oxidative Stress Biomarkers in Asthenozoospermia Infertile Men: a Randomized, Triple-Blind, Placebo-Controlled Clinical Trial.; Reproductive sciences (Thousand Oaks, Calif.); 2022; vol. 29 (no. 3); 823-835

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	October 2018 - August 2020
Inclusion criteria	Men with infertility (unable to have a baby after at least 1 year of unprotected sex), asthenozoospermia, normal fertile woman partner, no medical history that could lead to infertility, no job and environmental toxin exposure, no alcohol or drug abuse, BMI <30 kg/m2, and no medical treatment ≤3 months before the start of the study
Exclusion criteria	Attendance at another research study, any acute illness, leaving the study based on the personal desire, admission of <90% of the supplement, immigration, and lost to follow-up
Patient characteristics	Male age in years, mean (SD): Vit D3: 35.13 (5.51) Placebo: 34.44 (5.07) Female age in years: NR BMI in kg/m^2, mean (SD): Vit D3: 28.40 (2.96) Placebo: 27.95 (2.51) Duration of infertility in months, mean (SD): Vit D3: 2.75 (2.25) Placebo: 3.27 (1.97) Percentage of sperm DNA fragmentation at baseline; mean (SD):

	Vit D3: 25.07 (1.23) Placebo: 24.82 (1.9) Male factor infertility, N (%): 86 (100%) Female factor infertility, N (%): 0 (0%) Previous implantation failure: NR
Intervention(s)/control	Vit D3: vitamin D3 (cholecalciferol) 4000 IU daily 3 months Placebo: identical placebo for 3 months
Duration of follow-up	Semen samples were assessed at 3 months after treatment
Sources of funding	Not industry funded - The study was a part of a PhD project.
Sample size	N=86 N randomised: Vit D3: 43 Placebo: 43 N included in final analysis: Antioxidants: 43 Placebo: 43
Other information	Sperm DNA fragmentation tests: SCD test Threshold for defining sperm DNA fragmentation: NR Analysis of covariance (ANCOVA), adjusting for baseline values and covariates (BMI, age, sunlight exposure, physical activity, dietary intake of macro and micronutrients, season, serum vitamin D3, calcium, and parathyroid hormone), was used.

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCD: sperm chromatin dispersion test; SD: standard deviation

Outcomes

Vit D3 versus Placebo

Outcome	Vit D3, N = 43	Placebo, N = 43
Percentage of DNA fragmentation in sperm samples (SCD test, at 3 months of treatments) Mean (SD)	24.88 (8.58)	24.97 (1.5)

SCD: sperm chromatin dispersion test; SD: standard deviation

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was conducted by third party using a computer-generated program.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of assigned interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported result for the outcome do not correspond to intended outcome measurement and analyses.)*
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Martínez-Soto, 2016

Bibliographic Reference	Juan Carlos Martínez-Soto, Joan Carles Domingob , Begoña Cordobillab , María Nicolása , Laura Fernándeza , Pilar Alberoa , Joaquín Gadea c AJL; Dietary supplementation with docosahexaenoic acid (DHA) improves seminal antioxidant status and decreases sperm DNA fragmentation; SYSTEMS BIOLOGY IN REPRODUCTIVE MEDICINE; 2016; vol. 62 (no. 6); 387–395

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	2009 - 2010
Inclusion criteria	Men aged over 18 years undergoing evaluation for infertility
Exclusion criteria	People with metabolic disease, chromosomal or genetic alterations, and anticoagulant treatment, and oncological patients
Patient characteristics	Male age in years, mean (SE): DHA: 35 (0.8) Placebo: 35.6 (1.0) Female age in years: NR BMI in kg/m^2: NR

	Duration of infertility: NR Percentage of sperm DNA fragmentation at baseline; mean (SE): DHA: 22.0 (2.1) Placebo: 20.1 (2.8) Male factor infertility, N (%): 74 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	DHA: docosahexaenoic acid 1500 mg (three 500 mg capsules) daily for 10 weeks Placebo: identical placebo capsules for 10 weeks
Duration of follow-up	Semen samples were assessed 10 weeks after treatment
Sources of funding	None
Sample size	N=74 N randomised: DHA: 42 Placebo: 32 N included in final analysis: Antioxidants: 32 (as n=10 lost to follow up mainly because of bad breath and heartburn or reflux after the intake of DHA capsules) Placebo: 25 (as n=7 lost to follow up)
Other information	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DHA: docosahexaenoic acid; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

DHA versus Placebo

Outcome	DHA, N = 42	Placebo, N = 32
Percentage of DNA fragmentation in sperm samples (TUNEL, at 10 weeks of treatment) Mean (SE)	9.3 (1.3)	23 (2.8)

SE: standard error; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment, but no baseline differences between interventions groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Per-protocol analysis excluding participants who discontinued interventions was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data were available for only 77% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were not aware of interventions.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported results for the outcomes do not correspond to intended outcome measurements and analyses.)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Mathieu d'Argent, 2021

Bibliographic Reference	Mathieu d'Argent, Emmanuelle; Ravel, Celia; Rousseau, Alexandra; Morcel, Karine; Massin, Nathalie; Sussfeld, Julie; Simon, Tabassome; Antoine, Jean-Marie; Mandelbaume, Jacqueline; Darai, Emile; Kolanska, Kamila; High-Dose Supplementation of Folic Acid in Infertile Men Improves IVF-ICSI Outcomes: A Randomized Controlled Trial (FOLFIV Trial).; Journal of clinical medicine; 2021; vol. 10 (no. 9)

Study details

Country/ies where study was carried out	France
Study type	Randomised controlled trial (RCT)
Study dates	November 2011 - September 2015
Inclusion criteria	Men aged 18-60 years with at least one abnormal spermatic WHO 2010 criterion and fertile female partner aged 18-38 years, who required IVF-ICSI treatment for male factor infertility and can speak and write French
Exclusion criteria	Chronic viral infections (hepatitis C, hepatitis B, human immunodeficiency virus infections), a poorly controlled chronic health conditions (such as diabetes, heart disease, hypertension, and cancer), epilepsy, previous cancer management, the need for frozen sperm or testicular sperm, permanent obstructive disease of the deferent canal in male partner, folic

	acid supplementation before the study, or medical intolerance to folic acid, and couples with known etiology of female factor infertility or ovarian failure
Patient characteristics	Male age in years, mean (SD): Folic acid: 37.1 (6.7) Placebo: 36.5 (6.2) Female age in years, mean (SD): Folic acid: 31.3 (4.5) Placebo: 31.7 (4.1) Male BMI in kg/m^2, median (IQR): Folic acid: 26.5 (23.4-28.7) Placebo: 25.3 (22.8-27.7) Female BMI in kg/m^2, median (IQR): Folic acid: 24.1 (21.5-26.1) Placebo: 23.3 (20.9-26.6) Duration of infertility: NR Percentage of sperm DNA fragmentation assessed with TUNEL at baseline; mean (SD): Folic acid: 15.0 (6.5) Placebo: 8.4 (4.6) Male factor infertility, N (%): Folic acid: 65 (78.3%) Placebo*: 61 (77.2%) Mixed infertility, N (%): Folic acid: 18 (21.7%) Placebo*: 17 (21.5%) Previous implantation failure: NR *For placebo group, data on a participant was not reported, so unclear whether n=1 had male factor infertility or mixed infertility

Intervention(s)/control	Folic acid: folic acid 15 mg (5 mg 3 tablets) daily for 3-4 months Placebo: identical placebo (3 tables) daily for 3-4 months After 3-4 months of treatment, participants had one IVF/ICSI cycle
Duration of follow-up	Semen samples were assessed at baseline and 3 months of treatment, and female participants were followed until 7 weeks of gestation if serum hCG test was positive.
Sources of funding	Not industry funded - The study was supported by FRENCH MINISTRY OF HEALTH
Sample size	N=162 N randomised: Folic acid: 83 Placebo: 79 N included in final analysis of sperm samples: Folic acid: 53 Placebo: 51 N included in final analysis of pregnancy outcomes: Folic acid: 59 Placebo: 49
Other information	Sperm DNA fragmentation tests: TUNEL Threshold for defining sperm DNA fragmentation: NR Method used to confirm clinical pregnancy: presence of a gestational sac with at least one foetal heart rate on ultrasound at the 7 weeks of gestation Miscarriage: undefined

BMI: body mass index; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IQR: interquartile range; IVF: in vitro fertilisation NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Outcomes

Folic acid versus Placebo

Outcome	Folic acid, N = 83	Placebo, N = 79
Clinical pregnancy (pregnancy after IVF/ICSI and spontaneous pregnancy confirmed by US at 7 weeks of gestation, denominator: N randomised) Folic acid: n=5 spontaneous pregnancy and n=21 pregnancy after IVF/ICSI; Placebo: n=5 spontaneous pregnancy and n=10 pregnancy after IVF/ICSI No of events	26/83	15/79
Miscarriage (undefined, denominator: clinical pregnancy) No of events	5/26	1/15
Percentage of DNA fragmentation in sperm samples (TUNEL; at 3 months of treatment) Mean (SD)	6.5 (4.6)	7.4 (4.6)

DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; SD: standard deviation; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment, but no baseline differences between interventions groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of intervention allocations. Appropriate analysis was used.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Per-protocol analysis and intention to treat analysis confirmed that the results were not biased by missing outcome data.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate for sperm DNA fragmentation, and clinical pregnancy, but method used to confirm miscarriage was not provided. No difference in measurement of the outcome between intervention groups.* *Low: sperm DNA fragmentation, and clinical pregnancy* *Some concerns: miscarriage)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported results for the outcomes do not correspond to intended outcome measurements and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(About 20% of participants had mixed infertility.)*
Overall bias and Directness	Risk of bias variation across outcomes	None

DNA: deoxyribonucleic acid; RoB: risk of bias

Micic, 2019

Bibliographic Reference	Micic, Sava; Lalic, Natasa; Djordjevic, Dejan; Bojanic, Nebojsa; Bogavac-Stanojevic, Natasa; Busetto, Gian Maria; Virmani, Ashraf; Agarwal, Ashok; Double-blind, randomised, placebo-controlled trial on the effect of L-carnitine and L-acetylcarnitine on sperm parameters in men with idiopathic oligoasthenozoospermia.; Andrologia; 2019; vol. 51 (no. 6); e13267

Study details

Country/ies where study was carried out	Serbia
Study type	Randomised controlled trial (RCT)
Study dates	December 2014 - January 2016
Inclusion criteria	Infertile men (pregnant not achieved after 12 months) with total sperm count ≤15 million per ml, normal viscosity and normal leucocytes number (<1 × 106 /ml), sperm vitality ≤58% live, progressive motility <32%, total ejaculate volume 1.0 ml, or normal sperm morphology <4% (according to WHO 2010), fertile female partners aged <40 years with regular period or infertile female partners with no fertility-related procedures (including planned artificial insemination or IVF or ICSI for the next 90 days)
Exclusion criteria	Sperm concentration <1 × 106 /ml; motility <5%; history of undescended testes; endocrine disorders affecting the hypothalamic-pituitary axis; hypersensitivity to ingredients of study intervention; history of post-pubertal mumps; history of endocrine disease; presence of anti-sperm antibodies; autoimmune disease, cystic fibrosis, or testicular cancer; leucocytospermia, leucocyte count >1 × 106 /ml; use of vitamin or natural treatment for infertility at any time; use of antioxidant agents or vitamins during the 8 weeks before the study (for subjects using vitamin supplementation, an 8-week wash-out period needed prior to inclusion in the study); history of any therapy for infertility during the last 2 months including vitamin supplementation and over-the-counter treatment; history of excessive alcohol consumption during 90 days prior to the start of the study; and subjects who participated in other clinical trials.
Patient characteristics	Male age in years, mean (range): 31.5 (19-44) Female age in years: NR BMI in kg/m^2: NR Duration of infertility in years: at least 1 year

	Percentage of sperm DNA fragmentation assessed with SCD test at baseline; median (IQR): Antioxidants: 38.50 (32.00-48.70) Placebo: 37.00 (34.50-41.00) Male factor infertility, N (%): 175 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Antioxidants: 1000 g L-carnitine, 0.5 g L-acetylcarnitine, 50 mg citric acid, 10 mg zinc, 20 mg coenzyme Q10, 50 µg selenium, 0.725 g fumarate, 1 g fructose, 90 mg vitamin C, 200 µg folic acid, and 1.5 µg vitamin B12 two times a day for 6 months Placebo: placebo two times a day for 6 months
Duration of follow-up	Semen samples were assessed at 3 months and 6 months of treatments
Sources of funding	Not reported
Sample size	N=175 N randomised: Antioxidants: 125 Placebo: 50 N included in final analysis: Antioxidants: 125 Placebo: 50
Other information	Sperm DNA fragmentation tests: SCD test Threshold for defining sperm DNA fragmentation: NR

BMI: body mass index; DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IQR: interquartile range; IVF: in vitro fertilisation; NR: not reported; RCT: randomised controlled trial; SCD: sperm chromatin dispersion test; SD: standard deviation

Outcomes

Antioxidants versus Placebo

Outcome	Antioxidants, N = 125	Placebo, N = 50
Percentage of DNA fragmentation in sperm samples (SCD test, at 6 months of treatment) Median (IQR)	31 (25 to 41)	38 (34 to 39)

IQR: interquartile range; SCD: sperm chromatin dispersion test

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of intervention allocations. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is no reason to believe that eligible reported results for the outcome do not correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Patki, 2023

Bibliographic Reference	Patki, Ameet; Shelatkar, Rohit; Singh, Monica; Agarwal, Sweta; M, Venugopal; Umbardand, Shashikant; Reddy, Apoorva; Kannan, Priya; Gorthi, Srilatha; Khastgir, Gautam; Kulshreshtha, Anita; Ganu, Gayatri; Impact of antioxidants in improving semen parameters like count, motility and DNA fragmentation in sub-fertile males: a randomized, double-blind, placebo-controlled clinical trial.; Translational and clinical pharmacology; 2023; vol. 31 (no. 1); 28-39

Study details

Country/ies where study was carried out	India
Study type	Randomised controlled trial (RCT)
Study dates	NR
Inclusion criteria	Men aged 25-45 years with asthenozoospermia, oligospermia, teratozoospermia, and sperm DNA fragmentation >20%, and female partners with no reported infertility
Exclusion criteria	History of vasectomy, hypogonadism, undescended testis, varicocele, prostate cancer, hydrocele, chemotherapy or radiation for malignant condition, and azoospermia
Patient characteristics	Male age in years, mean (SD): Antioxidants: 35 (5.1) Placebo: 34 (5.0) Female age in years: NR

	BMI in kg/m^2: NR Duration of infertility: NR Percentage of sperm DNA fragmentation assessed with SCSA at baseline; mean (SD): Antioxidants: 32.59 (12.67) Placebo: 31.38 (10.71) Male factor infertility, N (%): 300 (100%) Female factor infertility, N (%): 0 (0%) Previous implantation failure: NR
Intervention(s)/control	Antioxidants: coenzyme Q10 50 mg, L-carnitine 50 mg, vitamin C 40 mg, vitamin E 10 mg, ginseng extract 10 mg, L-arginine 10 mg, elemental zinc (zinc sulphate) 7.5 mg (20.588 mg), elemental iron (as ferrous fumarate) 5 mg (15.21 mg), L-glutathione 2.5 mg, vitamin B6 2 mg, elemental manganese (as manganese sulphate) 2 mg (6.152 mg), lycopene 2 mg, vitamin B1 1.4 mg, elemental copper (as cupric sulphate) 1 mg (2.795 mg), vitamin A 375 µg (1250 IU), folic acid 100 µg, elemental selenium (as sodium selenate) 40 µg (95.716 µg), vitamin D 10 µg (400 IU), and vitamin B12 1 µg once daily for 3 months Placebo: identical placebo tablet once daily for 3 months
Duration of follow-up	Sperm samples were assessed after 90 days of treatment
Sources of funding	Industry funded - The study was supported by Mprex Healthcare Pvt. Ltd., Pune, Maharashtra
Sample size	N=300 N randomised: Antioxidants: 150 Placebo: 150 N included in final analysis: Antioxidants: 66 Placebo: 75

Other information	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: >20%

BMI: body mass index; DNA: deoxyribonucleic acid; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation

Outcomes

Antioxidants versus Placebo

Outcome	Antioxidants, N = 150	Placebo, N = 150
Percentage of DNA fragmentation in sperm samples (SCSA, at 3 months of treatment) Mean (SD)	26.81 (11.61)	28.45 (14.35)

DNA: deoxyribonucleic acid; SCSA: sperm chromatin structure assay; SD: standard deviation

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Per-protocol analysis excluding participants who discontinued intervention was used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data were available for only 47% of participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate, and no difference in measurement of the outcome between intervention groups.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported result for the outcome correspond to intended outcome measurement and analyses)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Steiner, 2020

Bibliographic Reference	Steiner, Anne Z; Hansen, Karl R; Barnhart, Kurt T; Cedars, Marcelle I; Legro, Richard S; Diamond, Michael P; Krawetz, Stephen A; Usadi, Rebecca; Baker, Valerie L; Coward, R Matthew; Huang, Hao; Wild, Robert; Masson, Puneet; Smith, James F; Santoro, Nanette; Eisenberg, Esther; Zhang, Heping; The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial.; Fertility and sterility; 2020; vol. 113 (no. 3); 552-560e3

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	December 2015 - December 2018
Inclusion criteria	Couples with male factor infertility for at least 12 months, male partners aged 18 years or over, presence of at least one abnormal semen parameter in previous 6 months (such as DNA fragmentation ≥25%, oligospermia, asthenospermia,

	and teratospermia), female partners aged 18-40 years with regular period, evidence of ovulation (assessed by biphasic basal body temperature, ovulation predictor kits, or luteal serum progesterone level ≥3 ng/ml), and at least one patent fallopian tube with a normal uterine cavity
Exclusion criteria	Male partners with a sperm concentration <5 million/ml on the screening semen analysis or taking testosterone or fertility medication
Patient characteristics	Male age in years, median (IQR): Antioxidants: 34.0 (30.0-38.0) Placebo: 34.0 (30.0-37.0) Female age in years, median (IQR): Antioxidants: 31.0 (29.0-35.0) Placebo: 32.0 (29.0-35.0) BMI in kg/m^2, median (IQR): Antioxidants: 27.8 (24.2-31.7) Placebo: 27.6 (24.4-31.0) Duration of infertility in months, median (IQR): Antioxidants: 24.0 (18.0-48.0) Placebo: 24.0 (15.0-36.0) Percentage of sperm DNA fragmentation at baseline; median (IQR): Antioxidants: 18.7 (14.3-28.3) Placebo: 21.1 (14.1-28.6) Male factor infertility, N (%): 171 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Antioxidants: vitamin C 500 mg, vitamin E 400 mg, selenium (L-selenomethionine) 0.20 mg, L-carnitine 1000 mg, zinc 20 mg, folic acid 1000 mcg, lycopene 10 mg, vitamin D 2000 IU daily for 3 to 6 months Placebo: placebo daily for 3 to 6 months

Duration of follow-up	All participants were followed at 3 months after treatment, and couples who conceived were followed through pregnancy and delivery
Sources of funding	Not industry funded - The study was supported by National Institutes of Health (NIH)/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Grants
Sample size	N=171 N randomised: Antioxidants: 85 Placebo: 86 N included in final analysis: Antioxidants: 67 (as n=1 lost to follow up, n=4 lost contact, n=6 no longer interested in participating, n=1 moving out of the area, n=1 not responding to Clomid, n=2 had side effect of medication, n=2 possible Zika exposure, and n=1 other reason) Placebo: 77 (as n=2 no longer interested in participating, n=2 no compliant with protocol, n=1 globozoospermia/no change of pregnancy, n=1 participant and spouse separated, n=1 unable to continue because of personal constraints, n=1 needed rest cycle because of right ovary cyst and unable to complete 3rd IUI cycles, and n=1 other reason)
Other information	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: ≥25% Method used to confirm live birth: a delivery of a live infant after 20 weeks of gestation Method used to confirm clinical pregnancy: NR Method used to confirm pregnancy: positive home pregnancy test Male participants were requested not to take vitamins for 4 weeks before randomisation. Participants who had not conceived after 3 months of timed intercourse received ovarian stimulation (up to 3 cycles) with clomiphene citrate and intrauterine insemination.

BMI: body mass index; DNA: deoxyribonucleic acid; IQR: interquartile range; IUI: intrauterine insemination; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation

Placebo (N = 86)

Outcomes

Antioxidants versus Placebo

Outcome	Antioxidants, N = 85	Placebo, N = 86
Live birth (a delivery of a live infant after 20 weeks of gestation; denominator: N randomised) No of events	13/85	21/86
Clinical pregnancy (undefined, denominator: N randomised) No of events	15/85	22/86
Miscarriage (first trimester pregnancy loss, denominator: total pregnancy) No of events	4/18	5/26
Stillbirth (denominator: clinical pregnancy) No of events	1/15	0/22
Percentage of DNA fragmentation in sperm samples (change from baseline to month 3; SCSA) Median (IQR)	0.8 (-3.4 to 3.8)	0.2 (-5.7 to 6.4)

DNA: deoxyribonucleic acid; IQR: interquartile range; SCSA: sperm chromatin structure assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was carried out using computer-mediated random digits table and a web-based randomisation service)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of intervention allocations. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for only 85% of participants, but per-protocol analysis and intention to treat analysis confirmed that pregnancy outcomes were not biased by missing outcome data. However, no sensitivity analysis was conducted for sperm DNA fragmentation.* *Low: clinical pregnancy, live birth, miscarriage, and stillbirth* *Some concerns: sperm DNA fragmentation)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate for sperm DNA fragmentation, live birth, miscarriage, and stillbirth, but method used to confirm clinical pregnancy was not provided. No difference in measurement of the outcome between intervention groups.* *Low: sperm DNA fragmentation, live birth, miscarriage, and stillbirth* *Some concerns: clinical pregnancy)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcomes correspond to intended outcome measurements and analyses)*
Overall bias and Directness	Risk of bias judgement	Low *(Live birth, miscarriage, and still birth: The study is judged to be at low risk of bias for all domains for these outcomes.*

Section	Question	Answer
		Clinical pregnancy and sperm DNA fragmentation: The study is judged to raise some concerns in at least one domain for these outcomes.)
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Yes

DNA: deoxyribonucleic acid; RoB: risk of bias

Stenqvist, 2018

Bibliographic Reference	Stenqvist, A; Oleszczuk, K; Leijonhufvud, I; Giwercman, A; Impact of antioxidant treatment on DNA fragmentation index: a double-blind placebo-controlled randomized trial.; Andrology; 2018; vol. 6 (no. 6); 811-816

Study details

Country/ies where study was carried out	Sweden
Study type	Randomised controlled trial (RCT)
Study dates	June 2015 - August 2016
Inclusion criteria	Men aged 18-50 years with at least one year of unsuccessful attempt to achieve pregnancy, sperm DNA fragmentation ≥25%, no history of smoking, no history of hormones, antihypertensive drugs, statins, psychotic drugs, oral cortisone use and antioxidant supplementation for the last six months, and no history of anabolic steroids use
Exclusion criteria	BMI ≥30 kg/m2, LH outside the normal range (2-10 IU/L), FSH outside the normal range (2-8 IU/L, g), testosterone lower than 10 nmol/L, and sperm DNA fragmentation index <25%
Patient characteristics	Male age in years, mean (SD): Antioxidants: 38.0 (5.2)

	Placebo: 37.3 (4.9) Female age in years: NR BMI in kg/m^2, mean (SD): Antioxidants: 24.5 (2.8) Placebo: 25.0 (2.7) Duration of infertility: ≥1 year Percentage of sperm DNA fragmentation at baseline; median (IQR): Antioxidants: 30.0 (27.0-41.5) Placebo: 35.5 (30.3-44.8) Male factor infertility, N (%): 77 (100%) Female factor infertility: NR Previous implantation failure: NR
Intervention(s)/control	Antioxidants: vitamin C 30 mg, vitamin E 5 mg, vitamin B12 0.5 µg, L-carnitine 750 mg, coenzyme Q10 10 mg, folic acid 100 µg, zinc 5 mg and selenium 25 µg twice daily for 6 months Placebo: identical placebo twice daily for 6 months
Duration of follow-up	Sperm DNA fragmentation was assessed at 3 months and 6 months of treatment
Sources of funding	Industry funded - The study was supported by Octean AB (Gothenburg, Sweden) and Laboratorios Q Pharma S.L. (Alicante, Spain)
Sample size	N=79 (N=77 randomised as n=2 discontinued after screening visit) N randomised: Antioxidants: 37 Placebo: 40 N included in final analysis:* Antioxidants: 37

	Placebo: 40 *The study stated that n=2 missed 3-months visit and n=2 missed 6-months visit, but it was unclear whether they were from antioxidant group or placebo group.
Other information	Sperm DNA fragmentation tests: SCSA Threshold for defining sperm DNA fragmentation: ≥25% Method used to confirm clinical pregnancy: NR

BMI: body mass index; DNA: deoxyribonucleic acid; FSH: follicular stimulating hormone; IQR: interquartile range; LH: luteinising hormone; NR: not reported; RCT: randomised controlled trial; SCSA: sperm chromatin structure assay; SD: standard deviation

Outcomes

Antioxidants versus Placebo

Outcome	Antioxidants, N = 37	Placebo, N = 40
Clinical pregnancy (undefined, denominator: N randomised) All are spontaneous pregnancy, except one pregnancy (IVF) from antioxidants group. No of events	3/37	4/40
Percentage of DNA fragmentation in sperm samples (SCSA, at 6 months of treatment) Median (IQR)	34 (26.3 to 41.8)	29.5 (22.5 to 41.3)

DNA: deoxyribonucleic acid; IQR: interquartile range; IVF: in vitro fertilisation; SCSA: sperm chromatin structure assay

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation sequence was concealed, and there is no reason to*

Section	Question	Answer
		suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel were not aware of assigned interventions and appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data were available for nearly all (95%) participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate for sperm DNA fragmentation, but method used to confirm clinical pregnancy was not provided. No difference in measurement of the outcome between intervention groups.* *Low: sperm DNA fragmentation* *Some concerns: clinical pregnancy)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that eligible reported results for the outcomes correspond to intended outcome measurements and analyses)*
Overall bias and Directness	Risk of bias judgement	Low *(Sperm DNA fragmentation: The study is judged to be at low risk of bias for all domains for this outcome.* *Clinical pregnancy: The study is judged to raise some concerns in at least one domain for this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	Yes

DNA: deoxyribonucleic acid; RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

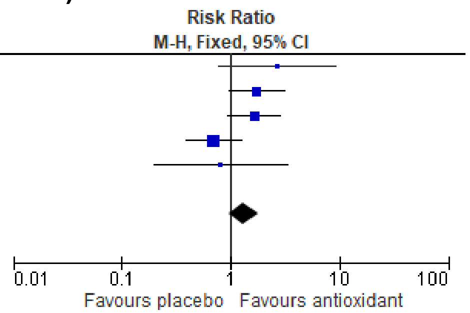
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Antioxidant versus placebo

Figure 2: Clinical pregnancy (denominator: N randomised)

	Antioxidant		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Habibi 2022	8	35	3	35	5.1%	2.67 [0.77, 9.23]
Lahimer 2023	26	131	15	132	25.3%	1.75 [0.97, 3.14]
Mathieu d'Argent 2021	26	83	15	79	26.0%	1.65 [0.95, 2.88]
Steiner 2020	15	85	22	86	37.1%	0.69 [0.38, 1.24]
Stenqvist 2018	3	37	4	40	6.5%	0.81 [0.19, 3.38]
Total (95% CI)		**371**		**372**	**100.0%**	**1.32 [0.97, 1.79]**
Total events	78		59			

Heterogeneity: Chi² = 7.91, df = 4 (P = 0.09); I² = 49%
Test for overall effect: Z = 1.76 (P = 0.08)

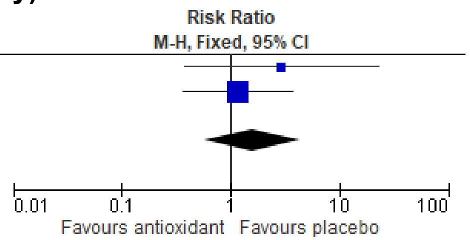


CI: confidence interval; M-H: Mantel-Haenszel

Figure 3: Miscarriage (denominator: clinical pregnancy)

	Antioxidant		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Mathieu d'Argent 2021	5	26	1	15	23.7%	2.88 [0.37, 22.43]
Steiner 2020	4	18	5	26	76.3%	1.16 [0.36, 3.72]
Total (95% CI)		**44**		**41**	**100.0%**	**1.56 [0.57, 4.30]**
Total events	9		6			

Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)

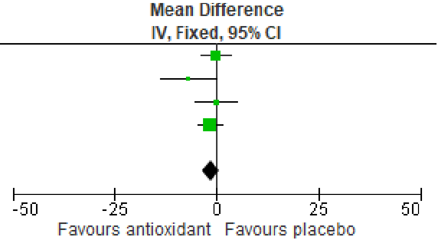


CI: confidence interval; M-H: Mantel-Haenszel

Figure 4: Percentage of DNA fragmentation in sperm samples (SCSA)

	Antioxidant			Placebo				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Abbasi 2021	25.19	7.22	28	25.32	6.66	28	30.3%	-0.13 [-3.77, 3.51]
Habibi 2022	25.38	14.68	35	32.41	14.62	35	8.5%	-7.03 [-13.89, -0.17]
Kumar 2011	41.7	9	25	41.8	9.5	25	15.2%	-0.10 [-5.23, 5.03]
Patki 2023	26.81	11.61	150	28.45	14.35	150	46.0%	-1.64 [-4.59, 1.31]
Total (95% CI)			**238**			**238**	**100.0%**	**-1.41 [-3.41, 0.60]**

Heterogeneity: Chi² = 3.32, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 1.38 (P = 0.17)



CI: confidence interval; IV: inverse variance

Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Table 6: Evidence profile for comparison between antioxidant and placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antioxidant	Placebo	Relative (95% CI)	Absolute		
Live birth (denominator: N randomised) (follow-up up to 24 months)												
1 (Lahimer 2023)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/131 (13%)	7/132 (5.3%)	RR 2.45 (1.05 to 5.7)	77 more per 1000 (from 3 more to 249 more)	VERY LOW	CRITICAL
Live birth (denominator: N randomised) (follow-up until delivery)												
1 (Steiner 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/85 (15.3%)	21/86 (24.4%)	RR 0.63 (0.34 to 1.17)	90 fewer per 1000 (from 161 fewer to 42 more)	LOW	CRITICAL
Clinical pregnancy (denominator: N randomised) (follow-up until delivery)												
5[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	78/371 (21%)	59/372 (15.9%)	RR 1.32 (0.97 to 1.79)	51 more per 1000 (from 5 fewer to 125 more)	LOW	CRITICAL
Miscarriage (denominator: clinical pregnancy) (follow-up until delivery)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	9/44 (20.5%)	6/41 (14.6%)	RR 1.56 (0.57 to 4.3)	82 more per 1000 (from 63 fewer to 483 more)	LOW	IMPORTANT
Stillbirth (denominator: clinical pregnancy) (follow-up until delivery)												
1 (Steiner 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	1/15 (6.7%)	0/22 (0%)	RR 4.31 (0.19 to 99.27)	70 more per 1000 (from 90 fewer to 220 more)[7]	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antioxidant**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Embryo quality/grading (defined as maturation rate) (Better indicated by higher values) (MID: 17.9)												
1 (Lahimer 2023)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	131	132	-	MD 10.23 higher (1.19 to 19.27 higher)	LOW	IMPORTANT
Embryo quality/grading (defined as fertilisation rate) (Better indicated by higher values) (MID: 16.85)												
1 (Lahimer 2023)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	131	132	-	MD 9.23 higher (0.45 lower to 18.91 higher)	LOW	IMPORTANT
Embryo quality/grading (defined as cleavage rate) (Better indicated by higher values) (MID: 24.5)												
1 (Lahimer 2023)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	132	-	MD 9.7 higher (2.25 lower to 21.65 higher)	MODERATE	IMPORTANT
Embryo quality/grading (defined as blastocyst rate) (Better indicated by higher values) (MID: 15.75)												
1 (Lahimer 2023)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	131	132	-	MD 4.6 higher (7.5 lower to 16.7 higher)	LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (SCSA) (follow-up up to 3 months; Better indicated by lower values) (MID: 10.76)												
4[8]	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	238	238	-	MD 1.41 lower (3.41 lower to 0.60 higher)	LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 2 months; Better indicated by lower values) (MID: 3.9)												
1 (Greco 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	MD 13.8 lower (17.5 to 10.1 lower)	MODERATE	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 80 days; Better indicated by lower values) (MID: 4.6)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antioxidant	Placebo	Relative (95% CI)	Absolute		
1 (Habibi 2022)	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[4]	none	35	35	-	MD 6.84 lower (11.32 to 2.36 lower)	VERY LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 3 months; Better indicated by lower values) (MID: 0.29)												
1 (Hosseini 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	53	-	MD 22.77 lower (22.92 to 22.62 lower)	HIGH	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 3 months; Better indicated by lower values) (MID: 10.9)												
1 (Kumalic 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 1.40 higher (6.23 lower to 9.03 higher)	MODERATE	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 10 weeks; Better indicated by lower values) (MID: 7.92)												
1 (Martínez-Soto 2016)	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[4]	none	42	32	-	MD 13.70 lower (19.75 to 7.65 lower)	VERY LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 3 months; Better indicated by lower values) (MID: 2.3)												
1 (Mathieu d'Argent 2021)	randomised trials	serious[1]	no serious inconsistency	serious[10]	serious[4]	none	83	79	-	MD 0.90 lower (2.32 lower to 0.52 higher)	VERY LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (SCD) (follow-up 3 months; Better indicated by lower values) (MID: 0.95)												
1 (Maghsoumi-Norouzabad 2022)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	43	43	-	MD 0.09 lower (2.69 lower to 2.51 higher)	LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (SDFA) (follow-up 3 months; Better indicated by lower values) (MID: 0.85)												
1 (Dadgar 2023)	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35	35	-	MD 4.8 lower (5.79 to 3.81 lower)	LOW	IMPORTANT

CI: confidence interval; DNA: deoxyribonucleic acid; IQR: interquartile range; MD: mean difference; MID: minimally important difference; RR: risk ratio; SCD: sperm chromatin dispersion test; SCSA: sperm chromatin structure assay; SDFA: sperm DNA fragmentation assay; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Studies included in analysis of clinical pregnancy: Habibi 2022; Lahimer 2023; Mathieu d'Argent 2021; Steiner 2020; Stenqvist 2018
[4] 95% CI crosses 1 MID
[5] Studies included in analysis of miscarriage: Mathieu d'Argent 2021; Steiner 2020
[6] 95% CI crosses 2 MIDs
[7] Absolute effect calculated based on risk difference
[8] Studies included in analysis of percentage of sperm DNA fragmentation in sperm samples (SCSA): Abbasi 2021; Habibi 2022; Kumar 2011; Patki 2023
[9] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[10] Population is indirect because of 20% of participants with mixed infertility

Table 7: Evidence profile for comparison between post-varicocelectomy antioxidant and post-varicocelectomy placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-varicocelectomy antioxidant**	**Post-varicocelectomy placebo**	**Relative (95% CI)**	**Absolute**		
Percentage of DNA fragmentation in sperm samples (TUNEL) (follow-up 80 days; Better indicated by lower values) (MID: 6.68)												
1 (Abbasi 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 1.88 higher (0.96 lower to 4.72 higher)	LOW	IMPORTANT
Percentage of DNA fragmentation in sperm samples (SCSA) (follow-up 80 days; Better indicated by lower values) (MID: 6.33)												
1 (Abbasi 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 1.92 higher (1.81 lower to 5.65 higher)	LOW	IMPORTANT

CI: confidence interval; DNA: deoxyribonucleic acid; MD: mean difference; MID: minimally important difference; SCSA: sperm chromatin structure assay; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 8: Evidence profile for comparison between post-varicocelectomy antioxidant and no post-varicocelectomy treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-varicocelectomy antioxidant	No post-varicocelectomy treatment	Relative (95% CI)	Absolute		
Clinical pregnancy (denominator: N randomised)												
1 (Barekat 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/20 (25%)	2/20 (10%)	RR 2.5 (0.55 to 11.41)	150 more per 1000 (from 45 fewer to 1000 more)	VERY LOW	CRITICAL
Percentage of DNA integrity in sperm samples (TUNEL) (follow-up 3 months; Better indicated by higher values) (MID: 0.85)												
1 (Barekat 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 3.9 higher (2.93 to 4.87 higher)	LOW	IMPORTANT

CI: confidence interval; DNA: deoxyribonucleic acid; MD: mean difference; RR: risk ratio; MID: minimally important difference; TUNEL: terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate nick-end labelling assay

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] 95% CI crosses 2 MIDs

Table 9: Evidence profile for comparison between testicular sperm retrieval plus ICSI and ICSI (with ejaculated sperm)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Testicular sperm retrieval and ICSI	ICSI (with ejaculated sperm)	Relative (95% CI)	Absolute		
Clinical pregnancy (denominator: N randomised)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/73 (56.2%)	37/72 (51.4%)	RR 1.09 (0.81 to 1.48)	46 more per 1000 (from 98 fewer to 247 more)	LOW	CRITICAL
Miscarriage (denominator: clinical pregnancy)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Testicular sperm retrieval and ICSI	ICSI (with ejaculated sperm)	Relative (95% CI)	Absolute		
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/41 (4.9%)	4/37 (10.8%)	RR 0.45 (0.09 to 2.32)	59 fewer per 1000 (from 98 fewer to 143 more)	VERY LOW	IMPORTANT
Embryo quality/grading (percentage of high-quality blastocysts [graded >3BB]) (Better indicated by higher values) (MID: 15.15)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73	72	-	MD 14.5 lower (24.66 to 4.34 lower)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; ICSI: intracytoplasmic sperm injection; RR: risk ratio

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*

[2] *95% CI crosses 1 MID*

[3] *95% CI crosses 2 MIDs*

Table 10: Evidence profile for comparison between testicular sperm retrieval plus ICSI and PICSI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Testicular sperm retrieval and ICSI	PICSI	Relative (95% CI)	Absolute		
Clinical pregnancy (denominator: N randomised)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/73 (56.2%)	54/78 (69.2%)	RR 0.81 (0.63 to 1.04)	132 fewer per 1000 (from 256 fewer to 28 more)	LOW	CRITICAL
Miscarriage (denominator: clinical pregnancy)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/41 (4.9%)	5/54 (9.3%)	RR 0.53 (0.11 to 2.58)	44 fewer per 1000 (from 82 fewer to 146 more)	VERY LOW	IMPORTANT
Embryo quality/grading (percentage of high-quality blastocysts [graded >3BB]) (Better indicated by higher values) (MID: 15.15)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73	78	-	MD 9 lower (18.68 lower to 0.68 higher)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; ICSI: intracytoplasmic sperm injection; PICSI: physiological intracytoplasmic sperm injection; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] 95% CI crosses 1 MID

[3] 95% CI crosses 2 MIDs

Table 11: Evidence profile for comparison between PICSI versus ICSI (with ejaculated sperm)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICSI	ICSI (with ejaculated sperm)	Relative (95% CI)	Absolute		
Clinical pregnancy (denominator: N randomised)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICSI	ICSI (with ejaculated sperm)	Relative (95% CI)	Absolute		
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/78 (69.2%)	37/72 (51.4%)	RR 1.35 (1.03 to 1.76)	180 more per 1000 (from 15 more to 391 more)	LOW	CRITICAL
Miscarriage (denominator: clinical pregnancy)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/54 (9.3%)	4/37 (10.8%)	RR 0.86 (0.25 to 2.98)	15 fewer per 1000 (from 81 fewer to 214 more)	VERY LOW	IMPORTANT
Embryo quality/grading (percentage of high-quality blastocysts [graded >3BB]) (Better indicated by higher values) (MID: 15.15)												
1 (Hozyen 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78	72	-	MD 5.5 lower (14.9 lower to 3.9 higher)	MODERATE	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; ICSI: intracytoplasmic sperm injection; PICSI: physiological intracytoplasmic sperm injection; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] 95% CI crosses 1 MID

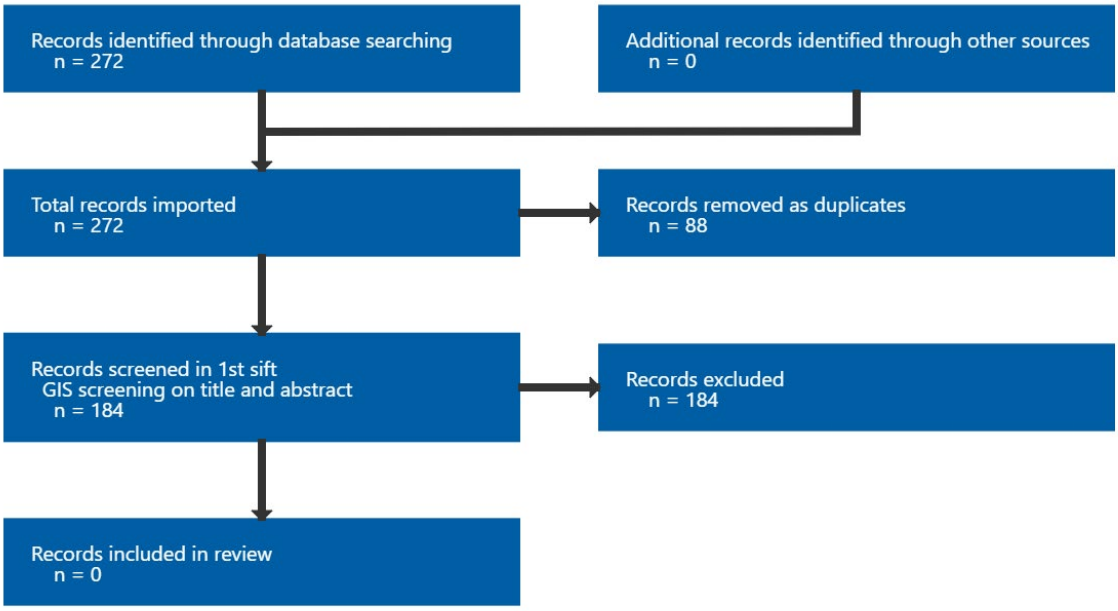
[3] 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

No health economic evidence was identified for this review question.

Figure 5: Study selection flow chart



Appendix H Economic evidence tables

No evidence was identified which was applicable to this review question.

Appendix I Economic model

No health economic modelling was undertaken for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

Excluded effectiveness studies

Table 12: Excluded studies and reasons for their exclusion

Study	Reason
Agarwal, Ashok, Cannarella, Rossella, Saleh, Ramadan et al. (2023) Impact of Antioxidant Therapy on Natural Pregnancy Outcomes and Semen Parameters in Infertile Men: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The world journal of men's health 41(1): 14-48/	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and primary studies that meet our inclusion criteria (e.g., Barekat 2016; Steiner 2020; Stenqvist 2018) are already included in our review*
Agarwal, Ashok, Leisegang, Kristian, Majzoub, Ahmad et al. (2021) Utility of Antioxidants in the Treatment of Male Infertility: Clinical Guidelines Based on a Systematic Review and Analysis of Evidence. The world journal of men's health 39(2): 233-290	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and primary studies that meet our inclusion criteria (e.g., Stenqvist 2018) are already included in our review*
Agarwal, Ashok and Sekhon, Lucky H (2010) The role of antioxidant therapy in the treatment of male infertility. Human fertility (Cambridge, England) 13(4): 217-25	- Study design not in PICO *Narrative review*
Agarwal, Ashok, Sharma, Rakesh K, Desai, Nisarg R et al. (2009) Role of oxidative stress in pathogenesis of varicocele and infertility. Urology 73(3): 461-9	- Study design not in PICO *Narrative review*
Aghajani, Mir Mohammad Reza, Mahjoub, Soleiman, Mojab, Faraz et al. (2021) Comparison of the Effect of Ceratonia siliqua L. (Carob) Syrup and Vitamin E on Sperm Parameters, Oxidative Stress Index, and Sex Hormones in Infertile Men: a Randomized Controlled Trial. Reproductive sciences (Thousand Oaks, Calif.) 28(3): 766-774	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Akbari, Hakimeh, Elyasi, Leila, Khaleghi, Ali Asghar et al. (2023) The effect of zinc supplementation on improving sperm parameters in infertile diabetic men. Journal of obstetrics and gynaecology of India 73(4): 316-321	- Data cannot be extracted
Akhavan Rezayat, Alireza, Soleimanian, Amirmohammad, Kamandi, Neda et al. (2023) Semen's parameters after varicocelectomy surgery with mast cell stabilizers treatment in	- Comparison not in PICO *Varicocelectomy vs. Ketotifen vs. Varicocelectomy plus Ketotifen*

Study	Reason
infertile varicocele patients: Randomized clinical trial study. Health science reports 6(7): e1431	
Alahmar, A.T. (2017) Effect of vitamin C, vitamin E, zinc, selenium, and coenzyme Q10 in infertile men with idiopathic oligoasthenozoospermia. International Journal of Infertility and Fetal Medicine 8(2): 45-49	- Study design not in PICO
Alahmar, Ahmed T and Sengupta, Pallav (2021) Impact of Coenzyme Q10 and Selenium on Seminal Fluid Parameters and Antioxidant Status in Men with Idiopathic Infertility. Biological trace element research 199(4): 1246-1252	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Alahmar, Ahmed T and Singh, Rajender (2022) Comparison of the effects of coenzyme Q10 and Centrum multivitamins on semen parameters, oxidative stress markers, and sperm DNA fragmentation in infertile men with idiopathic oligoasthenospermia. Clinical and experimental reproductive medicine 49(1): 49-56	- Comparison not in PICO *Comparison between CoQ10 and Centrum multivitamins*
Alizadeh, Fatemeh, Javadi, Maryam, Karami, Ali Akbar et al. (2018) Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: A randomized clinical trial. Phytotherapy research : PTR 32(3): 514-521	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Ambar, Rafael F, Agarwal, Ashok, Majzoub, Ahmad et al. (2021) The Use of Testicular Sperm for Intracytoplasmic Sperm Injection in Patients with High Sperm DNA Damage: A Systematic Review. The world journal of men's health 39(3): 391-398	- Systematic review, included studies checked for relevance *Systematic review of observational studies and case-crossover studies*
Arhin, S.K., Ocansey, S., Barnes, P. et al. (2021) Efficacy of combined antioxidant therapy in male subfertility-A systematic review and meta-analysis. Cellular and Molecular Biology 67(4): 239-247	- Systematic review, included studies checked for relevance *Included participants without DNA fragmentation*
Asr Badr, Y.A., Sepehran, E., Del Azar, A. et al. (2017) The effect of saffron on semen analysis in infertile men with clinical varicocele after varicocelectomy. Nephro-Urology Monthly 9(5): e59939	- Population not in PICO *Population without sperm DNA fragmentation and outcomes not of interest for review*
Awaga, Hatem A, Bosdou, Julia K, Goulis, Dimitrios G et al. (2018) Testicular versus ejaculated spermatozoa for ICSI in patients without azoospermia: A systematic review. Reproductive biomedicine online 37(5): 573-580	- Systematic review, included studies checked for relevance *Included RCT did not specify whether participants had sperm DNA fragmentation because DNA fragmentation at baseline or at the end of the study was not reported*

Study	Reason
Azadi, L, Abbasi, H, Deemeh, M R et al. (2011) Zaditen (Ketotifen), as mast cell blocker, improves sperm quality, chromatin integrity and pregnancy rate after varicocelectomy. International journal of andrology 34(5pt1): 446-52	- Comparison not in PICO *Ketotifen vs. No intervention*
Baazeem, Abdulaziz, Belzile, Eric, Ciampi, Antonio et al. (2011) Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. European urology 60(4): 796-808	- Systematic review, included studies checked for relevance *Systematic review of before-and-after studies*
Bahmyari, R., Ariafar, A., Sayadi, M. et al. (2021) The effect of daily intake of selenium, vitamin E and folic acid on sperm parameters in males with idiopathic infertility: A single-blind randomized controlled clinical trial. International Journal of Fertility and Sterility 15(1): 8-14	- Population not in PICO *Population without sperm DNA fragmentation and outcomes not of interest for review*
Bahmyari, Rezvan, Zare, Morteza, Sharma, Rakesh et al. (2020) The efficacy of antioxidants in sperm parameters and production of reactive oxygen species levels during the freeze-thaw process: A systematic review and meta-analysis. Andrologia 52(3): e13514	- Systematic review, included studies checked for relevance *Included studies with fertile men*
Banks, Nicole, Sun, Fangbai, Krawetz, Stephen A et al. (2021) Male vitamin D status and male factor infertility. Fertility and sterility 116(4): 973-979	- Secondary analysis of included study *Secondary analysis of a study, and no additional information provided*
Barbagallo, F., Cannarella, R., Crafa, A. et al. (2022) The Impact of a Very Short Abstinence Period on Conventional Sperm Parameters and Sperm DNA Fragmentation: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine 11(24): 7303	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Barbonetti, Arcangelo, Tienforti, Daniele, Castellini, Chiara et al. (2024) Effect of antioxidants on semen parameters in men with oligo-astheno-teratozoospermia: a network meta-analysis. Andrology 12(3): 538-552	- Systematic review, included studies checked for relevance *Systematic review of RCT, but unclear whether participants had sperm DNA fragmentation because DNA fragmentation at baseline or at the end of the study was not reported*
Birowo, Ponco, Rahendra Wijaya, J, Atmoko, Widi et al. (2020) The effects of varicocelectomy on the DNA fragmentation index and other sperm parameters: a meta-analysis. Basic and clinical andrology 30: 15	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Boonyarangkul, Arthit, Vinayanuvattikhun, Nipattha, Chiamchanya, Charoenchai et al. (2015) Comparative Study of the Effects of Tamoxifen Citrate and Folate on Semen Quality of the Infertile Male with Semen Abnormality.	- Outcome not in PICO *DNA tail length rather than % of sperm DNA fragmentation reported*

Study	Reason
Journal of the Medical Association of Thailand = Chotmaihet thangphaet 98(11): 1057-63	
Bozhedomov, VA, Epanchintseva, EA, Bozhe-Domova, GE et al. (2021) Hydrophilic and lipophilic nutrients for the treatment of male idiopathic infertility: a randomized, comparative, open-label, multicenter, prospective, controlled study. Urologiia (Moscow, Russia : 1999): 70-78	- Study not reported in English
Busetto, G M, Agarwal, A, Virmani, A et al. (2018) Effect of metabolic and antioxidant supplementation on sperm parameters in oligo-astheno-teratozoospermia, with and without varicocele: A double-blind placebo-controlled study. Andrologia 50(3)	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Busetto, Gian Maria, Del Giudice, Francesco, Virmani, Ashraf et al. (2020) Body mass index and age correlate with antioxidant supplementation effects on sperm quality: Post hoc analyses from a double-blind placebo-controlled trial. Andrologia 52(3): e13523	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Busetto, Gian Maria, Rodrigues, Bernarde F, Virmani, Ashraf et al. (2024) Antioxidant treatment for oligoasthenoteratozoospermia and varicocele: a DBPC trial to evaluate the impact of age and body mass index. Asian journal of andrology	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Cannarella, Rossella, Shah, Rupin, Saleh, Ramadan et al. (2024) Effects of Varicocele Repair on Sperm DNA Fragmentation and Seminal Malondialdehyde Levels in Infertile Men with Clinical Varicocele: A Systematic Review and Meta-Analysis. The world journal of men's health 42(2): 321-337	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Check, J H, Bollendorf, A, Summers-Chase, D et al. (2013) Isolating sperm by selecting those with normal nuclear morphology prior to intracytoplasmic sperm injection (ICSI) does not provide better pregnancy rates compared to conventional ICSI in women with repeated conception failure with in vitro fertilization. Clinical and experimental obstetrics & gynecology 40(1): 15-7	- Comparison not in PICO *High magnification ICSI vs. Conventional ICSI*
Chen, X, Sun, ZX, Zhao, SP et al. (2020) Yishen Tongluo Recipe combined with minimally invasive surgery for the treatment of varicocele-associated asthenospermia. Zhonghua nan ke xue [National journal of andrology] 26(4): 341-345	- Study not reported in English
Cheng, JB, Zhu, J, Ni, F et al. (2018) L-carnitine combined with coenzyme Q10 for idiopathic	- Study not reported in English

Study	Reason
oligoasthenozoospermia: a double-blind randomized controlled trial. Zhonghua nan ke xue [National journal of andrology] 24(1): 33-38	
Ciftci, Halil, Verit, Ayhan, Savas, Murat et al. (2009) Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology 74(1): 73-6	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Condorelli, Rosita A, Cannarella, Rossella, Crafa, Andrea et al. (2022) Advances in non-hormonal pharmacotherapy for the treatment of male infertility: the role of inositols. Expert opinion on pharmacotherapy 23(9): 1081-1090	- Study design not in PICO *Narrative review*
Cui, Xiangrong, Jing, Xuan, Wu, Xueqing et al. (2016) Protective effect of resveratrol on spermatozoa function in male infertility induced by excess weight and obesity. Molecular medicine reports 14(5): 4659-4665	- Comparison not in PICO *Quinn's Advantage™ Fertilization Medium vs. Quinn's Advantage™ Fertilization Medium plus 0.1% dimethyl sulfoxide vs. Resveratrol added to the medium*
da Silva, T.M., Maia, M.C.S., Arruda, J.T. et al. (2013) Folic acid does not improve semen parametrs in subfertile men: A double-blin, randomized, placebo-controlled study. Jornal Brasileiro de Reproducao Assistida 17(3): 152-157	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study. Outcomes not of interest for review.*
de Ligny, Wiep, Smits, Roos M, Mackenzie-Proctor, Rebecca et al. (2022) Antioxidants for male subfertility. The Cochrane database of systematic reviews 5: cd007411	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and primary studies that meet our inclusion criteria (e.g., Steiner 2020; Stenqvist 2018) are already included in our review*
De Rosa, Michele, Boggia, Bartolomeo, Amalfi, Biagio et al. (2005) Correlation between seminal carnitine and functional spermatozoal characteristics in men with semen dysfunction of various origins. Drugs in R&D 6(1): 1-9	- Study design not in PICO *Observational study and non-randomised study (before-and-after study was conducted in a subgroup)*
Di Renzo, Laura, De Lorenzo, Antonino, Fontanari, Marco et al. (2022) Immunonutrients involved in the regulation of the inflammatory and oxidative processes: implication for gamete competence. Journal of assisted reproduction and genetics 39(4): 817-846	- Systematic review, included studies checked for relevance *Umbrella review included narrative reviews or review of female sub-fertility*
Dimitriadis, Fotios, Symeonidis, Evangelos N, Tsounapi, Panagiota et al. (2021) Administration of Antioxidants in Infertile Male: When it may have a Detrimental Effect?. Current pharmaceutical design 27(24): 2796-2801	- Study design not in PICO *Narrative review*
Dimitriadis, Fotios, Tsounapi, Panagiota, Zachariou, Athanasios et al. (2021) Therapeutic Effects of Micronutrient Supplements on Sperm	- Study design not in PICO *Narrative review*

Study	Reason
Parameters: Fact or Fiction?. Current pharmaceutical design 27(24): 2757-2769	
Durg, Sharanbasappa; Shivaram, Shivakumar Badamaranahalli; Bavage, Sachin (2018) Withania somnifera (Indian ginseng) in male infertility: An evidence-based systematic review and meta-analysis. Phytomedicine : international journal of phytotherapy and phytopharmacology 50: 247-256	- Systematic review, included studies checked for relevance *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Ener K, Aldemir M, I¸sık E et al. (2016) The impact of vitamin E supplementation on semen parameters and pregnancy rates after varicocelectomy: A randomised controlled study. Andrologia 48: 829–834	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Eslamian, Ghazaleh, Amirjannati, Naser, Noori, Nazanin et al. (2020) Effects of coadministration of DHA and vitamin E on spermatogram, seminal oxidative stress, and sperm phospholipids in asthenozoospermic men: a randomized controlled trial. The American journal of clinical nutrition 112(3): 707-719	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study. Outcomes not of interest for review*
Esteves, Sandro C, Roque, Matheus, Bradley, Cara K et al. (2017) Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmentation in semen: systematic review and meta-analysis. Fertility and sterility 108(3): 456-467e1	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Esteves, Sandro C; Santi, Daniele; Simoni, Manuela (2020) An update on clinical and surgical interventions to reduce sperm DNA fragmentation in infertile men. Andrology 8(1): 53-81	- Study design not in PICO *Narrative review*
Fan, Q, Chang, FJ, Xue, JG et al. (2022) Efficacy of Jujing Decoction combined with lipoic acid in the treatment of asthenospermia and teratospermia. Zhonghua nan ke xue [National journal of andrology] 28(2): 157-161	- Study not reported in English
Fathi, Atef, Mohamed, Omar, Mahmoud, Osama et al. (2021) The impact of varicocelectomy on sperm DNA fragmentation and pregnancy rate in subfertile men with normal semen parameters: A pilot study. Arab journal of urology 19(2): 186-190	- Study design not in PICO *Non-RCT and no matching or control for confounding variables between groups*
Ficarra, Vincenzo, Crestani, Alessandro, Novara, Giacomo et al. (2012) Varicocele repair for infertility: what is the evidence?. Current opinion in urology 22(6): 489-94	- Study design not in PICO *Narrative review*

Study	Reason
Gamidov, SI; Ovchinnikov, RI; Popova, AY (2019) Double-blind, randomized placebo-controlled study of efficiency and safety of complex acetyl-L-carnitine, L-carnitine fumarate and alpha-lipoic acid (Spermactin Forte) for treatment of male infertility. Urologiia (Moscow, Russia : 1999): 62-68	- Study not reported in English
Gamidov, SI, Ovchinnikov, RI, Popova, AY et al. (2017) Adjuvant antioxidant therapy in varicocele infertility. Urologiia (Moscow, Russia : 1999): 64-72	- Study not reported in English
Garolla, A., Petre, G.C., Francini-Pesenti, F. et al. (2022) Systematic Review and Critical Analysis on Dietary Supplements for Male Infertility: From a Blend of Ingredients to a Rationale Strategy. Frontiers in Endocrinology 12: 824078	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and identified a study (Martinez-Soto 2016) that might meet our inclusion criteria and was not picked up by our search, so that study was now added manually*
Ghafarizadeh, Aliasghar, Malmir, Mahdi, Naderi Noreini, Samira et al. (2021) Antioxidant effects of N-acetylcysteine on the male reproductive system: A systematic review. Andrologia 53(1): e13898	- Study design not in PICO *Narrative review*
Giulioni, Carlo, Maurizi, Valentina, Castellani, Daniele et al. (2022) The environmental and occupational influence of pesticides on male fertility: A systematic review of human studies. Andrology 10(7): 1250-1271	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Gonzalez-Ravina, Cristina, Aguirre-Lipperheide, Mercedes, Pinto, Francisco et al. (2018) Effect of dietary supplementation with a highly pure and concentrated docosahexaenoic acid (DHA) supplement on human sperm function. Reproductive biology 18(3): 282-288	- Data cannot be extracted *No measure of variance reported for DNA fragmentation*
Gual-Frau, Josep, Abad, Carlos, Amengual, Maria J et al. (2015) Oral antioxidant treatment partly improves integrity of human sperm DNA in infertile grade I varicocele patients. Human fertility (Cambridge, England) 18(3): 225-9	- Study design not in PICO *Before-and-after study (non-randomised study)*
Guo, Li, Jing, Jun, Feng, Yu-Ming et al. (2015) Tamoxifen is a potent antioxidant modulator for sperm quality in patients with idiopathic oligoasthenospermia. International urology and nephrology 47(9): 1463-9	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Haghighian, Hossein Khadem, Haidari, Fatemeh, Mohammadi-Asl, Javad et al. (2015) Randomized, triple-blind, placebo-controlled clinical trial examining the effects of alpha-lipoic acid supplement on the spermatogram and	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study. Outcomes not of interest for review*

Study	Reason
seminal oxidative stress in infertile men. Fertility and sterility 104(2): 318-24	
Hajizadeh Maleki, Behzad and Tartibian, Bakhtyar (2020) High-intensity interval training modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A randomized controlled trial. Cytokine 125: 154861	- Retracted article
Hajizadeh Maleki, Behzad and Tartibian, Bakhtyar (2017) Moderate aerobic exercise training for improving reproductive function in infertile patients: A randomized controlled trial. Cytokine 92: 55-67	- Retracted article
Hajizadeh Maleki, Behzad and Tartibian, Bakhtyar (2018) Resistance exercise modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A RCT. Life sciences 203: 150-160	- Data cannot be extracted *Percentage of DNA fragmentation at baseline not reported in the text or tables, so unable to interpret whether participants had high DNA fragmentation*
Hajizadeh Maleki, Behzad and Tartibian, Bakhtyar (2017) Combined aerobic and resistance exercise training for improving reproductive function in infertile men: a randomized controlled trial. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 42(12): 1293-1306	- Data cannot be extracted *Percentage of DNA fragmentation at baseline not reported in the text or tables, so unable to interpret whether participants had high DNA fragmentation*
Hajizadeh Maleki, Behzad; Tartibian, Bakhtyar; Chehrazi, Mohammad (2022) Effectiveness of Exercise Training on Male Factor Infertility: A Systematic Review and Network Meta-analysis. Sports health 14(4): 508-517	- Systematic review, included studies checked for relevance *Included studies checked for relevance*
Halpern, Joshua A and Schlegel, Peter N (2018) Should A Couple with Failed In Vitro Fertilization/Intracytoplasmic Sperm Injection and Increased Sperm DNA Fragmentation Use Testicular Sperm for the Next Cycle?. European urology focus 4(3): 299-300	- Study design not in PICO *Narrative review*
Hanson, Brent M, Aston, Kenneth I, Jenkins, Tim G et al. (2018) The impact of ejaculatory abstinence on semen analysis parameters: a systematic review. Journal of assisted reproduction and genetics 35(2): 213-220	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and identified a study (Sanchez-Martin 2013) that might meet our inclusion criteria but was not picked up by our search, so that study was now added manually*
Hasanen, Eman, Elqusi, Khaled, ElTanbouly, Salma et al. (2020) PICSI vs. MACS for abnormal sperm DNA fragmentation ICSI cases: a prospective randomized trial. Journal of assisted reproduction and genetics 37(10): 2605-2613	- Comparison not in PICO *Physiological intracytoplasmic sperm injection (PICSI) vs. Magnetic activated cell sorting (MACS)*

Study	Reason
Helli, Bijan, Kavianpour, Maria, Ghaedi, Ehsan et al. (2022) Probiotic effects on sperm parameters, oxidative stress index, inflammatory factors and sex hormones in infertile men. Human fertility (Cambridge, England) 25(3): 499-507	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study. Outcomes not of interest for review*
Henriques, Magda Carvalho, Loureiro, Susana, Fardilha, Margarida et al. (2019) Exposure to mercury and human reproductive health: A systematic review. Reproductive toxicology (Elmsford, N.Y.) 85: 93-103	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Hua, Z, Chen, RB, Wang, C et al. (2020) Luobufukebiri Pills improve semen quality and seminal plasma-related biochemical indexes in patients with asthenospermia. Zhonghua nan ke xue [National journal of andrology] 26(11): 1020-1024	- Study not reported in English
Huang, Wen-Jie, Lu, Xi-Lan, Li, Jun-Tao et al. (2020) Effects of folic acid on oligozoospermia with MTHFR polymorphisms in term of seminal parameters, DNA fragmentation, and live birth rate: a double-blind, randomized, placebo-controlled trial. Andrology 8(1): 110-116	- Data cannot be extracted *Data cannot be extracted as participants can be in more than 1 genotype group so not possible to calculate a combined mean for DNA fragmentation*
Javadi, M, Gholaminejad, F, Haghighian, HK et al. (2018) Effect of propolis oral supplements on sperm parameters and oxidative stress indicator in idiopathic infertile men: a double-blind randomized clinical trial. Iranian journal of obstetrics, gynecology and infertility 21(8)	- Study not reported in English
Jin, B, Huang, Y, Xia, X et al. (2006) Effect of Yangjing capsule and Xinxibao on sperm DNA integrity of patients with male infertility. Chinese journal of andrology 20(12): 45-49	- Study not reported in English
Joseph, Treasa, Mascarenhas, Mariano, Karuppusami, Reka et al. (2020) Antioxidant pretreatment for male partner before ART for male factor subfertility: a randomized controlled trial. Human reproduction open 2020(4): hoaa050	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Kabukcu, Cihan, Cil, Nazli, Cabus, Umit et al. (2021) Effect of ejaculatory abstinence period on sperm DNA fragmentation and pregnancy outcome of intrauterine insemination cycles: A prospective randomized study. Archives of gynecology and obstetrics 303(1): 269-278	- Population not in PICO *Unclear whether participants had male factor infertility*
Kallinikas, Georgios, Tsoporis, James N, Haronis, Georgios et al. (2024) The role of oral antioxidants in the improvement of sperm parameters in infertile men. World journal of urology 42(1): 71	- Study design not in PICO *Narrative review*

Study	Reason
Keskes-Ammar, L, Feki-Chakroun, N, Rebai, T et al. (2003) Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. Archives of andrology 49(2): 83-94	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Khaw, Shen Chuen, Wong, Zhen Zhe, Anderson, Richard et al. (2020) l-carnitine and l-acetylcarnitine supplementation for idiopathic male infertility. Reproduction & fertility 1(1): 67-81	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Khoo, Christopher C, Cayetano-Alcaraz, Axel Alberto, Rashid, Razi et al. (2023) Does Testicular Sperm Improve Intracytoplasmic Sperm Injection Outcomes for Nonazoospermic Infertile Men with Elevated Sperm DNA Fragmentation? A Systematic Review and Meta-analysis. European urology focus	- Systematic review, included studies checked for relevance *Systematic review of prospective or retrospective cohort studies and case crossover trials*
Kirkman-Brown, Jackson, Pavitt, Sue, Khalaf, Yacoub et al. (2019) Sperm selection for assisted reproduction by prior hyaluronan binding: the HABSelect RCT.	- Data cannot be extracted *Only 39% of participants had sperm DNA fragment assessment, and the data on relevant outcomes not reported for this group separately*
Knez, K., Tomazevic, T., Zorn, B. et al. (2012) Intracytoplasmic morphologically selected sperm injection improves development and quality of preimplantation embryos in teratozoospermia patients. Reproductive BioMedicine Online 25(2): 168-179	- Comparison not in PICO *Intracytoplasmic morphologically selected sperm injection vs. Conventional ICSI*
Knudtson, Jennifer F, Sun, Fangbai, Coward, R Matthew et al. (2021) The relationship of plasma antioxidant levels to semen parameters: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. Journal of assisted reproduction and genetics 38(11): 3005-3013	- Outcome not in PICO *Relationship between serum antioxidant levels and semen parameters reported (secondary analysis of RCT)*
Kopa, Zsolt; Keszthelyi, Marton; Sofikitis, Nikolaos (2021) Administration of Antioxidants in the Infertile Male: When it may have a Beneficial Effect?. Current pharmaceutical design 27(23): 2665-2668	- Study design not in PICO *Narrative review*
Kuchakulla, M. and Ramasamy, R. (2021) Re: The Effect of Antioxidants on Male Factor Infertility: The Males, Antioxidants, and Infertility (MOXI) Randomized Clinical Trial. European Urology 79(1): 159-160	- Study design not in PICO *Comments on a study*
Kumar, S.; Sharma, A.; Sedha, S. (2022) Occupational and environmental mercury exposure and human reproductive health-a review. Journal of the Turkish German Gynecology Association 23(3): 199-210	- Study design not in PICO *Narrative review*

Study	Reason
Kuzmenko, AV; Kuzmenko, VV; Gyaurgiev, TA (2018) The effectiveness of the Speroton complex in the management of male factor infertility. Urologiia (Moscow, Russia : 1999): 78-82	- Study not reported in English
Kızılay F and Altay B (2019) Evaluation of the effects of antioxidant treatment on sperm parameters and pregnancy rates in infertile patients after varicocelectomy: A randomized controlled trial. Int. J. Impot. Res. 31: 424–431	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Lafuente, Rafael, Gonzalez-Comadran, Mireia, Sola, Ivan et al. (2013) Coenzyme Q10 and male infertility: a meta-analysis. Journal of assisted reproduction and genetics 30(9): 1147-56	- Systematic review, included studies checked for relevance *Systematic review of RCTs, but unclear whether participants had sperm DNA fragmentation because DNA fragmentation at baseline or at the end of the study was not reported*
Lanzafame, Francesco M, La Vignera, Sandro, Vicari, Enzo et al. (2009) Oxidative stress and medical antioxidant treatment in male infertility. Reproductive biomedicine online 19(5): 638-59	- Study design not in PICO *Narrative review*
Leandri, R D, Gachet, A, Pfeffer, J et al. (2013) Is intracytoplasmic morphologically selected sperm injection (IMSI) beneficial in the first ART cycle? a multicentric randomized controlled trial. Andrology 1(5): 692-7	- Comparison not in PICO *IMSI vs. conventional ICSI*
Li, B, Shen, YH, Wang, GJ et al. (2022) "Water-pathogen" theory-based Juanyin Tongluo Recipe for varicocele complicated with oligozoospermia: a clinical observation. Zhonghua nan ke xue [National journal of andrology] 28(6): 524-528	- Study not reported in English
Liang, M, Yang, HL, Meng, FW et al. (2023) Compound Amino Acid Capsule (8-11) combined with L-carnitine for the treatment of asthenospermia. Zhonghua nan ke xue [National journal of andrology] 29(3): 233-238	- Study not reported in English
Lira Neto, Filipe Tenorio; Roque, Matheus; Esteves, Sandro C (2021) Effect of varicocelectomy on sperm deoxyribonucleic acid fragmentation rates in infertile men with clinical varicocele: a systematic review and meta-analysis. Fertility and sterility 116(3): 696-712	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Lo Giudice, Arturo, Asmundo, Maria Giovanna, Cimino, Sebastiano et al. (2024) Effects of long and short ejaculatory abstinence on sperm parameters: a meta-analysis of randomized-controlled trials. Frontiers in endocrinology 15: 1373426	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and identified a study (Martinez-Soto 2016) that might meet our inclusion criteria and was not picked up by our search, so that study was now added manually*

Study	Reason
Lu, X-L, Liu, J-J, Li, J-T et al. (2018) Melatonin therapy adds extra benefit to varicecelectomy in terms of sperm parameters, hormonal profile and total antioxidant capacity: A placebo-controlled, double-blind trial. Andrologia 50(6): e13033	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Mahdiani, E, Khadem Haghighian, H, Javadi, M et al. (2018) Effect of carob (Ceratonia siliqua L.) oral supplementation on changes of semen parameters, oxidative stress, inflammatory biomarkers and reproductive hormones in infertile men. Scientific journal of kurdistan university of medical sciences 23(3): 56-66	- Study not reported in English
Majzoub, Ahmad and Agarwal, Ashok (2018) Systematic review of antioxidant types and doses in male infertility: Benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate. Arab journal of urology 16(1): 113-124	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Maleki, Behzad Hajizadeh and Tartibian, Bakhtyar (2017) High-Intensity Exercise Training for Improving Reproductive Function in Infertile Patients: A Randomized Controlled Trial. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 39(7): 545-558	- Data cannot be extracted *Numerical data were not reported*
Malmir, Mahdi, Naderi Noreini, Samira, Ghafarizadeh, Aliasghar et al. (2021) Ameliorative effect of melatonin on apoptosis, DNA fragmentation, membrane integrity and lipid peroxidation of spermatozoa in the idiopathic asthenoteratospermic men: In vitro. Andrologia 53(2): e13944	- Study design not in PICO *In vitro study*
Mantravadi, Krishna Chaitanya and Rao, Durga (2024) In cases with raised sperm DNA fragmentation, can sperm selection by magnetic-activated cell sorting or testicular sperm aspiration help improve reproductive outcomes?. Journal of assisted reproduction and genetics	- Comparison not in PICO *Testicular sperm retrieval vs. Magnetic-activated cell sorting*
Margiana, R., Lestari, S.W., Muharam et al. (2020) Suitable diet with anti-oxidant food have a good effect to embryo quality resulting from assisted reproductive technology and the increase of sperm quality of infertile male especially with asthenozoospermia. International Journal of Research in Pharmaceutical Sciences 11(3): 3595-3600	- Study design not in PICO *Narrative review*
Martinez, Maria Angeles, Marques, Montse, Salas-Huetos, Albert et al. (2023) Lack of association between endocrine disrupting	- Systematic review, included studies checked for relevance *Systematic review of observational studies*

Study	Reason
chemicals and male fertility: A systematic review and meta-analysis. Environmental research 217: 114942	
Mauri, Ana L, Petersen, Claudia G, Oliveira, Joao Batista A et al. (2010) Comparison of day 2 embryo quality after conventional ICSI versus intracytoplasmic morphologically selected sperm injection (IMSI) using sibling oocytes. European journal of obstetrics, gynecology, and reproductive biology 150(1): 42-6	- Comparison not in PICO *Intracytoplasmic morphologically selected sperm injection (IMSI) vs. Conventional ICSI*
Mei, Jie, Chen, Lin-Jun, Zhu, Xin-Xin et al. (2022) Magnetic-activated cell sorting of nonapoptotic spermatozoa with a high DNA fragmentation index improves the live birth rate and decreases transfer cycles of IVF/ICSI. Asian journal of andrology 24(4): 367-372	- Comparison not in PICO *Magnetic-activated cell sorting vs. Standard technique*
Miller, David, Pavitt, Susan, Sharma, Vinay et al. (2019) Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect): a parallel, two-group, randomised trial. Lancet (London, England) 393(10170): 416-422	- Population not in PICO *Unclear whether participants had male factor infertility*
Mirsanei, Jamileh Sadat, Sheibak, Nadia, Zandieh, Zahra et al. (2022) Microfluidic chips as a method for sperm selection improve fertilization rate in couples with fertilization failure. Archives of gynecology and obstetrics 306(3): 901-910	- Comparison not in PICO *Microfluidic chips vs. Conventional density gradient centrifugation technique*
Mongaut, Ana Laura, Zavaleta, Christabell, Lopez, Gemma et al. (2011) Use of high-magnification microscopy for the assessment of sperm recovered after two different sperm processing methods. Fertility and sterility 95(1): 277-80	- Comparison not in PICO *Density-gradient centrifugation vs. Swim-up method*
Mora-Esteves, Cesar and Shin, David (2013) Nutrient supplementation: improving male fertility fourfold. Seminars in reproductive medicine 31(4): 293-300	- Study design not in PICO *Narrative review*
Moskovtsev, Sergey I, Jarvi, Keith, Mullen, J Brendan M et al. (2010) Testicular spermatozoa have statistically significantly lower DNA damage compared with ejaculated spermatozoa in patients with unsuccessful oral antioxidant treatment. Fertility and sterility 93(4): 1142-6	- Study design not in PICO *Observational study*
Mu, YY, Hua, QX, Yao, B et al. (2019) Effect on sperm quality of asthenospermia and oligospermia treated with grain-moxibustion combined with medicine therapy. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 39(8): 843-848	- Study not reported in English

Study	Reason
Nada, E A, El Taieb, M A, Ibrahim, H M et al. (2015) Efficacy of tamoxifen and l-carnitine on sperm ultrastructure and seminal oxidative stress in patients with idiopathic oligoasthenoteratozoospermia. Andrologia 47(7): 801-10	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Nadjarzadeh, A, Sadeghi, M R, Amirjannati, N et al. (2011) Coenzyme Q10 improves seminal oxidative defense but does not affect on semen parameters in idiopathic oligoasthenoteratozoospermia: a randomized double-blind, placebo controlled trial. Journal of endocrinological investigation 34(8): e224-8	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Nadjarzadeh, A, Shidfar, F, Amirjannati, N et al. (2014) Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial. Andrologia 46(2): 177-83	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Nasr Esfahani, Mohammad Hossein, Deemeh, Mohammad Reza, Tavalaee, Marziyeh et al. (2016) Zeta Sperm Selection Improves Pregnancy Rate and Alters Sex Ratio in Male Factor Infertility Patients: A Double-Blind, Randomized Clinical Trial. International journal of fertility & sterility 10(2): 253-60	- Comparison not in PICO *Density gradient centrifugation vs. Density gradient centrifugation/Zeta procedure*
Neimark A, Neimark B, Davydov A et al. (2018) Rehabilitation of patients with male infertility after varicocelectomy. Eff. Pharmacother: 8–12	- Study not reported in English
Nematollahi-Mahani, S N, Azizollahi, G H, Baneshi, M R et al. (2014) Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy. Andrologia 46(3): 240-5	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Niederberger, Craig (2016) Re: Randomized, Triple-Blind, Placebo-Controlled Clinical Trial Examining the Effects of Alpha-Lipoic Acid Supplement on the Spermatogram and Seminal Oxidative Stress in Infertile Men. The Journal of urology 195(4pt1): 1076	- Study design not in PICO *Editorial comment on a study*
Noegroho, Bambang Sasongko; Siregar, Safendra; Tampubolon, Kevin Anthony Glorius (2022) Antioxidant Supplementation on Sperm DNA Fragmentation and Sperm Parameters: A Systematic Review and Meta-Analysis. Turkish journal of urology 48(5): 375-384	- Systematic review, included studies checked for relevance *Included studies checked for relevance*
Noorimotlagh, Zahra, Haghighi, Neemat Jaafarzadeh, Ahmadimoghadam, Mehdi et al. (2017) An updated systematic review on the possible effect of nonylphenol on male fertility.	- Systematic review, included studies checked for relevance *Systematic review of observational study and preclinical studies*

Study	Reason
Environmental science and pollution research international 24(4): 3298-3314	
Oliveira, Licia Cristina Silva de Lima, Costa, Elton Carvalho, Martins, Fernanda Domingues Gomes et al. (2024) Probiotics supplementation in the treatment of male infertility: A Systematic Review. JBRA assisted reproduction 28(2): 341-348	- Systematic review, included studies checked for relevance *Systematic review of before-and-after studies*
Omu, A E, Al-Azemi, M K, Kehinde, E O et al. (2008) Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Medical principles and practice : international journal of the Kuwait University, Health Science Centre 17(2): 108-16	- Data cannot be extracted *Percentage of sperm DNA fragmentation was not reported*
Ozaltin, S., Celik, H.G., Kocyigit, Y. et al. (2023) Comparison of Reproductive Outcomes in ICSI Cycles Using Sperm Chip Technique and Density Gradient Technique in Men with Normal Semen Analysis. Clinical and Experimental Obstetrics and Gynecology 50(3): a46	- Comparison not in PICO *Density gradient technique vs. Sperm chip technique*
Pan, Z.; Deng, N.; Zou, Z. (2016) Clinical observation of effect of diosmin combined with Jinshuibao capsule treatment on improvement of semen quality in patients with varicocele. Medical Science Technology 57: 42-46	- Comparison not in PICO *Diosmin plus Jinshiubao plus Zinc selenium vs. Zinc selenium vs. Jinshuibao plus Zinc selenium*
Paradiso Galatioto, G., Gravina, G.L., Angelozzi, G. et al. (2008) May antioxidant therapy improve sperm parameters of men with persistent oligospermia after retrograde embolization for varicocele?. World Journal of Urology 26(1): 97-102	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Parmegiani, Lodovico, Cognigni, Graciela Estela, Bernardi, Silvia et al. (2010) "Physiologic ICSI": hyaluronic acid (HA) favors selection of spermatozoa without DNA fragmentation and with normal nucleus, resulting in improvement of embryo quality. Fertility and sterility 93(2): 598-604	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study (This paper included 3 studies: 2 non-randomised trials and 1 randomised trial. Unclear whether participants included in randomised trial had DNA fragmentation)*
Pawłowicz, P, Stachowiak, G, Bielak, A et al. (2001) Administration of natural anthocyanins derived from chokeberry (aronia melanocarpa) extract in the treatment of oligospermia in males with enhanced autoantibodies to oxidized low density lipoproteins (oLAB). The impact on fructose levels. Ginekologia polska 72(12): 983-988	- Study not reported in English
Perrin, A., Nguyen, M.H., Douet-Guilbert, N. et al. (2013) Intracytoplasmic morphologically selected sperm injection or intracytoplasmic	- Study design not in PICO *Narrative review*

Study	Reason
sperm injection: Where are we 12 years later?. Expert Review of Obstetrics and Gynecology 8(3): 261-270	
Pizzol, Damiano, Foresta, Carlo, Garolla, Andrea et al. (2021) Pollutants and sperm quality: a systematic review and meta-analysis. Environmental science and pollution research international 28(4): 4095-4103	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Pourmand G, Movahedin M, Dehghani S et al. (2014) Does anti-oxidant therapy add any extra benefit to standard inguinal varicocelectomy in terms of DNA damage or sperm quality factor indices? A randomized study. Int. J. Reprod. Biomed. 12: 40	- Conference abstract.
Pourmand, G., Movahedin, M., Dehghani, S. et al. (2014) Does l-carnitine therapy add any extra benefit to standard inguinal varicocelectomy in terms of deoxyribonucleic acid damage or sperm quality factor indices: A randomized study. Urology 84(4): 821-825	- Data cannot be extracted *No measure of variance reported for DNA fragmentation*
Pourmasumi, S., Ghasemi, N., Talebi, A. et al. (2019) Protective effects of antioxidant supplements on sperm parameters, sperm DNA damage and level of seminal ROS in RPL patients: A clinical trial study. Iranian Red Crescent Medical Journal 21(11): e94197	- Population not in PICO *Participants with recurrent pregnancy loss were included (so they do not have infertility), and they received interventions for recurrent miscarriage*
Povelitsa E, Leanovich V, Dosta N et al. (2020) Combined treatment of oligoasthenospermia by postoperative Speroton therapy in patients with varicocele. Androl. Genit. Surg 21: 64–69	- Study not reported in English
Pyrgidis, Nikolaos, Sokolakis, Ioannis, Palapelas, Vasileios et al. (2021) The Effect of Antioxidant Supplementation on Operated or Non-Operated Varicocele-Associated Infertility: A Systematic Review and Meta-Analysis. Antioxidants (Basel, Switzerland) 10(7)	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and identified studies (eg., Ener 2016) that might meet our inclusion criteria and were not picked up by our search, so these studies were now added manually*
Qiu, Daoxian; Shi, Qingjing; Pan, Lianjun (2021) Efficacy of varicocelectomy for sperm DNA integrity improvement: A meta-analysis. Andrologia 53(1): e13885	- Systematic review, included studies checked for relevance *Systematic review of observational studies (e.g., case-control study and case series)*
Quinn, Molly M, Ribeiro, Salustiano, Juarez-Hernandez, Flor et al. (2022) Microfluidic preparation of spermatozoa for ICSI produces similar embryo quality to density-gradient centrifugation: a pragmatic, randomized controlled trial. Human reproduction (Oxford, England) 37(7): 1406-1413	- Comparison not in PICO *Microfluidic preparation of spermatozoa vs. Conventional density gradient centrifugation*

Study	Reason
Raad, Georges, Tanios, Judy, Kerbaj, Simone et al. (2021) Stress Management during the Intracytoplasmic Sperm Injection Cycle May Slow Down First Embryo Cleavage and Accelerate Embryo Compaction: A Pilot Randomized Controlled Trial. Psychotherapy and psychosomatics 90(2): 119-126	- Comparison not in PICO *Stress management during ICSI vs. ICSI alone*
Ribas-Maynou, Jordi, Yeste, Marc, Becerra-Tomas, Nerea et al. (2021) Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis. Biological reviews of the Cambridge Philosophical Society 96(4): 1284-1300	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
Rozati, Roya, Reddy, P P, Reddanna, P et al. (2002) Role of environmental estrogens in the deterioration of male factor fertility. Fertility and sterility 78(6): 1187-94	- Study design not in PICO *Case-control study*
Sabetian, Soudabeh, Jahromi, Bahia Namavar, Vakili, Sina et al. (2021) The Effect of Oral Vitamin E on Semen Parameters and IVF Outcome: A Double-Blinded Randomized Placebo-Controlled Clinical Trial. BioMed research international 2021: 5588275	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation because it was not assessed at baseline or at the end of the study*
Salas-Huetos, Albert, Moraleda, Rocio, Giardina, Simona et al. (2018) Effect of nut consumption on semen quality and functionality in healthy men consuming a Western-style diet: a randomized controlled trial. The American journal of clinical nutrition 108(5): 953-962	- Population not in PICO *People without fertility problem (healthy and fertile)*
Salvio, Gianmaria, Cutini, Melissa, Ciarloni, Alessandro et al. (2021) Coenzyme Q10 and Male Infertility: A Systematic Review. Antioxidants (Basel, Switzerland) 10(6)	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and primary study that meet our inclusion criteria (e.g., Stenqvist 2018) was already included in our review*
Schisterman, Enrique F, Sjaarda, Lindsey A, Clemons, Traci et al. (2020) Effect of Folic Acid and Zinc Supplementation in Men on Semen Quality and Live Birth Among Couples Undergoing Infertility Treatment: A Randomized Clinical Trial. JAMA 323(1): 35-48	- Population not in PICO *>50% of participants did not have male factor fertility problem*
Service, Chad Austin, Puri, Dhruv, Al Azzawi, Sultan et al. (2023) The impact of obesity and metabolic health on male fertility: a systematic review. Fertility and sterility 120(6): 1098-1111	- Systematic review, included studies checked for relevance *Systematic review of observational studies investigating the impact of obesity and metabolic health on male infertility*
Sharma, DS (2021) Pregnancy rate in male factor infertility with oligoastheneteratozoospermia - evaluation of Letrozole and Coenzyme Q10 supplementation	- Conference abstract.

Study	Reason
on sperm parameter. Human reproduction. 37th virtual annual meeting of the european society of human reproduction and embryology 36suppl1: i169	
Showell, Marian G, Brown, Julie, Clarke, Jane et al. (2013) Antioxidants for female subfertility. The Cochrane database of systematic reviews: cd007807	- Population not in PICO *People with female fertility problems*
Song, B, He, XJ, Jiang, HH et al. (2012) Compound Xuanju Capsule combined with vitamin E improves sperm chromatin integrity. Zhonghua nan ke xue [National journal of andrology] 18(12): 1105-1107	- Study not reported in English
Sonmez, Mehmet G and Haliloglu, Ahmet H (2018) Role of varicocele treatment in assisted reproductive technologies. Arab journal of urology 16(1): 188-196	- Systematic review, included studies checked for relevance *Included studies checked for relevance, and primary study that meet our inclusion criteria was already included in our review*
Sun, Xiao-Lei, Wang, Jiu-Lin, Peng, Yun-Peng et al. (2018) Bilateral is superior to unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele: a prospective randomized controlled study. International urology and nephrology 50(2): 205-210	- Comparison not in PICO *Bilateral varicocelectomy vs. Unilateral varicocelectomy*
Sun, ZG, Lian, F, Jiang, KP et al. (2012) Shengjing prescription improves semen parameters of oligoasthenozoospermia patients: efficacy and mechanism. Zhonghua nan ke xue [National journal of andrology] 18(8): 764-767	- Study not reported in English
Sánchez-Martín P, Sánchez-Martín F, González-Martínez M et al. (2013) Increased pregnancy after reduced male abstinence. Systems biology in reproductive medicine 59(5): 256-260	- Population not in PICO *Unclear whether participants had sperm DNA fragmentation*
Tas, Derya Ozdemir, Ozkavukcu, Sinan, Inanc, Irem et al. (2023) The effects of coenzyme Q10 and curcumin supplementation in freezing medium for human sperm cryopreservation. European journal of obstetrics, gynecology, and reproductive biology 287: 36-45	- Population not in PICO *Healthy (i.e., fertile) men were included*
Tehrani, M.S., Amirian, M., Jalali, M. et al. (2019) Comparison of intracytoplasmic sperm injection outcome with sperm selection techniques in oligoasthenozoospermic males: A randomized controlled trial. Iranian Red Crescent Medical Journal 21(1): e70656	- Data cannot be extracted *Percentage of DNA fragmentation at baseline not reported in the text or tables, so unable to interpret whether participants had high DNA fragmentation*
Tremellen, Kelton, Miari, George, Froiland, David et al. (2007) A randomised control trial	- Population not in PICO

Study	Reason
examining the effect of an antioxidant (Menevit) on pregnancy outcome during IVF-ICSI treatment. The Australian & New Zealand journal of obstetrics & gynaecology 47(3): 216-21	*About 50% of participants had combined infertility, and only 50% of participants had male infertility*
Vinogradov, IV, Gamidov, SI, Gabliya, MY et al. (2019) Docosahexaenoic acid in the treatment of idiopathic male infertility. Urologiia (Moscow, Russia : 1999): 78-83	- Study not reported in English
Vyshnavi, M.S., Palani, K., Muthiah, S.S. et al. (2024) Ejaculatory Abstinences On DNA Fragmentation in Obese and Normal Men with Infertility and Fertility. International Journal of Pharma and Bio Sciences 15(2): 18-30	- Full text paper not available
Wang, Yang, Zhang, Rui, Pan, Weijun et al. (2021) Effects of L-carnitine combined with pancreatic kininogenase on thioredoxin 2, thioredoxin reductase 1, and sperm quality in patients with oligoasthenospermia. Translational andrology and urology 10(8): 3515-3523	- Comparison not in PICO *L-carnitine vs. L-carnitine plus pancreatic kininogenase*
Wang, Ying-Jun, Zhang, Rong-Qiu, Lin, Yan-Jun et al. (2012) Relationship between varicocele and sperm DNA damage and the effect of varicocele repair: a meta-analysis. Reproductive biomedicine online 25(3): 307-14	- Systematic review, included studies checked for relevance *Systematic review of observational studies*
West, Robert, Coomarasamy, Arri, Frew, Lorraine et al. (2022) Sperm selection with hyaluronic acid improved live birth outcomes among older couples and was connected to sperm DNA quality, potentially affecting all treatment outcomes. Human reproduction (Oxford, England) 37(6): 1106-1125	- Study design not in PICO *Non RCT*
Wilding, Martin, Coppola, Gianfranco, di Matteo, Loredana et al. (2011) Intracytoplasmic injection of morphologically selected spermatozoa (IMSI) improves outcome after assisted reproduction by deselecting physiologically poor quality spermatozoa. Journal of assisted reproduction and genetics 28(3): 253-62	- Comparison not in PICO *Intracytoplasmic injection of morphologically selected spermatozoa vs. Conventional ICSI*
Williams, Elizabeth A, Parker, Madeleine, Robinson, Aisling et al. (2020) A randomized placebo-controlled trial to investigate the effect of lactolycopene on semen quality in healthy males. European journal of nutrition 59(2): 825-833	- Population not in PICO *Unclear whether participants had fertility problems as they were healthy males (the study stated that participants were healthy volunteers with no known fertility issues)*
Xie, ZT, Li, KY, Weng, ZW et al. (2020) Traditional Chinese therapy of tonifying the kidney and invigorating blood circulation reduces sperm DNA damage and improves natural pregnancy in infertile males. Zhonghua	- Study not reported in English

Study	Reason
nan ke xue [National journal of andrology] 26(1): 74-77	
Xu, Y, Nisenblat, V, Lu, C et al. (2018) Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reproductive biology and endocrinology : RB&E 16(1): 29	- Population not in PICO *People with female fertility problems*
Yakovlev, IB, Teplykh, SV, Vilesova, VV et al. (2022) CLINICAL STUDY OF THE EFFICACY AND SAFETY OF PROSTATE EXTRACT PREPARATION IN COMBINATION WITH ZINC ARGINYL GLYCINATE FOR THE CORRECTION OF DNA FRAGMENTATION AND OXIDATIVE ACTIVITY OF SPERM PLASMA AS FACTORS OF MALE INFERTILITY. Eksperimental'naya i klinicheskaya farmakologiya 85(2): 11-15	- Study not reported in English
Yamasaki, Kazumitsu, Uchida, Masahiro, Watanabe, Noriko et al. (2022) Effects of antioxidant co-supplementation therapy on spermatogenesis dysfunction in relation to the basal oxidation-reduction potential levels in spermatozoa: A pilot study. Reproductive medicine and biology 21(1): e12450	- Outcome not in PICO *Report 8-OHdG levels (a biomarker of oxidative DNA damage) rather than percentage of DNA fragmentation*
Yazdanpanah, Zeynab; Nasrabadi, Mitra Heydari; Piravar, Zeynab (2021) Comparison of three sperm selection methods for ICSI-DGC, Cumulus column, and incubation with supernatant product of adipose tissue-derived adult stem cells: An experimental study. International journal of reproductive biomedicine 19(1): 97-104	- Comparison not in PICO *Density gradient centrifugation vs. Cumulus column vs. Incubation with supernatant products of adipose tissue-derived adult stem cells*
Yildiz, K, Ucar, U, Deniz, D et al. (2021) A new sperm preparation technique for ICSI. Human reproduction. 37th virtual annual meeting of the european society of human reproduction and embryology 36suppl1: i143	- Conference abstract.
Yildiz, Koray and Yuksel, Sengul (2019) Use of microfluidic sperm extraction chips as an alternative method in patients with recurrent in vitro fertilisation failure. Journal of assisted reproduction and genetics 36(7): 1423-1429	- Comparison not in PICO *Density gradient method vs. Microfluidic chip*
Zaazaa, A, Adel, A, Fahmy, I et al. (2018) Effect of varicocelectomy and/or mast cells stabilizer on sperm DNA fragmentation in infertile patients with varicocele. Andrology 6(1): 146-150	- Comparison not in PICO *Varicocelectomy vs. Ketotifen vs. Varicocelectomy plus Ketotifen*
Zafar, M.I. and Chen, X. (2024) Effects of Calorie Restriction on Preserving Male Fertility	- Study not reported in English *Narrative review*

Study	Reason
Particularly in a State of Obesity. Current Obesity Reports	
Zhang, F, Zhao, P, Sun, Z et al. (2023) Clinical Observation on Herb-partitioned Moxibustion on Navel Combined with Yishen Tongluo Prescription in Treatment of Infertility Induced by Idiopathic Asthenozoospermia with Kidney-Yang Deficiency and Collateral Obstruction Syndrome. Chinese journal of experimental traditional medical formulae 29(4): 97-103	- Study not reported in English
Zhang, Jiyue, Xue, Huiying, Qiu, Fenglong et al. (2019) Testicular spermatozoon is superior to ejaculated spermatozoon for intracytoplasmic sperm injection to achieve pregnancy in infertile males with high sperm DNA damage. Andrologia 51(2): e13175	- Study design not in PICO *Non-RCT and no matching or control for confounding variables between groups*
Zhao, P; Wang, Z; Chen, R (2023) Effect of Wuwei Fuzheng Yijing Decoction on Sperm DNA Integrity in Male Infertility Patients. Chinese journal of experimental traditional medical formulae 29(3): 127-132	- Study not reported in English
Zou, Yu-Jie, Yang, Jing, Chang, Shuo et al. (2017) Acetyl-L-carnitine: An effective antioxidant against cryo-damage on human spermatozoa with asthenospermia. Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban 37(6): 915-921	- Study design not in PICO *In vitro study*

DNA: deoxyribonucleic acid; ICSI: intracytoplasmic sperm injection; IMSI: intracytoplasmic morphologically selected sperm injection; MACS: magnetic activated cell sorting; PICSI: physiological intracytoplasmic sperm injection; RCT: randomised controlled trial

Excluded economic studies

None.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes for people with male factor fertility problems?

No research recommendations were made for this review.