ANTIOXIDANTS' USE IN THE TREATMENT OF MALE INFERTILITY, SYSTEMIC REVIEW AND ANALYSIS OF EVIDENCE – BASED CLINICAL GUIDELINES.

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ABSTRACT

It's commonly acknowledged that antioxidants may play a key role in treating male infertility and that oxidative stress is a major factor in the pathophysiology of male infertility. This study's primary goals are to, 1) thoroughly examine the available data about the effectiveness of antioxidants in treating male infertility, and 2) provide evidence-based clinical recommendations for the application of antioxidants in treating male infertility. A manual screening of papers accessible on Scopus was conducted as part of a systematic review of the clinical evidence that was available. The type of antioxidant employed, the clinical conditions being studied, the assessment of semen parameters, and the results of reproduction were among the data that were extracted. For every included study, the compliance with the JADAD score, the Cambridge Quality Checklist, the Cochrane Risk of Bias for randomized controlled trials (RCTs), and CONSORT criteria was examined. Furthermore, in order to assess the present and potential importance of antioxidants in male infertility, we offered a Strength Weakness Opportunity Threat (SWOT) study. Antioxidant supplementation improves semen parameters, as the current systematic research on antioxidants and male infertility clearly demonstrates. Furthermore, it offers the indications for antioxidant treatment in some clinical situations, such as changed semen quality, varicocele, and unexplained and idiopathic male infertility.

Keywords, Antioxidants, Oxidative stress, Practice guideline, Semen analysis, Sperm maturation

INTRODUCTION

Infertility affects 15% of couples worldwide, with 2.5%–12% being exclusively caused by male factors. Geographical location affects the occurrence of male factor infertility, which can range from 20% to 70% [1]. Factors contributing to male infertility include varicocele, azoospermia, male hypogonadism, anti-sperm antibodies, and hereditary reasons. However, a significant fraction of cases remain idiopathic (30%–50%) or unexplained (15%) [2.3]. Low reproductive results in males are linked to environmental and lifestyle factors. Oxidative stress is a key mediator in male infertility, accounting for 30% to 80% of IMI cases [2,5]. There is growing interest in using antioxidants to mitigate oxidative stress from various male infertility etiologies and risk factors. Oral antioxidants are widely accessible, have excellent safety and bioavailability profiles, and are reasonably priced. As a result, there is an increasing trend of giving antioxidants to all male infertile patients, even in the absence of a thorough assessment or pertinent guidelines [7]. The effects of multiple antioxidants on male fertility have been extensively documented in the literature, and exogenous antioxidant administration has been the subject of decades' worth of research [8–11]

A Cochrane meta-analysis in 2011 and subsequent reviews [8,9,11] summarized the topic of male antioxidant treatment for assisted reproductive technology (ART) in infertile males. The studies found that low-level evidence supports antioxidant therapy to enhance pregnancy and live birth rates, with no evidence for increased risk of miscarriage [8.9.11]. However, Majzoub and Agarwal (2018) [10] concluded that antioxidants improve male fertility, advanced sperm function, live birth rates, and semen parameters. Antioxidants like zinc, selenium, and folic acid are frequently used in clinical and scientific research. Systemic reviews of certain studies shows no clinical effect and serious negative effects either [16 -20]. Examples of these antioxidants include carnitine, N-acetyl cysteine, vitamin A, vitamin C, vitamin E, and lycopene. (Fig. 1) [12-15]. However, the results of clinical studies vary widely due to the lack of placebo-controlled trials, varying treatment regimens, doses, and durations, and limited patient numbers. Many trials only assessed specialized factors, such as seminal volume, sperm concentration, and morphology, rather than assessing reproductive outcomes like live birth rate. Additionally, antioxidants were often administered at unproven dosages, ignoring the delicate balance of redox in the body [21]. High antioxidant dosages can lead to reductive stress, which can cause infertility [22 – 24]. High doses of vitamin E can have negative effects [20]. while balanced antioxidant formulations have shown positive outcomes like decreased oxidative stress, improved sperm function, and successful

pregnancies [25,26]. This study aims to review recent research supporting antioxidant use in male infertility and propose updated clinical guidelines. The current rationale and inconsistent data call for a systematic review of current evidence to effectively treat male infertility.

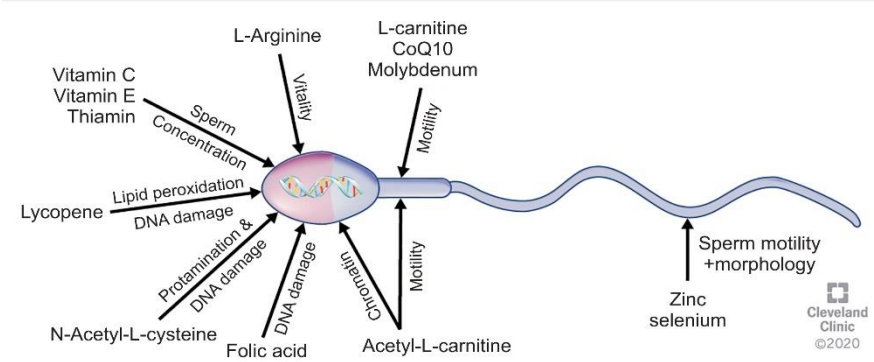

fig no,1 certain anti oxidant substances that significantly impact the sperm function. CoQ, Co enzyme Q.

MATERIALS AND METHODS

1. LITERATURE SEARCH STRATERGY

A comprehensive literature analysis was conducted to identify clinical trials examining the effect of antioxidant therapy on semen quality in male infertility. The PRISMA The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria [27] were followed, and the Scopus database was selected due to its vast collection of over 70,000 indexed articles and over 1.4 billion cited references. The search was conducted on July 15, 2020, and the database was automatically filtered to include only original English articles. The articles were manually evaluated for eligibility based on title, keywords, and abstract. Three researchers (RF, KL and MKPS) independently conducted the screening, tracking the number of publications rejected. The number of full-text articles excluded listed in table 1 was noted after the evaluation. Information from eligible articles included the design of the clinical trial, antioxidant formulation, clinical condition, assessment of semen parameters and/or sperm function tests (such as sperm DNA fragmentation [SDF], oxidative stress markers, capacitation/acrosome reaction, and zona binding test), as well as reproductive outcomes (such as fertilization, implantation, pregnancy, miscarriage, and live birth rates.

2. EVALUATION OF STUDY QUALITY

The study assessed the quality of studies using the Cambridge Quality Checklist, Cochrane Risk of Bias, JADAD score, and CONSORT principles [31]. The studies were categorized into “low” and “high” quality categories, with uncontrolled studies considered low-quality Table 2 . A new grading system was developed, considering factors such as study design, sample size analysis, inclusion/exclusion criteria,

antioxidant regimen, treatment duration, oxidative stress markers evaluation, pregnancy and live birth rates, and recent clinical trials published between January 2019 and July 2020. The system assigns a maximum total score of 12 points and classifies articles into “low” and “high” quality categories. The Oxford Centre for Evidence-Based Medicine (2011) Levels of Evidence classification system classified the evidence into A, B, C, and D categories, based on which clinical recommendations were made.

A search using a keyword search approach led to 1,978 articles, with 97 papers included in Table 2. The study included individuals from both IMI and UMI, and included information about the population, treatment's reported effect on reproductive outcomes, quality assessment, and potential bias. Out of the 97 publications, 33 (34.0%) were blinded RCTs, 12 (12.4%) were unblinded RCTs, and 52 (53.6%) were uncontrolled clinical trials. Of the papers that examined different types of antioxidants, 44 (45.4%) tested single antioxidants, 21 (22.0%) tested a combination of multiple products at varying dosages, and 22 (22.7%) used registered antioxidant products. Statistical analysis showed that antioxidant treatment had positive effects on semen and sperm function parameters in 65.0% and 58.3% of high-quality studies, respectively.

However, 85.7% and 89.6% of low-quality studies reported significant improvement in semen and sperm function parameters in infertile men after antioxidant supplementation. The underpowering of statistical analysis resulted

Table 1. Proposed inclusion and exclusion for article selection

Inclusion	Exclusion
Human participants	Animal and in vitro studies
Anti oxidants used as intervention individually or combined	Intervention not clearly reported as an anti oxidant
Open or controlled clinical trials	Abstracts only, conference abstracts, book chapters, case series, review articles
Sperm function measures (sperm DNA fragmentation, seminal oxidative stress markers, mitochondrial membrane integrity) and/ or semen parameters (sperm concentration, motility, morphology, vitality) reported following anti oxidant treatment	Non – English studies

3.STATISTICAL ANALYSIS

The study used MedCalc statistical software to analyze the effects of antioxidant treatment on sperm function and semen parameters like oxidative stress and SDF. The chi-square test was used to assess the relationship between the study's quality and results [25, 26,32 -121] with p-values less than 0.05 considered statistically significant. A sample size calculation was performed for $p<0.05$.

RESULTS

from the availability of a small number of studies reporting sperm functions and semen parameters. To achieve a statistical significance of $p<0.05$ for reproductive outcomes, a total of 95 and 292 studies reporting the results of semen parameters and sperm functions, respectively, were included. However, these values were not significant due to the limited number of studies in the literature. Therefore, 33 low-quality and 202 high-quality studies are needed overall to achieve a statistical significance of $p<0.05$ for reproductive outcomes.

T**able 2**. articles investigating the impact of antioxidant treatment

CLINICAL CONDITION	SN	REFERENCE	CLINICAL TRIAL DESIGN	ANTIOXIDANT FORMULATION DOSAGE AND LENGTH OF TREATMENT	STUDY POPULATION	REPRODUCTIVE OUTCOMES AFTER ANTIOXIDANT TREATMENT	CAMBRIDGE QUALITY CHECKLIST			COCHRANE RISK OF BIAS FOR RCT	CONSORT GUIDELINES (OUT OF 25)	JADAD (OXFORD QUALITY) (OUT OF 5)	QUALITY OF EVIDENCE PUBLISHED
							CHECKLIST FOR CORRELATE (OUT OF 5)	CHECKLIST FOR RISK FACTORS (OUT OF 3)	CHECKLIST FOR CASUAL RISK FACTORS				
INFERTILE MEN	1	KESSOPOULOU et al (1995) (19)	RCT blinded	α - Tocopheryl acetate (Ephynal, F. Hoffman – La Roche ltd) 300 mg?daily for 3 months	30 infertile men	No difference in semen parameters before and after treatment No difference in ROS levels improved zona binding	2	3	7	Unclear risk of bias for random sequence generation, allocation concealment, selective reporting, other sources and blinding (outcome assessment)	20	4	1
	2	Keskes – ammar et al (2003) [33]	RCT unblinded	Vitamin E (400 mg) (ephynal 100 mg, 2 tablets) or selenium (225 µg) for 3 months	54 infertile men	Improved sperm motility Reduced MDA levels	1	3	4	No risk o bias identified	12	3	0
	3	Menezo et al (2007) [20]	Uncontrolled (open label)	Vitamins C and E (400 mg each) β- carotene (18 mg), zinc (500 µmoL), selenium (1 µmoL) for 3 months	58 patients experiencing 2 previous failures of IVF or ICSI and DFI and chromatin decondensation >15%	Reduced SDF but higher sperm decondensation	0	3	3	N/A	N/A	N/A	0
	4	Da silva et al (2013) [17]	RCT blinded	Folic cid 5 mg/daily for 3 months	70 infertile men	No difference in semen parameters	3	3	7	No risk of bias identified	15	5	1
	5	Chattopadhyay et al (2016) [16]	Uncontrolled (open label)	L- caritine, Acetyl – L- Carnitine, CoQ10, lycopene, Zinc, folic acid, vitamin B12, selenium for 6 months	115 infertile men	Increased sperm count, motility, TAC Reduced ROS levels	0	3	3	N/A	N/A	N/A	0
	6	Stenqvist et al (2018) [39]	RCT blinded	Vitamin c (30 mg), vitamin E (5 mg), vitamin B12 (0.5 µg) l – carnitine (750 mg), coenzyme Q10 (10 mg), folic acid (100 mg), zinc (5 mg), selenium (25 µg)	77 infertile men with DFI >25%	Improved sperm concentration, no change in DNA damage	4	3	7	No risk of bias identified	19	5	1
	7	Salehi et al (2019) [42]	Uncontrolled (open label)	Vitamin E (50 mg) vitamin c (500 mg) and CoQ10 (100 mg) for 3 months	485 infertile men with DFI >27% by SCSA	Improved volune, sperm count, motility and normal morphology	2	3	3	N/A	N/A	N/A	N/A
	8	Hasoon (2019) [43]	Uncontrolled (open label)	L – arginine (1g) and CoQ10 (200 mg) for 8 months	24 infertile men	Improved volume, sperm count, motility and normal morphology	2	3	3	N/A	N/A	N/A	0
	9	Hadi et al (2020) [45]	Uncontrolled (open label)	L – caritine 2g/daily for 3 months	598 infertile men	Improved sperm count, total motility and normal morphology In serum reduced FSH and LH level, increased testosterone and inhibin levels	2	3	3	N/A	N/A	N/A	0
	10	Schistermann et al (2020) [46]	RCT blinded	Folic acid 5 mg/ daily and 30 mg zinc for 6 months	1,185 male partners of couple planning IVF for infertility treatment	No changes in semen paraneters; improved SDF by comet assay : no significant differences in β- HCG-detected pregnancy, clinical intrauterine pregnancy, ectopic pregnancy, pregnancy with multiple fetuses, live birth rate	2	3	7	Unclear risk of bias for random sequence generation, allocation concealment, other sources, selective reporting and blinding	14	3	0

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Varicocele	11	Comhaire et al (2000) [47]	Uncontrolled (open label)	β - carotene (30 mg0 and α - tocopherol (180 mg)/daily.	7 idiopathic patients 11 varicocele patiennts History of cryptorchidism (n =2), patients with male accessory gland infection (n=7), immunological infertility (n =4), endocrine cause	Improved sperm concentration and acrosome reaction Reduced ROS levels and 8-OH – dG levels	2	3	3	N/A	N/A	N/A	N/A
	12	Festa et al (2014) [51]	Uncontrolled (open label)	CoQ10 100 mg/daily for 3 months	38 varicocele patients	Sperm concentration, progressive motility, and TAC No changes in semen parameters, SDF and Protamine damage ssay	0	3	7	Unclear risk of bias for ranom sequence generation, allocation concealment and incomplete outcome data	14	2	0
	13	Cyrus et al (2015) [53]	RCT blinded	Vitamin C 250 mg/daily for 3 months	115 varicocele patients	Improved semen parameters	2	3	6	Unclear risk of bias for random sequence generation, allocation,concealment, selective reporting	18	5	0
	14	Gual – frau et al (2015) [54]	Uncontrolled (open label)	L –carnitine (1500 mg), vitamin C (60 mg), CoQ10 (20 mg), vitamin E (10 mg), vitamin B12 (200 µg), zinc (10 mg), selenium (50 µg) for 3 months	20 varicocele patients	Improved total sperm count and reduced SDF	2	3	3	N/A	N/A	N/A	0

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	15	KIZILAY AND ALTAY (2019)	RCT unblinded	Vitamin c (180 mg), zinc (20 mg), folic acid (400 mg), selenium (100 mg), coenzyme Q 10 (40 mg), vitamin B12 (3 mg/daily for 6 months)	90 varicocele patients	Improved semen parameters Higher pregnancy rate	3	3	7	High risk bias for random sequence generation, allocation concealment, other sources, blinding, incomplete outcome data	19	2	0
	16	Ardestani Zadeh et al (2019) [57]	RCT unblinded	Folic acid (5 mg), selenium (200 µg) and vitamin E (400 IU)/ daily for 6 months	60 varicocele patients	Improved sperm count and motility	2	3	7	Unclear risk of bias for allocation concealment, other sources, high risk of bias for blinding	24	4	1
Abnormal semen quality	17	Suleiman et al (1996) [58]	RCT blinded	Vitamin E 300 mg/daily for 6 months	Oligoastheno (n=74), azoospermic (n=38), astheospermic (n=94), oligospermic (n=30) patients high viscosity (n=22), oligospermic with high viscosity (n=6) asthenospermic with high viscosity (n=12) oligoastheno spermic with high viscosity (n=10)	Improved sperm motility Reduced MDA levels Higher pregnancy and live birth rates	4	3	7	Unclear risk of bias from random sequence generation, allocation concealment, other sources,blinding (participants and persnnel outcomes assessment) incomplete outcome data	12	3	0

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	18	Rolf et al (1999) [59]	RCT blinded	Vitamin C (1000 mg) and vitamin E (800 mg)daily for 56 days	31 asthemozoos permic patients	No changes in semen parameters	0	3	7	No risk of bias	21	5	1
	19	Balercia et al (2004) [62]	Ucontrolled (open label)	CoQ10 400 mg/daily for 56 months	22 asthenozoopermic patients	Improved progressive motility after treatment, which reduced after 6 months of wash out	4	3	4	N/A	N/A	N/A	0
	20	Nadjarzadeh et al (2011) [66]	RCT blinded	CoQ1 capsules 200 mg/daily	60 OAT patients	No change in semen parameters Reduced MDA and improved TAC	4	3	7	Unclear risk of bias random sequence generation, allocation concealment, other sources and blinding. High risk of bias for incomplete outcome data	20	4	1
	21	Moslemi and tavanbakhsh (2011) [70]	Uncontrolled (open label)	Selenium (200 µg 0, vitamin E (400 units)/daily for 100 days	690 asthenoteratospermic patients	Improved semen parameters Higher spontaneous pregnancy No changes in semen parameters , SOD and catalase – like activity	1	3	3	N/A	N/A	N/A	0
	22	Safarinejad (2012) [72]	Uncontrolled (open label)	CoQ10 300 mg/daily for 12 months	287 OAT patients	Improved semen parameters No changes in pregnancy and miscarriage rates2	3	4	4	N/A	N/A	N/A	0
	23	Ajayi et al (2013) [74]	Uncontrolled (open label)	Vitamin C (200 mg), vitamin E (200 mg), folic acid (1 mg), zinc (50 mg), selenium (200 µg), n-acetyl-L-cysteine (100 mg), L- carnitine (600 mg)	Oligo – (n=20) astheno (n=33) OAT (n=42) patients 65 healthy men	Imprved semen parameters	3	3	3	N/A	N/A	N/A	0

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	24	Nadjarzadeh et at (2014) [75]	RCT blinded	CoQ10 20 mg/daily for 3 months	60 OAT patients	No changes in semen parameters Increased seminal level of CoQ10, catalase and SOD activity: reduced level f seminal plasma 8 isoprostane	4	3	7	Unclear risk for bias for random sequence generation, allocation concealment, selective rporting, other sources , blinding	18	3	0
	25	Raigani et al (2014) [76] RCT blinded	RCT blinded	Folic acid (5 mg)	83 OAT patients	No difference in semen parameters Increased sperm chromtin integrity	2	3	7	Unclear risk of bias for allocation concealment, other sources	20	4	1
	26	Kobori et al (2014) [77]	Uncontrolled (open label)	CoQ10 (120 mg), vitamin c (80 mg), vitamin E (40 mg)/daily for 6 months	169 OAT patients	Improved sperm concentration and motility 48 928.4%) pregnancies achieved, of those 16 were spontaneous and 32 by using ART	0	3	3	N/A	N/A	N/A	0
	27	EL sheikh et al (2015) [84]	RCT unblinded	Vitamin E (400 mg/daily) Clomiphene citrate (25 mg/day),vitamin E for 6 months	90 oligosthenozoospermic patients	Improved sperm concentration in group B and C, while total sperm motility improved in all groups	0	3	7	Unclear risk of bias for other sources	15	3	0
	28	Magdi et al (2017) [89]	Uncontrolled (open label)	Vitamin C (1g), vitamin e (400 mg) and L – carnitine (2g/daily for 6 months	210 OAT patients	Improved sperm count, total and progressive motility, normal morphology after treatment	0	3	3	N/A	N/A	N/A	0
	29	Alsalman et al (2018) [90]	Uncontrolled (open label)	Zinc 220 mg/daily for 3 months	60 asthenozoospermic patients	Improved volume progressive motility, normal morphology	3	3	6	N/A	N/A	N/A	0

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	30	Nouri et al	RCT blinded	Lycopene 25 mg/daily for 3 months	44 oligozoospermic patients	Improved volume total sperm count, concentration, total motility, TAC	2	3	7	Unclear risk of bias for allocation concealment other sources	18	4	0
	31	Busetto et al (2020) [96]	RCT blinded	L – carnitine (1g) CoenzymeQ10 (20 mg), vitamin C(90 mg), zinc (10 mg), folic acid (200 µg), vitamin B12 (1.5 µg)daily for 6 months	104 patients with altered semen quality. Of those, 52 showed grade i-iii varicoceles	Improved total sperm count , total and progressive motility Higher pregnancy rate	4	3	7	No risk of bias identified	22	5	1
	32	Alahmar et al (2020) [97]	Uncontrolled (open label)	CoQ10 200 mg/daily for 3 months	65 oligoasthenozoospermic patients	Improved sperm concentration, progressive and total motility, CoQ 10 level, TAC and GPx Reduced ROS levels and SDF	4	2	4	N/A	N/A	N/A	0
	33	Terai et al (2020) [98]	RCT unblinded	L- carnitine (750, 1 mg), zinc (30 mg), CoQ1 (90.26 mg), vitamin C (1g), vitamin B12 (60,1 µg), vitamin E (150 mg)	31 oligoasthenozoospermic patients	Increased total motile sperm count after treatment in group A	0	3	3	Unclear risk of allocation concealment, selective reporting, ther sources, no blindness of participants and person nel	16	3	0
	34	Steiner et al (2020) [99]	RCT blinded	Vitamin c (500 mg), vitamin E (400 mg), selenium (0.20 mg), L- carnitine (1g), zinc (20 mg), folic acid (1g0, lycopene (10 mg), vitamin D (2000 IU/daily) for maximum of 6 months	174 oliozoospermic patients	Improved sperm concentration No change in SDF No change in pregnancy and live birth rates	2	3	7	No risk of bias identified	20	5	1

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	32	Alahmar et al (2020) [97]	Uncontrolled (open label)	CoQ10 200 mg/daily for 3 months	65 oligoasthenozoospermic patients	Improved sperm concentration, progressive and total motility, CoQ 10 level, TAC and GPx Reduced ROS levels and SDF	4	2	4	N/A	N/A	N/A	0
	33	Terai et al (2020) [98]	RCT unblinded	L- carnitine (750, 1 mg), zinc (30 mg), CoQ1 (90.26 mg), vitamin C (1g), vitamin B12 (60,1 µg), vitamin E (150 mg)	31 oligoasthenozoospermic patients	Increased total motile sperm count after treatment in group A	0	3	3	Unclear risk of allocation concealment, selective reporting, ther sources, no blindness of participants and person nel	16	3	0
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	35	Alkumait et al (2020) [100]	RCT unblinded	CoQ10 (200 mg) for 6 months	51 OAT patients	Improved semen parameters	2	3	7	Unclear risk of bias for allocation concealment, other sources, high risk of bias for blinding	13	3	0
Healthy men	36	Goyal et al (2007) [102]	Uncontrolled (open label)	Lycopene 22.8 mg/day for 2 weeks	6 healthy men	Increased seminal lycopene. No increase in TAC levels	2	3	3	N/A	N/A	N/A	0
	37	Chayachinda et al (2020) [107]	RCT blinded	CoQ10 200 mg/day for 1 month	Leukocytospermia (n=84)	No difference in sperm concentration, motility, normal morphology	0	3	3	No risk of bias identified	22	5	1
	38	Gupta and kumar (2002) [108]	Uncontrolled (open label)	Lycopene 4 mg/daily for 3 months	30 idiopathic patients	Improved sperm concentration and motility Higher pregnancy rate	3	3	3	N/A	N/A	N/A	0
	39	Soleimani and masoumi (2017) [114]	Uncontrolled (open label)	Grape seed extract 600 mg/daily for 3 months	29 idiopathic patients	Increased catalase, reduced MDA	2	1	3	N/A	N/A	N/A	0

CLINICAL CONDITION	SN	REFERENCE	CLINICAL TRIAL DESIGN	ANTIOXIDANT FORMULATION DOSAGE AND LENGTH OF TREATMENT	STUDY POPULATION	REPRODUCTIVE OUTCOMES AFTER ANTIOXIDANT TREATMENT	CAMBRIDGE QUALITY CHECKLIST			COCHRANE RISK OF BIAS FOR RCT	CONSORT GUIDELINES (OUT OF 25)	JAN/ADAD (OXFORD QUALITY) (OUT OF 5)	QUALITY OF EVIDENCE PUBLISHED
							CHECKLIST FOR CORRELATE (OUT OF 5)	CHECKLIST FOR RISK FACTORS (OUT OF 3)	CHECKLIST FOR CASUAL RISK FACTORS				
	40	Kopets et al (2020) [115]	RCT blinded	L carnitine, l arginine (250 mg), co enzyme Q (40 mg), zinc (7.5 mg), vitamin B9 (234 mcg), vitamin B 12 (2 mcg), selenium (50 mcg) for 6 month daily	83 idiopathic patients	Increased /5 of normozoospermia in treated patients after 2 – 4 months in companies with placebo, higher pregnancy rate	0	3	7	No risk of bias identified	24	5	1
	41	Greco et al (2005) [116]	uncontrolled (open label)	Vitamin C (1g) and vitamin E (1g)/daily for 2 months	Oligoteratozoospermia (n=6) patients, 6 unexplained infertile men	Improved semen parameters and SDF No change in fertilization and cleavage rates after treatment Higher implantation and pregnancy rates	2	3	3	N/A	N/A	N/A	N/A
	42	Greco et al (2005) [117]	Uncontrolled (open label)	Vitamin C and E 1g/ daily for 2 months	64 unexplained infertile men	No difference in semen parameters Reduced SDF	1	3	7	N/A	N/A	N/A	0
	43	Safarinejad et al (2012) [118]	RCT blinded	CoQ10 200 mg/daily for 26 weeks	228 unexplained infertile men	Improved semen parameters, seminal catalase, and SOD	4	3	7	No risk of bias identified	18	5	1
	44	Hamidian et al (2020) [121]	Uncontrolled (open label)	Vitamin C 250 mg/daily for 3 months	20 patients with recurrent pregnancy loss	Improved sperm morphology Reduced SDF Changes in mRNA levels of PRM1, PRM2 and the PRM1/PRM2 ratio after treatment	2	3	4	N/A	N/A	N/A	0

1.**THE VARICOCELE**

A study of eleven research on male varicocele found that 90.9% of the publications included reported positive effects on semen parameters following antioxidant treatment. This suggests that antioxidant supplements may be beneficial for patients with varicocele. 75% and 83 % of low quality literature showed a positive impact on semen function (Table 3) However, the statistical significance of these findings is not significant, as a total of 41 and 24 studies reporting sperm function and semen parameters would be required to achieve a $p<0.05$ significance.

increase in semen and sperm function parameters in men with abnormal semen quality following antioxidant supplementation (Table 3). To achieve a statistical significance of $p<0.05$, 204 studies reporting sperm function results are needed.

3. IDIOPATHIC INFERTILITY IN MEN

A study of Idiopathic infertility in men found that 7 out of 10 (70 %) studies recorded sperm function biomarkers, while semen parameters were reported in 90% of the included publications (Table 3). High-quality studies showed improved sperm and semen function metrics ($p<0.0001$) following antioxidant treatment. However, a large number of low-quality trials indicated that males with IMI who took antioxidant supplements had improvements in semen and sperm function indices, although these differences were not statistically significant.

Table 3. number of low and high quality studies analysing semen paraneters and/or sperm function after antioxidant treatment. overall as well as in each clinical condition

GROUP	CATEGORY	REPORT OF SEMEN PARAMETERS		REPORT OF SPERM FUNCTION	
		Articles on the overall number of studies	% of studies reporting improvement after AOX treatment	Articles on the overall number of studies	% of studies reporting improvement after AOX treatment
Overall (n=97)	Low quality	70/90	85.7	50/60	89.6
	High quality	20/90	65.0	12/60	58,3
Varicocele (n=11)	Low quality	9/11	75.0	6/11	83.0
	High quality	2/11	-	0/11	-
Abnormal semen quality (n=45)	Low quality	36/44	94.4	20/25	90.0**
	High quality	8/44	50.0	5/25	60.0
Idiopathic male infertility (n=10)	Low quality	6/9	83.0	5/7	80.0
	High quality	3/9	100**	2/7	100***
Unexplained male infertility (n=5)	Low quality	4/5	83.3	3/4	100***
	High quality	1/5	100**	1/4	100***

2.UNUSUAL QUALITY OF SEMEN

A study of 45 studies on males with abnormal Table 2. semen quality found that 25 out of 45 (55.6 %) identified sperm function biomarkers, and 97.8% (n =44/45) reported semen parameters following antioxidant treatment. Although not statistically significant in high-quality trials, most studies showed a significant

A total of 24 and 30 studies reporting sperm function and semen parameters reached statistical significance.

4.UNKNOWN CAUSE OF INFERTILITY IN MEN

Five studies examined the impact of antioxidant therapy on male infertiles (Table 2). All studies observed 100% improvement in semen parameters after antioxidant treatment, while sperm function biomarkers were reported in 4 out of 5 studies (80.0%) (Table 3).

However, all low-quality studies reported improvements in sperm function, requiring 41 low-quality studies to achieve a statistical significance of $p<0.05$. High-quality trials showed significant improvements in semen and sperm function measures in males with UMI after antioxidant treatment.

5. A REVIEW OF THE MOST CURRENT WORKS

Antioxidant treatment on semen quality in total of 21 studies published between January 2019 and July 2020 was provided in Table 4.A study examining the impact of antioxidant treatment on semen quality found that 66.7% of the 21 studies reported significant improvements in sperm function and 90.5% in semen parameters. However, there were few studies examining the effects of antioxidant treatment on reproductive outcomes, with only 60% reporting an increase in pregnancy rate and no differences in birth rate found in the two studies evaluating it.

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/ SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
1	Terai et al (2020) [98]	RCT unblinded	31 oligoasthenozoospermic patients	Age 20 – 60 yearsold, presence of oligozoospermia and? asthenozoospermia	Azoospermia Sperm concentration <5x10^6/mL Sperm motility <5% TMSC >30X10^6 Clinical conditions resulting in infertility History of cancer, chemotherapy, drug abuse Administration of androgens, anti – androgens, and immunosuppresants	0	N/A	Improved TMSC (p=0.04)	N/A	0	1
2	Schisterman et al (2020) [46]	Double-blind RCT	Treatment (n=1,185) vs. placebo (n=1,185)	Male partners of couples planning IVF for infertility treatment	Planning of donor sperm use or a gestational surrogate Pregnancy at enrollment Obstructive azoospermia Chronic diseases	0	N/A	No difference in semen parameters between both groups. Increase in SDF by Comet assay in treatment group vs. placebo group (Adjusted MD 2.4, 95% CI 0.5–4.4) No significant differences in β-HCG–detected pregnancy, clinical intrauterine pregnancy, ectopic pregnancy, pregnancy with multiple fetuses LBR: Treatment group 404 (34%) vs. placebo group 416 (35%) (ns)	90% power at a 2-sided α level of 0.05 to detect a risk difference of 7% in LBR (implying a risk ratio of 1.10), with continuity correction and allowing for a dropout rate of 15% Esteem of risk differences and risk ratios Sequential approach of Lan and DeMets with Bonferroni adjustment to distribute the 1-sided type I error rate among 3 continuous semen quality parameters Post hoc sensitivity analyses	2	0

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/ EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
3	Steiner et al (2020) [99]	Double-blind RCT	Treated (n=85) vs. placebo (n=86)	infertile men with abnormal semen analysis in the last 6 months or DFI≥25%	Sperm concentration <5×106/mL Consumption of fertility medication or testosterone	0	yes	No difference in semen parameters, DFI by SCSA and PR LBR: 15% AOX vs. 24% placebo (ns) LBR=35% in the treated group and 25% in the placebo group with a 17% dropout	Sample size calculation, assuming a 20% dropout rate, ≥80% power at α=0.05	3	0
4	Kopets et al (2020) [115	Double-blind RCT	treated (n=42) vs. placebo (n=41)	Age: 21–50 years, with IMI	Allergy to any component Any clinical cause of male or female infertility Alcohol or drug addiction Use of any investigational product within the previous 3 months	0	N/A	Significant difference between both groups as regards normalization of semen parameters at 2 months (26/42 [61.9%]) males in treatment group vs. 8/41 [19.5%] males in placebo group) and at 4 months (29/42 [69.0%] vs. 9/41 [22.0%]). Significant change from baseline in mean values for all main semen parameters at 2 and 4 months, except for sperm morphology At 6 months higher PR in treatment than placebo group (10/42 [23.8%] vs. 2/41 [4.9%])	Sample size calculation assuming 1-beta error 0.80 and type I error alpha 5% Control for confounders by ANCOVA analysis	2	0
5	Arafa et al (2020) [25]	Prospective study	Idiopathic (n=119) and unexplained male infertility (n=29)	Infertile men (20–50 years) with unknown etiology and female infertility factor	Azoospermia Sperm concentration <1×106/mL Leucocytospermia Any cause for infertility Chemotherapy Clinical endocrinopathy Abnormal hormonal profile AOXs in the past 6 months Dietary, social habits or medical conditions which may impact on oxidative stress Use of drugs	1	yes	MI: significant improvement in sperm concentration (p<0.001), total motility (p=0.001), normal morphology (p<0.001), ORP (p<0.001), SDF (p=0.001) by Halosperm UMI: significant improvement in progressive motility (p=0.002), ORP (p=0.03), SDF (p=0.02)	N/A	3	3

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/ SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/ EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
6	Nazari et al (2020) [101]	Prospective study	59 patients with idiopathic OAT	Infertile patients with at least 1 abnormal semen parameter; age<45 years, BMI<30	Azoospermia Prostatitis Any clinical condition causing infertility History of hormonal therapy, drug addition, alcohol abuse, smoking, exposure to potential reproductive toxins	1	no	Significant improvements in sperm concentration (p=0.004) and normal morphology (p=0.01)	N/A	1	1
7	Nurmawati et al (2020) [44]	Single-blinded RCT	25 infertile men	Inclusion criteria not clearly stated	Exclusion criteria not clearly stated	0	no	Improved sperm concentration, motility, and morphology (p<0.05) Reduced levels of 8-OHdG levels (p<0.01) and MDA, with the value<1.98 being able to predict 100% of the normal sperm motility level (>40)	Sample size calculation assuming that the prevalence of male infertile couples with idiopathic causes in the world is 15% and in Indonesia 1.11%	2	2
8	Hadi et al (2020) [45]	Uncontrolled (open label	58 infertile men	Inclusion criteria not clearly stated	Presence of varicocele, orchitis, cryptorchidism Consumption of herbals or medications that might affect seminal parameters in the last 3 months prior to the study	0	no	Improved sperm volume, count, total motility, and normal morphology (p<0.05)	N/A	1	1
9	Busetto et al (2020) [96]	Double-blinded RCT	104 patients with altered semen quality. Of those, 52 showed grade I–III varicoceles	Oligo- and/or astheno- and/ or teratozoospermia, with or without varicocele (not surgically treated) and men from infertile couples	Known hypersensitivity to any of the compound History of undescended testes or cancer, endocrine disorders, post-pubertal mumps, genitourinary surgery, obstructive azoospermia or obstructive pathology of the urogenital system, autoimmune disease, cystic fibrosis History of taking any therapy affecting fertility, alcohol or drug abuse Subjects following any special diet or taking AOXs Involvement in any other clinical trials	0	yes	Improved total sperm count (p<0.0001), total (p<0.0001) and progressive motility (p=0.0012) Higher PR in treated group vs. placebo (10 vs. 2 pregnancies, respectively; p=0.0141)	Sample size calculation assuming α=0.05 (significance), β=0.20 (power of 80%), and up to 15% of patients dropping out of the study esteemed	3	1
10	Alahmar et al (2020) [97]	Uncontrolled (open label	65 oligoasthenozoo spermic patients	Infertile patients showing oligoasthenozoospermia	Azoospermia Anatomical abnormalities of genital tract, varicocele, genital infection, scrotal surgery, systemic diseases Smoking Female factor Consumption of ntioxidant and selective serotonin reuptake inhibitors intake in the last 6 months	1	No	Improved sperm concentration, progressive and total motility (p<0.05), levels of CoQ 10 (p<0.001), TAC (p<0.01) and GPx (p<0.001) Reduced ROS levels (p<0.05) and SDF by SCD assay (p<0.01)	N/A	2	2

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/ SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/ EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
11	Alkumait et al (2020) [100	RCT unblinded	51 OAT patients	Normal female factor with idiopathic OAT	Presence of chronic diseases, neoplasm, trauma, hypospadias, vas deference obstruction, varicocele, and genital tract infection Receiving treatment recently	1	No	Improved sperm concentration, motility (p=0.01) and morphology (p=0.03	N/A	1	1
12	Williams et al (2020) [104]	Double-blinded RCT	0 healthy men	Healthy male volunteers, aged 18–30 years, lived within 1 h of the clinic or planning to live in the region for the duration of the study	Previous testicular surgery Existing or previous cancer Allergy to tomato, whey protein or soy derivatives	0	No	Improved % of fast progressive (p=0.006) and normal morphology (p<0.001) No difference in SDF by TUNEL	N/A	3	1
13	Hamidian et al (2020) [121	Uncontrolled (open label	20 patients with recurrent pregnancy loss	Recurrency of pregnancy loss, age<40 years, no history of alcohol/drug abuse or smoking, altered semen quality	Obesity, diabetes, and varicocele Previous treatments with AOXs or other medications For the female partners, the presence of hormonal imbalance, chromosomal alterations, tubal obstruction, and bacterial or viral infections	1	yes	Improved sperm morphology (p=0.000) Reduced SDF by TUNEL (p=0.00) Reduced sperm protamine deficiency assessed by CMA3-based assay (p=0.00)	N/A	2	3
14	alehi et al (2019) [42	Uncontrolled (open label	485 infertile men with DFI>27% by SCSA	Aged 20–40 years	History of varicocele, surgery, and inflammation	1	no	Improved sperm concentration (p=0.003), total motility (p=0.001). Reduced DFI by SCSA (p=0.001) PR=16.8% for AOX treated patients	N/A	2	2
15	Hasoon (2019) [43	Uncontrolled (open label)	24 infertile men	Unexplained subfertility	Presence of organic or obstructive infertility	1	no	Improved volume, sperm count, motility, and normal morphology (p<0.005)	N/A	0	1
16	Ardestani Zadeh et al (2019) [57	Single blind RCT	60 varicocele patients	Varicocele patients who underwent sub-inguinal varicocelectomy	Usage of supplements Alcohol and/or drug addiction, smoking Diabetes mellitus, hormonal disorders, chronic or active infections Presenting side effects, and delayed complications of varicocelectomy	0	no	Improved sperm count (p=0.021) and motility (p=0.003)	N/A	2	1

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/ SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/ EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
17	Kızılay and Altay (2019) [56]	RCT unblinded	90 varicocele patients	Varicocele patients treated with varicocelectomy, with spouses<35 years old, regular hormone profiles and menstrual cycles and no identified cause of infertility	Previous genitourinary system and/or varicocele surgery IMI Any clinical condition affecting fertility for the previous 3 months Patients following a fertility specific diet Alcohol or drug abuse, smoking	0	yes	Improved TSC, sperm concentration, sperm count in normal morphology, and total and progressive motile sperm count (p<0.05) Higher PR in AOX treated patients than placebo group (29% vs. 17.9%, respectively; p=0.029)	Study powered to detect an effect size of d≥0.70 as statistically significant in a two-tailed test with α=0.05 and power of 0.80 with n=24 per condition.	3	1
18	Gambera et al (2019) [93]	Uncontrolled (open label)	32 OAT patients	nfertile patients with normal sexual development, medical history, serum hormone levels and physical examination	Azoospermia and infertility due to the female factor	0	yes	Improved sperm concentration, sperm count, progressive motility, normal morphology, and vitality Oxisperm test: reduced seminal oxidative stress after therapy (no pvalues reported	N/A	2	2
19	Jannatifar et al (2019) [92]	Uncontrolled (open label)	50 asthenozoospermic patients	Infertile couples with no previous report of pregnancy, normal female and male partners	Varicocele, leukospermia, hormonal abnormalities, and/or obstruction, cryptorchidism, vasectomy, abnormal liver function Smoking, alcohol consumption Anatomical disorders, Klinefelter's syndrome, cancer, fever in the 90 days prior to sperm analysis, seminal sperm antibodies	1	no	Improved sperm concentration (p=0.02), total (p=0.01) and progressive motility (p=0.001), normal morphology (p=0.001), TAC (p=0.01) Reduced levels of MDA (p=0.01), SDF by TUNEL (p=0.001), % of sperm showing protamine deficiency by CMA3-based assay (p=0.009)	N/A	1	3
20	Nouri et al (2019) [95]	Double-blind RCT	44 oligozoospermic patients	Infertile men (25–45 years), sperm count<20×106/ mL, normal sperm <65% and average motility <60%	History of anatomical disorders, endocrinopathy, previous hormonal therapy, use of androgens, antiandrogens, anticoagulants, cytotoxic drugs, or immunosuppressants Alcohol and drug abuse BMI≥30 kg/m	1	no	Improved volume, TSC, concentration, total motility, TAC (p<0.05)	N/A	2	2

SN	REFERENCE	STUDY DESIGN	STUDY POPULATION/ SAMPLE SIZE	INCLUSION CRITERIA	EXCLUSION CRITERIA	STRICT MALE INCLUSION/ EXCLUSION	FEMALE FACTOR	MAIN OUTCOMES REPORTED	POWER OF STATISTICAL ANALYSIS	STUDY QUALITY SCORE	STUDY OUTCOME (OUT OF 3)
21	Micic et al (2019) [94]	Double-blind RCT	Treatment (n=125) vs. placebo (n=50)	Total sperm number ≤15×106/ mL; progressive motility <32%; normal viscosity and normal leucocytes number (<1×106/mL); sperm vitality ≤58%; normal sperm morphology <4%	Motility<5% Sperm concentration <1×106/mL History of therapy for infertility within the last 2 months Alcohol consumption Undescended testes, post-pubertal mumps, endocrine and autoimmune diseases, cystic fibrosis, or testicular cancer Hypersensitivity to ingredients in Proxeed Plus Presence of endocrine disorders, anti-sperm antibodies, leukocytospermia Use of antioxidant agents or vitamins Involvement in other clinical trials	0	yes	Improved ejaculated volume (p=0.001), progressive motility (p<0.001), vitality (p=0.002) after treatment Reduced SDF by Halosperm test Increased seminal carnitine and α-glucosidase activity, positively correlated with improved progressive motility	N/A	4	3

Data are summarized and ranked based on the study design, the population investigated, the inclusion/exclusion criteria, the analysis of the female partner, the main outcomes reported, and the power of the statistical analysis. SN: serial number, RCT: randomized controlled trial, TMSC: total motile sperm count, N/A: not available, IVF: in vitro fertilization, SDF: sperm DNA fragmentation, MD: median, CI: confidence interval, β-HCG: beta-human chorionic gonadotropin, LBR: live birth rate, ns: non-significant, DFI: DNA fragmentation index, SCSA: sperm chromatin structure assay, AOX: antioxidant, IMI: idiopathic male infertility, ORP: oxidation reduction potential, UMI: unexplained male infertility, BMI: body mass index, 8-OHdG: 8-hydroxy-2' -deoxyguanosine, MDA: malondialdehyde, PR: pregnancy rate, CoQ: coenzyme Q, TAC: total antioxidant capacity, GPx: glutathione peroxidase, ROS: reactive oxygen species, SCD: sperm chromatin dispersion, OAT: oligoasthenoteratozoospermia, TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling, CMA3: chromomycin A3, TSC: total sperm count.

DISCUSSION

Male infertility is a prevalent issue that negatively impacts couples' ability to conceive. Oxidative stress is a common mechanism mediating these etiologies and risk factors [1,2,5,6], and the use of antioxidants as a therapy option for male infertility has expanded. However, opinions on the effectiveness, indications, dosage, and duration of treatment are still divided [8-11]. This study aimed to comprehensively examine the literature of trials looking into the use of antioxidants in male infertility and suggest some general advice for practicing clinicians.A systematic review by Majzoub and Agarwal (2018) [10] found 26 studies that demonstrated the beneficial benefits of exogenous antioxidant intake on the quality of sperm and pertinent outcomes of assisted reproduction, such as live birth rates. However, these studies were administered to a small number of men for a brief length of time, lacking a standardized test to measure oxidative stress levels in sperm and seminal fluid. The variability of study designs made it difficult to compare the effects and draw a reliable conclusion.

The study examined 60 studies (61.9%) that examined a range of markers of seminal oxidative stress, such as oxidative DNA damage (8 – hydroxy – 2 – deoxyguanosine) , lipid peroxidation markers (malondialdehyde) levels of seminal ROS, and/or several endogenous antioxidants (e.g., total antioxidant capacity assay, superoxide dismutase, catalase, glutathione) and/or oxidative-reduction potential (ORP) (Table 2).The lack of standardization in the assessment of oxidative stress in seminal fluid prior to and following therapy, the absence of thorough methodological explanations in most publications evaluating oral antioxidant supplementation, and the varying length of therapy in the examined research further complicated the findings (Table 2).A meta-analysis utilizing data from seven randomized controlled trials (RCTs) found that men with idiopathic oligoastheratozoospermia can benefit from combined L-carnitine (LC) and L-acetyl carnitine (LAC) therapy [122]. The study found that increased pregnancy rates may result with LC+LAC combination therapy. However, a

strong conclusion is hampered by several limitations, including room for interpretation when making the clinical diagnosis of idiopathic oligoastheratozoospermia, substantial variation between studies in the number of patients selected, and the lack of knowledge on the chemicals' bioavailability.

CRITICAL EVALUATION OF THE NECESSITY OF ADDITIONAL DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIALS

Of the 90 studies examining the impact of antioxidant treatment on semen parameters, 70 were considered low quality, and only 20 were of excellent quality. Both low- and high-quality studies showed that antioxidant treatment significantly improved semen parameters. However, there is a lack of high-caliber research to produce meaningful findings. Fertilization is a complex process, and oocyte quality must be considered when examining fertilization, pregnancy, and live birth rates. A meta-analysis by Smits et al. (2019) found that oral antioxidant supplements can increase live birth rates and reproductive potential in infertile males. However, due to research restrictions, the evidence was considered poor or very low quality, making it difficult to compare and aggregate data for reliable statistical analysis. Clinical pregnancy and live delivery are crucial outcomes for couples undergoing fertility therapy, but these statistics are rarely reported in research. The majority of studies on the application and efficacy of antioxidants focus on male participants, not couple standardization[11]. Confounding variables such as female age, ovarian reserve, anatomic, inflammatory, and endocrine problems can affect these outcomes, making it difficult to evaluate the effectiveness of any fertility treatment.
To better understand the effectiveness of antioxidant treatments for men, it is essential to evaluate how well they improve seminal parameters and sperm function. This can have a significant negative impact on blastulation, embryo development, the onset and continuation of pregnancy, and live birth. Identifying the andrological illness that patients are receiving therapy for is essential to assess the efficacy of the intervention.21 papers published between January 2019 and July 2020 examined the impact of antioxidant therapy on semen quality, with most revealing improvements in sperm and semen parameters. However, many studies did not sufficiently establish criteria for female factors, which could impact the study's findings. In addition, individual research may highlight important topics, such as non-specific treatment off-site, early stop-ups, and compliance with antioxidant therapy. Overall, a comprehensive review of the literature is needed to better understand the impact of antioxidant treatments on fertility outcomes

Moreover, Terai et al. [98] used an experimental group studying a Chinese herbal compound rather than a placebo group. Improvements in semen parameters were reported by Hadi et al. [45], Alahmar et al. [97], Hamidian et al. [121],

Salehi et al. [42], Hasoon [43], Gambera et al. [93], Arafa et al. [25], Nazari et al. [101], and Jannatifar et al. [92], however these investigations are uncontrolled open label trials and are rather small in size. Additionally, unblinded experiments with relatively small sample sizes (n = 51 and 31, respectively) were conducted by Alkumait et al. [100] and Terai et al. [98]. However, there are a number of commendable aspects of the evaluated studies as well. For instance, Agarwal et al.'s work [129] examined how antioxidant therapy affected protein expression, which improved our knowledge of the molecular modifications to physiology. Numerous investigations evaluated how antioxidant therapy affected SDF levels (Table 2). Because of the previously mentioned factors, conducting additional double-blind RCT studies with a sizable enough sample size is not practical nor likely to yield the desired, definitive outcome of higher live birth rates following antioxidant treatment.

SWOT ANALYSIS,

STRENGTHS,WEAKNESSES, OPPORTUNITIES, AND THREATS

1.STRENGTH

Over the past decade, research has increasingly explored the use of antioxidant supplements to treat male infertility. Various formulations have been used to improve sperm quality and function, leading to improvements in reproductive outcomes like birth rate (Table 2). The growing body of research also examines how antioxidant therapy affects oxidative stress metrics, suggesting it may be a viable therapeutic option for individuals with altered seminal redox potential.

2. WEAKNESSES

The systematic use of antioxidants for treating male infertility is restricted due to conflicting results in trials, which did not consider female and embryological confounding factors (Table 2). The treatment was assumed to improve reproductive outcomes, and low quality evidence was inferred from benefit-reporting clinical trials due to non-homogenous study designs or inconsistent usage of individual or combination therapy regimens. Most studies did not account for confounding variables, such as female characteristics, crucial for pregnancy formation.

3. OPPORTUNITIES

Oxidative stress monitoring can identify potential candidates for antioxidant supplementation in idiopathic infertile males [25]. The concept of MOSI can help identify a subset of males who may benefit from the treatment [2]. Oral antioxidants can be a more affordable alternative for infertile couples who prefer not to undergo assisted reproduction (Fig 3) [129].

4.THREATS

A consensus among doctors remains elusive despite the result from Cochrane reviews that oral antioxidant therapy may improve semen parameters and the likelihood of conception [11].

This is due to a lack of sufficient high-quality evidence. Furthermore, the large range in the treatment plan prompts questions regarding the overuse of antioxidants. Reductive stress can have harmful consequences that are just as pathogenic as oxidative stress [23]. Furthermore, the frequently erratic results of antioxidant supplements in the presence of numerous confounding variables in reproduction may cause a delay in the start of the final course of treatment, especially for older couples.

Fig 3. Strength weakness opportunity treat (swot) analysis. The effect of antioxidant supplementation in the management of male inferyility has been examined using SWOT analysis,. Assisted reproductive technologies, or

CLINICAL GUIDELINES

Doctors have yet to reach a consensus on the effectiveness of oral antioxidant therapy in improving semen parameters and conception likelihood, despite Cochrane reviews showing promising results [11]. The large treatment plan raises concerns about overuse of antioxidants, as reductive stress can have harmful consequences [23]. Additionally, the erratic results of antioxidant supplements, combined with confounding variables in reproduction, may delay treatment, particularly for older couples. The use of antioxidant supplements for treating male factor infertility is not well-established, and a systematic review of 97 papers examined the impact of antioxidant treatment on different causes of male infertility. However, there is insufficient data to provide evidence-based recommendations for antioxidant use, as few studies have examined its impact on semen quality in men with genitourinary inflammation (n = 3) , hyperinsulinemic states (n = 1), and recurrent pregnancy loss (n=1)(Table 2)

The limited number of studies and challenges in recruiting a large enough patient population make statistical analysis difficult. However, some high-quality studies are available, but the number of investigations in specific conditions and using predetermined criteria would be too high. The use of antioxidant treatments would be futile without proper patient identification and testing for oxidative stress. Based on the evaluated research, recommendations for antioxidant treatment were developed for males with abnormal semen quality, IMI, UMI, and clinical varicocele. However, the previously published studies cannot be considered high-quality due to improper reporting of

characteristics. If oxidative stress is the cause of the illness, antioxidant treatment is feasible and may lead to improved male seminal parameters. However, therapy needs to be closely monitored to prevent antioxidant overdose and to determine if other therapies are necessary or if the therapy is not working as intended.

1.ABNORMAL QUALITY OF SEMEN

Antioxidants have been studied as a potential treatment for reactive oxygen species (ROS) toxicity, particularly in the reproductive system. Seminal oxidative stress is a prevalent pathology. A review found that low-quality studies claimed significant improvements in sperm function measurements and traditional semen parameters, but credible research did not find this. A recent Cochrane review showed gradual improvement in conventional semen characteristics, but the results were not trustworthy due to significant variation among trials [11].

2.THE VARICOCELE

About 40% of men with primary infertility and up to 80% of men with secondary infertility have varicocele, the most common correctable cause of male infertility. Research has shown that infertile men with varicocele exhibit elevated levels of oxidative stress, which could support the use of antioxidants as a preventative measure against varicocele. However, in most cases, the gold standard procedure for long-term improvements in semen characteristics and natural conception is still varicocelectomy [137]. Most research investigating the impact of antioxidant supplementation on sperm function and semen parameters was of poor quality, and there is insufficient data to justify the use of antioxidants as the only treatment for varicocele. A recent comprehensive review and meta-analysis investigated the effectiveness of antioxidants in enhancing semen quality following varicocelectomy [138]. The study found notable improvements in sperm concentration ($p<0.001$), overall motility ($p=0.03$), progressive motility ($p<0.001$),and normal morphology ($p<0.001$). for the therapy group, but pregnancy rates did not rise. This result confirms that antioxidant therapy has an additional benefit on individuals having varicocelectomy, and that antioxidants and varicocele ligation together lead to additional improvement in semen parameters (grade C recommended).

3.IDIOPATHIC MALE INFERTILITY AND INFERTILITY IN MEN WITHOUT APPARENT CAUSE

Antioxidants are often used to treat patients with Infertility-Metabolic Syndrome (IMS) or Uncontrolled Menstrual Infertility (UMI), which are characterized by abnormal semen and infertility. The prevalence of IMI and UMI is between 30%-58% and 6%-27%, respectively. Oxidative stress is present in 30%-40% of UMI patients and up to 80% of IMI patients, and it is believed to play a significant role in the pathophysiology of infertility. High-quality research shows that antioxidant use significantly improves sperm function and semen parameters

in men with IMI and UMI. However, further research is needed to achieve statistical significance. A systematic analysis of 32 trials found improvements in semen parameters, with sperm motility showing the greatest benefit. Antioxidant therapy has not been well studied in people with UMI, but a recent trial showed a significant drop in ORP levels and SDF levels after treatment. Antioxidants are strongly recommended to improve sperm quality in males with IMI and UMI, with a grade B recommendation.

THE PRESENT SITUATION AND RECOMMENDATIONS FOR ANTIOXIDANT RESEARCH IN THE FUTURE

Reactive oxygen species (ROS) play a crucial role in the physiological processes of sperm fertilization and their impact on sperm functionality. To achieve therapeutic effects, the proper ratio and concentration of antioxidants are critical. Oxidative stress assessment needs to be standardized, as many studies lack measurement or use various methods. Secondary Deoxygenated Peroxide (SDF) is a significant predictor of future fertility and is increasingly used in the assessment of male factor infertility. SDF testing can help identify patients who may benefit most from antioxidant therapy and how well they respond to it. Treatment options for high SDF results include recurrent ejaculation, antioxidant therapy, lifestyle changes, varicocelectomy, and using testicular sperm for ICSI or other sophisticated sperm selection techniques. Finding the secondary effects of bioactive substances and their molecular mechanisms of action is crucial for the safe application of oral antioxidants in a therapeutic environment. Oral antioxidant prescriptions should be tailored or modified based on variables such as antioxidant enzyme levels and reactive oxygen species (ROS) found in spermatozoa and seminal fluid. Reproduction should be seen as a shared responsibility of both partners, with both contributing equally to the reproductive outcome. High antioxidant levels have the

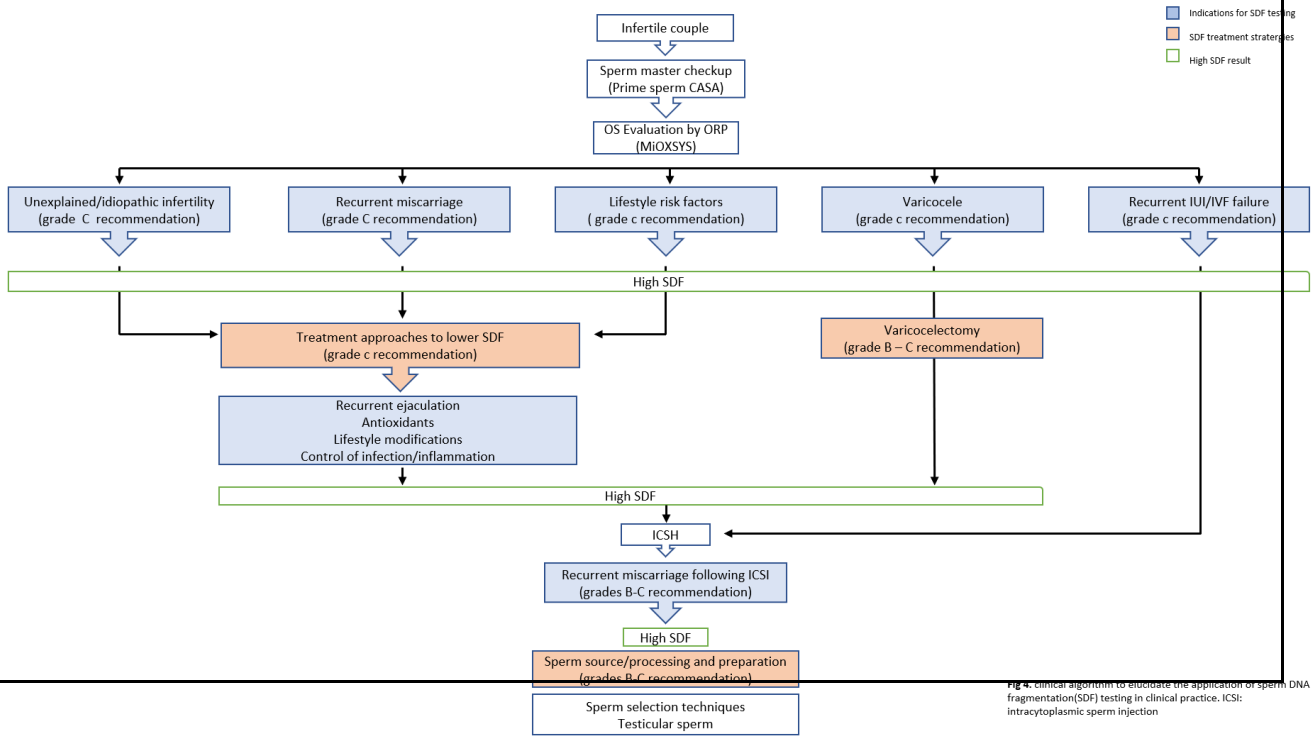

Fig 4. Clinical algorithm to elucidate the application of sperm DNA fragmentation(SDF) testing in clinical practice. ICSI: intracytoplasmic sperm injection

potential to cause teratogenic effects, and trials reporting antioxidants on male infertility are heterogeneous

CONCLUSION

This systematic review highlights the advantages of oral antioxidants in enhancing semen parameters and pregnancy outcomes. However, there are five primary obstacles that have hindered their widespread adoption in the management of male infertility: lack of randomized, placebo-controlled trials, type of antioxidant to be taken, dosage, length of therapy, and cost. To address these challenges, it is recommended to use antioxidants that can pass across the blood-epididymis and blood-testis barriers. A well-balanced formulation is essential to avoid paradoxical prooxidant effects and less than ideal antioxidant effects. Dosage should be high enough to minimize oxidative stress and restore normal physiological cellular functioning while maintaining the physiological role of reactive oxygen species (ROS) in sperm maturation and fertilization reactions. A minimum of two weeks of treatment is recommended to prevent damage caused by ROS in the epididymis. Antioxidant therapy should be advised until pregnancy is established, as oxidative stress in the epididymis is constitutive and antioxidants have no negative side effects. SDF testing is increasingly used in the evaluation of male factor infertility due to its impact on proper fertilization, embryo growth, and the efficacy of ART. High SDF results can improve patients' chances of becoming pregnant, and further research is needed to identify which cases need improved detection methods for sperm selected for ICSI. Lastly, the cost argument must be considered when considering the sponsors of excellent randomized, double-blind, placebo-controlled clinical trials. Natural antioxidant formulations are inexpensive and supported by safety, effectiveness, and cost savings for patients and healthcare systems. In conclusion, it is recommended to use antioxidants easily absorbed via the blood-epididymis and blood-testis barriers.

Conflict of interest

The author declared no conflict of interest

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