

Review

Pre-Conceptual Guidelines for Men: A Review of Male Infertility Experience, including Nutrition and Lifestyle Factors

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Abstract: Male fertility is declining and affects approximately one in seven couples. Reasons for this are multi-factorial and the subject of on-going research, though environmental contaminants (such as xenoestrogens) are believed to be contributory factors. Semen parameters can be improved through a healthy diet and nutritional supplementation has also been shown to improve semen parameters, clinical pregnancy and live birth rates significantly. Despite this, in medical care dietary modification beyond alcohol reduction is rarely recommended. The aim of this review was to consider the psychosocial impacts of infertility in males whilst assessing other nutritional and lifestyle interventions that can be used in personalized nutrition care. More tailored nutrition care needs to consider this and the taboo surrounding the male infertility experience. A systematic approach was used. Three electronic databases (CINAHL, Medline and Academic Search Complete) were searched using predetermined Boolean search terms and identified 125 papers for review. Hand searches were undertaken to ensure recent evidence was included. Duplicates were removed and predefined inclusion and exclusion criteria were applied. Narrative synthesis was used for review and to develop preconceptual guidelines. Review data indicates dietary modification or supplementation with antioxidants such as vitamin C, vitamin E, coenzyme Q10, selenium, carnitine and zinc have been shown to improve markers of male fertility and reduce markers of seminal oxidative damage. Also, a Mediterranean style diet is also associated with higher quality sperm counts. Weight loss is beneficial in terms of normalizing endocrine profiles but at present it is not possible to determine if this is the effect of weight loss alone, or the combined effect of weight loss alongside other dietary improvement. Further research is therefore needed to understand the role of the many potential confounding factors. Despite this, infertility is emotionally challenging for men and nutrition, and personalised nutrition and lifestyle therapies have potential to support men trying to conceive. Pre-conceptual nutrition and lifestyle guidelines for men have been developed from this review and the use should be considered as the basis for more tailored nutrition care in practice.



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1. Introduction

Clinical infertility is defined as a couple's failure to conceive following 12 months of unprotected intercourse without pregnancy [1]. It has been reported that male fertility is declining across the world [2], the World Health Organisation (WHO) estimates that there are between 45–80 million infertile couples globally [3,4]. It is estimated that one in seven couples in the UK experience problems conceiving [5], with male factor infertility accounting for 40–50% of all infertility cases [6]. Low sperm count is the most common cause of infertility, responsible for approximately 15% of all cases of male infertility [5]. Many factors may contribute to reduced fecundity such as poor sperm morphology, reduced motility, reduced DNA stability [7], genetics, environmental toxins, reduced testosterone levels and medical conditions.

To determine if a man is infertile, semen analysis and a physical examination are undertaken [8]. Semen analysis typically looks at: volume of ejaculate, sperm count, sperm motility and sperm morphology [9]. DNA fragmentation is not routinely assessed as part of fertility examinations and not considered as a part of typical semen analysis, but it has been shown to significantly increase the incidence of miscarriage [10].

WHO parameters for semen analysis were published in the laboratory guidance for measurement of human sperm [11]. A measure of infertility was not available for men until 1980 when the WHO published its first laboratory manual for the examination of human sperm [12]. In 2010, there were significant reductions to the parameters used to determine infertility. Sperm count was the most significant reduction, reducing from 20 million/mL to 15 million/mL [11]. To generate the WHO semen parameters Cooper et al. [13] pooled data from 5 studies to form centiles and determine upper and lower limits of fertility. Only one study was from the Southern Hemisphere, with the remaining studies from predominantly European cities, which may not accurately reflect fertility in other geographical or rural areas. Fisch & Goluboff [14] concluded there are significant variations in sperm counts by location, which presents an issue when developing global parameters that have not used a world-wide cohort. As a result, the reference values may not be relative or representative of male fertility in many areas of the world, or representative of ethnic minority populations living in western countries. It is estimated that at least 15% of infertile couples will now be classed as being in normal ranges, significantly reducing the number of couples referred for fertility treatment [15]. In the 6th edition of the WHO laboratory manual for the examination of human sperm the researchers did address the concerns regarding the data used for determining the upper and lower limits of sperm parameters [12]. The researchers highlighted that the 5th edition was the first publication that contained a comprehensive data set to determine centiles of sperm count, concentration, motility and morphology [12]. However the narrow range of data selection highlights the need to conduct high quality semen analysis studies in developing countries which can hopefully contribute the global picture of male fertility in time for the next updated manual.

In the UK, the National Health Service [16] recommends that couples visit their General Practitioner if they have not conceived after one year of trying to conceive and those struggling to conceive after one year should be sent for fertility testing [17]. At this point there is information provision of modifiable lifestyle behaviours such as smoking, alcohol consumption, recreational drug use, obesity, caffeine and tight underwear to maximise chances of conception [17]. However, it seems no western countries have published nutritional and lifestyle preconception guidelines for men [18].

Current evidence suggests significant improvements in semen parameters through diet and supplementation [19,20], but more detailed lifestyle or nutritional advice is rarely given by healthcare professionals. Despite the increasing trend in male factor infertility, it still remains largely taboo [21] and the male experience of infertility is a poorly researched area [22] hence improved understanding should help improve care of these individuals. Recent research suggests infertile men experience lower self-confidence, self-esteem and impaired sexual performance compared to fertile males [23]. Moreover, Rossi et al. [24] found that the majority of men undergoing fertility treatment did not believe diet, caffeine, artificial sweeteners, or over-the-counter medicines affected fertility. Additionally, it was reported that respondent's beliefs were influenced by their physicians (84%) and the internet (71%) [24], highlighting the need for wider awareness of the potential for lifestyle and personalised dietary therapies as adjuncts in the treatment of male infertility. Moreover, there are reports that men themselves perceive infertility as more stigmatizing for them than for females [25]. Therefore, the aim of this paper is to review evidence on the psychosocial impacts of infertility in males whilst assessing other nutritional and lifestyle interventions to facilitate improved nutrition counselling for infertile and sub-fertile men. This is also potentially important in terms of the health of offspring as the quality of sperm is related to both fetal outcomes and also significant in terms of health outcomes of offspring in later life. This theory is known as the Developmental Origins of Health and Disease [26]

and it highlights how later outcomes of health and disease (particularly regarding future metabolic health) occurs via the control of gene expression through mechanisms such as external environmental factors, including maternal or paternal diet.

2. Methodology

A systematic approach was used to search the following databases for full text articles and abstracts: Academic Search Complete, CINAHL, MEDLINE, additional hand searches of bibliographies were conducted using the Cochrane Library and Google scholar to ensure recent evidence has been identified. The databases were searched on four broad topics; psychosocial impact of male infertility, diet and lifestyle factors affecting sperm parameters, environmental factors affecting sperm health and the effect of supplementation on sperm health. The Boolean operatives used in all three searches along with the number of search results can be seen below in Table 1. The broad search terms returned a large number of results, so inclusion criteria were applied to search for research dated from the year 2000 until the present day. It is important to note some review papers included in the data analysis, reviewed publications prior to the year 2000. Duplicates and animal studies were excluded; and the results were then filtered by sex to include male only and by age to reduce the age range to 19–64 years old. Ethical guidance from the University of Worcester was followed, and ethical approval was granted for the project that this review is a part of in September 2020. This review project was followed by an empirical study investigating the lived experience of men with infertility, also exploring their views on lifestyle and nutritional interventions that can support fertility.

Table 1. Search terms, inclusion/exclusion criteria and search results.

Search 1—Psychosocial impact of male infertility
<p>Search terms used: mental health OR depression OR anxiety OR stress OR wellbeing OR well-being OR emotional health OR Psychosocial AND (male infertility or male fertility or sperm quality or semen quality)</p>
<p>Inclusion criteria Date published 2001–2021, Male, English, Age 19–64 years old</p>
<p>Exclusion criteria Animal studies, age 65+ years, age < 19 years, gender not specified.</p>
<p>Results returned: 33 Studies included in the narrative review: 18 13 studies excluded for not being relevant to the search terms or for including couples or women</p>
Search 2—Nutrition and male infertility
<p>Search terms used: male infertility or male fertility or sperm quality or semen quality OR astheonzoosperm) AND (Diet OR Nutrition OR Supplement OR Antioxidant OR Lifestyle OR Obesity)</p>
<p>Inclusion criteria Date published 2000–2021, Male, English, Age 19–64 years old</p>
<p>Exclusion criteria Animal studies, age 65+ years, age < 19 years, gender not specified</p>
<p>Results returned: 104 Studies included in the narrative review: 82 31 articles were excluded due to not being relevant to the search terms which included genetic polymorphisms interventions for couples and participants with varicoceles</p>
Search 3—Environmental toxins and male infertility
<p>male infertility OR male fertility OR sperm quality OR semen OR DNA fragmentation AND (environmental toxins OR chemicals OR radiation OR mobile OR plastics) NOT (Cancer OR Carcinoma OR Chemo* OR Radioth*)</p>
<p>Exclusion criteria Animal studies, age 65+ years, age < 19 years, gender not specified, infertility related to medical treatment</p>
<p>Results returned: 31 Studies included in the narrative review: 13 8 articles were excluded for not being relevant to the search terms including cancer patients and genetic poly morphisms</p>

Table 1. *Cont.*

Additional hand searches —Total 12 articles
Additional articles were found to include electronic devices and radiation (3) BPA/bisphenols (3) phthalates (2) pesticides (2) stress and fertility (2)

* Truncated search term.

3. Data Analysis

Studies were critically appraised, and the findings were analysed by narrative synthesis around the four broad topics aligned to the research aims and objectives. These included psychosocial impact of male infertility, diet and lifestyle and environmental factors affecting sperm parameters and the effect of nutritional supplements on sperm health. The papers were also organized into a table (see Supplementary Material Table S1) under the following themes with main findings and country of study reported (i). General male fertility information (trends, sperm parameters) (ii). Psychosocial impact (iii). Lifestyle factors and male fertility (iv). Dietary impacts on male fertility (food and drink) (v). Nutritional supplementation and male fertility (vi). Environmental impacts on male fertility. A paper was only allocated into one theme (considered most relevant by the researchers). A synoptic critical synthesis was then generated and is reported below.

4. Findings

There is a general lack of interventional studies investigating the impact of poor dietary patterns on semen parameters, presumably because it is not ethically justifiable to cause harm to participants through adherence to an unhealthy diet. Therefore, much of the data is observational. There are also differences in reporting, study design and outcome measures that make uniform conclusions from systematic reviews and meta-analysis challenging [27]. For example, there are many outcome measures indicative of sperm quality (these can include volume, motility, concentration, morphology and DNA fragmentation) which can make comparison of studies difficult. However, data from interventional studies on dietary supplements and findings from systematic review or meta-analysis are discussed further below.

4.1. Male Emotional Experience of Infertility

Relatively little is known or understood about the mental, emotional and psychological impact of male infertility. Arya and Dibb [25] conducted one of only two UK specific research projects investigating the male experience of infertility and concluded that research is limited globally. A large proportion of the research investigating the psychosocial impact of infertility was investigating the female experience or that of couples [28,29]. The scarcity of research makes drawing conclusions on the true impact of male infertility on men challenging, which may be attributed to the societal notion that men are reluctant to talk about their feelings or emotions [22]. This may explain why it has been suggested that women experience a greater level of distress and sense of loss when undergoing fertility treatment, due to a disproportionate lack of research from the male perspective [30,31]. In contrast, Patel et al. [32] found that stress was pervasive in infertile men, experienced by 72% of men attending a fertility clinic in India and that the level of stress could be predicted by the severity of their diagnosis. However, it is possible that cultural differences and expectations to father a child may contribute to higher levels of perceived stress in Indian men [33]. Indeed, infertility is still a taboo subject among black and minority ethnic (BAME) populations [34].

Stress during male fertility treatment can negatively affect testicular function and fertility [35]. It has been demonstrated that increased levels of stress suppress testosterone production [36]. Research has also linked chronic lifestyle stress as a potential mechanism contributing to reduced sperm quality. The researchers suggested that this is due to glucocorticoid receptor activation which impairs testicular function and germ cell maturation possibly due to a single nucleotide polymorphism (SNP) on the NRC31 gene [35]. Hanna and Gough [21] found that many men in the UK ‘suffer in silence’ for fear of being singled

out by their peers. A study by Hanna and Gough [37] qualitatively analysed posts from male fertility support groups which have international reach or included supporting male partners, findings mirror the results of Thorsby & Gill [38]. In both studies men reported having their virility undermined and being subjected to hurtful male culture. Research also suggests that men do not want to discuss their fertility in person [39] but that they are open to seeking help online from men undergoing the same experience [40]. The reluctance to talk about infertility contributes to the scarcity of research on the subject [41]. However, a recent thematic analysis of online male infertility chat forum posts found that men are committed and support each other with lifestyle changes to improve their chances of conception [42]. When men are infertile there is a great burden placed on the female partner as they are the subject for the majority of fertility interventions [43]. Unfortunately, this also leads to men feeling over overlooked and unacknowledged during fertility treatment [25,37].

4.2. Dietary and Lifestyle Factors Affecting Fertility

4.2.1. Obesity

Obesity is known to reduce fecundity in both men and women [44]. A systematic review by Sermondade et al. [45] investigating the association of obesity and semen health concluded that obesity is associated with reduced semen concentration. Håkonsen et al. [46] demonstrated that reducing BMI can improve semen parameters during a 14-week intensive weight loss programme with a small cohort of 43 men. Although it is difficult to determine whether the benefits are the result of weight loss or the change in lifestyle, there is no doubt that reducing BMI is beneficial for health overall [47]. High energy diets have been shown to reduce male fertility via alterations in testicular metabolism and increased sperm DNA damage [48,49].

4.2.2. Dietary Fats

Dietary fats are essential for human health and play a central role in cell membrane formation and normal maintenance of hormone levels in the human body. A recent systematic review and meta-analysis found that low fat diets reduce testosterone levels in men, with the greatest impact being on Caucasian men [50].

4.2.3. Trans Fatty Acids

Approximately 20% of trans fatty acids (TFA) occur naturally in meat and dairy products, industrially produced hydrogenated fats used in food manufacturing now account for 80% of TFA intake [51]. Most studies suggest a negative association between TFA intake and male fertility through disruptions in testosterone levels, testicular function and sperm cell membrane quality [52]. No studies were found demonstrating a positive association between TFA and sperm health, Chavarro et al. [53] found that there was a linear dose related decrease in sperm count with every increased quartile of TFA intake. A comprehensive review by Cekici & Akdevelioglu [54] reported a significant negative association between TFA intake, sperm health and fertilization rates, however this study had some distinct methodological issues. There were a total of 8 studies included in the review totaling 1355 men. The largest study in the review [55], had a cohort of 701 young Danish men. This one study made up over 50% of the total cohort, however it did not distinguish between saturated fat and TFA, which is a limitation. It is known that TFA intake is associated with several negative health consequences [56] and it is likely that decreased sperm quality is included in that list, however more research and better designed studies are needed to truly assess the risk.

4.2.4. Saturated Fat

Research relating to saturated fat intake is conflicting. Several studies have correlated increased saturated fat intake to declining sperm concentrations by as much as 38% [53,55,57]. In contrast, a study by Dadkhah et al. [58] only found a correlation between decreased total semen volume and saturated fat, reporting that no differences were

observed in any other measure of male fertility. The relationship with saturated fat and sperm health needs further investigation as high saturated fat intake is often related to other unhealthier dietary patterns in general that may adversely affect sperm health.

4.2.5. Polyunsaturated Fatty Acids

Polyunsaturated fat (PUFA) intake is correlated to a variety of positive health outcomes from improved blood lipid profiles to alleviation of joint pain and depression [59]. Increasing PUFA intake is a common intervention for improving markers of male fertility. Unfortunately, strong evidence is lacking, in the most part due to the nature of dietary analysis using food frequency questionnaires (FFQ), meaning that any relationship outlined cannot prove causation [57,60]. However, supplementation with eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega 3 fatty acids have been studied in controlled trials (RCTs). Three RCT's and one Meta-analysis were found which all showed beneficial effect of omega 3 supplementation on semen parameters at dosages ranging from 500 mg to 2000 mg/day [60–63].

A double-blind placebo controlled RCT by Gonzalez-Ravina et al. [63] found that DHA supplementation showed a dose dependent improvement in progressive motility and slight improvements in markers of oxidative stress in men with asthenozoospermia at dosages of 0.5 g, 1 g and 2 g per day. The systematic review and meta-analysis by Hosseini et al. [61] found that omega 3 supplementation significantly increased sperm motility and seminal DHA concentrations but no other markers of fertility significantly.

4.2.6. Mediterranean Diet

Healthy diets are correlated with better semen parameters [64], with higher intakes of foods rich in folates such as fruits and vegetables associated with reduced DNA fragmentation and increased motility [65]. Diet has been shown to effect sperm replication via alterations in ribonucleic acid (RNA) concentrations, both positively and negatively in as little as one week, depending on whether the participant is eating a healthy or unhealthy diet [66]. The Mediterranean diet is considered one of the healthiest diets in the world, typically minimally processed and rich in fruits, vegetables, beans, pulses, fish, nuts and seeds [67] and so naturally a rich source of vitamins and antioxidants including vitamins C, D, E, Beta Carotene, zinc, selenium and omega 3 [19]. This rich source of nutrients and antioxidants is what correlates the Mediterranean diet to increased sperm count, concentration [68] and increased rates of conception among those undergoing assistive reproductive technology (ART) [69]. Unfortunately, there were no randomised interventional studies that could be found investigating sperm health and the Mediterranean diet.

4.2.7. Caffeine

Evidence regarding caffeine's impact on sperm health is far from unanimous, with much of the data coming from observational studies. Jensen et al. [70] found that there was a relationship between high intake of caffeine and decreased semen quality although, only a significant relationship for cola consumption. It has been suggested that individuals who consume sweetened beverages regularly, including cola, are more likely to engage in other unhealthy lifestyle behaviors [71], which may also negatively affect semen parameters. Ricci et al. [72] found that men who drank 3 or more cups of coffee per day had higher levels of sperm DNA damage. Conversely the largest meta-analysis investigating the effect of lifestyle factors on fertility, with a cohort of 29,914 found no significant relationship between caffeine and semen health [73]. Therefore, low to moderate caffeine intake does not appear to have any significant impact on sperm health [74]. A recent meta-analysis and systematic review by Ricci et al. [72] found that caffeine was possibly associated with an increase in sperm DNA damage and increased time to pregnancy, although this was associated with high caffeine consumption above 400 mg/day. A large meta-analysis of 201 studies on caffeine and health outcomes by Poole et al. [75] deemed caffeine to have positive health outcomes for the majority of studies except pregnancy, where it was linked to miscarriage

and low birth weight in newborns. This highlights the need for individualised lifestyle recommendations for both men and women, as caffeine avoidance can be described as a significant challenge for many men. Low to moderate consumption of tea and coffee should not negatively impact sperm health.

4.2.8. Alcohol Consumption

It has been suggested that alcohol consumption has a negative impact on semen quality [76]. A lack of heterogeneity of participant selection and classification was a limiting factor for many studies such as the study by Martini et al. [77] in which non-drinkers were classed as those who consumed less than 500 mL wine or equivalent per day. This makes any uniform conclusions between studies difficult. A study by Jensen et al. [70] found that moderate to heavy alcohol consumption was associated with a 33% reduction in sperm concentration. The authors concluded that this was due to disruptions in testosterone and Sex hormone binding globulin (SHBG). The same study also concluded that independent episodes of bingeing were not associated with decreased semen quality. A recent meta-analysis of 15 cross sectional studies totaling 16,000 participants by Ricci et al. [78] found that there were significant reductions in semen volume and morphology in those who drink daily compared to occasional or never drinkers. The authors concluded that moderate consumption did not adversely affect semen parameters. In chronic heavy drinkers a steady decline in semen quality can be seen, which rapidly returns to normal within 3 months of abstinence [79]. Based on the available evidence it seems clear that moderate to high levels of alcohol have a significant detrimental effect on semen health. Low and occasional alcohol intake does not appear to have any significant effect on semen health.

4.2.9. Smoke (Tobacco and Surrogates)

Early research on the subject of tobacco smoking from 2004 was confounding, partly due to poor study design where smokers were compared to drinkers and there was no statistical difference in sperm quality in smokers regardless of the level of consumption [77]. However more recent research that analyzed smokers sperm health independently of drinkers found that tobacco smoking was associated with decreased concentration, motility, morphology, increased oxidative damage and increased levels of DNA damage in sperm cells [76].

4.2.10. Recreational Drugs (Marijuana and Analogues)

No searches in this study were returned specifically on recreation drugs such as marijuana, so even though these can be significant in terms of male fertility consideration of these is outside of the scope of this review.

4.3. Micronutrient Supplementation

The most comprehensive review of antioxidants, pregnancy and semen parameters comes from a Cochrane review [80]. Cochrane reviews are a stringent method of conducting systematic reviews and meta-analysis using only data from RCT's [81]. The study was originally conducted in 2011 with a total of 34 studies reviewed. The updated review in 2019 had 61 studies included dating from 1978 to 2018. Following appraisal with the Critical Appraisal Skills Programme (CASP) checklist for systematic reviews [82] it is unclear if appropriate studies were included in the review as only 18 studies reported on the authors primary outcome, which was live birth or clinical pregnancy. The 43 remaining studies did not report on this outcome, instead focusing on semen parameters. Therefore, it may not be justified for the researchers to conclude that the level of evidence is low due to not reporting on clinical pregnancy, when this was not the objective of the majority of studies in the review. Despite this potential limitation, the authors concluded that supplementation with vitamins and antioxidants may be beneficial in improving male fertility, with an increased in pregnancy rate of 26% compared to 11% for placebo or no treatment. This concurs with the findings of the systematic review and meta-analysis by Majzoub and

Agarwal [83], reporting that there is a significant positive effect of antioxidant therapy on semen parameters, assisted reproduction outcomes and live birth rate.

4.3.1. Antioxidant Effects on DNA Fragmentation

DNA fragmentation is the term used to refer to damage to the DNA structures contained within the sperm cell. This damage to DNA can occur through exposure to heat or as a result of oxidative damage caused by reactive oxygen species [84]. Increased levels of DNA fragmentation are associated with reduced fertilization rates, reduced motility [85] and increased incidence of miscarriage [10,86]. Several nutritional supplements have been shown to improve markers of fertility and reduce the amount of reactive oxygen species in the semen. These supplements will be summarised below.

4.3.2. Co Q10

Co Q10 or ubiquinol, is a naturally occurring antioxidant, found in meat, fish and nuts that plays an important role in cellular metabolism and energy production [87]. Co Q10 is found in high concentrations in seminal fluid, neutralizing reactive oxygen species that may damage the structure or function of the sperm cell [88]. Co Q10 is also found in the mitochondria of the spermatozoa where it facilitates energy production in the sperm to assist motility [89]. Supplementation with Co Q10 was shown in an RCT's of sixty infertile men to significantly improve sperm motility at 200 mg/day [90]. The greatest improvements in semen parameters and DNA fragmentation through Co Q10 supplementation appear to be in studies that are at least 6 months in duration and have a supplementation level of between 200–400 mg Co Q10/day [88,91]. Studies that were 3 months in duration also show a benefit to morphology but no significant effects on motility or sperm count [92].

4.3.3. Folic Acid

Folic acid (FA) is water soluble and a part of the B vitamin 'family' as it is known as vitamin B9. In foods, it naturally occurs as folate. FA is the synthetic form which is used in supplements and fortified foods. Folates are important in human reproduction as they are essential for DNA and RNA synthesis and protein synthesis; they are involved in a number of single carbon transfer reactions in the synthesis of purines and methionine. It has been established for some time that maternal deficiency of FA is linked to spina bifida in the offspring and supplementation in the first trimester of pregnancy is recommended in many countries. Interestingly, in terms of sperm parameters FA is also known to have antioxidant properties [93]. Three papers examining FA in male fertility (often in connection with the mineral zinc) were identified through the searches in this review [94–96], all studies used a 5 mg a day dose of FA though intervention timescale varied. Supplement therapy in varicocelectomized subjects was investigated in one study using a six-month intervention including FA 5 mg and a combination of FA 5 mg and zinc sulphate 66 mg and zinc sulfate 66 mg alone versus placebo [94]. Semen samples were taken before surgery, 3 months and 6 months post-surgery and analysed in terms of number of sperm, morphology, motility, progressive motility and in addition the researchers assessed acrosome integrity and protamine content [94]. The authors concluded mild improvements in most sperm parameters in the placebo group post-surgery and that most sperm parameters improved significantly with a combination of zinc and folic acid, with improved sperm numbers being reported in the group that received folic acid alone [94]. These results are discussed in further detail below in consideration of zinc. However, it is important to note the Cochrane review [80] reports on this study that there was no association in terms of FA and motility or with the FA and Zinc sulphate in terms of motility. Another study investigated a 16-week intervention with a combination of zinc sulphate 22 mg and 5 mg FA; the results are discussed further in Section 4.3.4 [96]. Additionally, a 26-week intervention study using both FA (5 mg/day) and zinc sulphate is discussed further below in Section 4.3.4.

4.3.4. Zinc

Zinc is essential in the formation of spermatozoa, and present in high concentrations in seminal fluid [97]. Two RCT's by the same author investigating (Zn) on semen parameters were found which showed a significant increase in sperm count, motility and antioxidant potential [98,99]. The same author also found that Zn supplementation significantly reduced DNA fragmentation and markers of oxidative stress [98]. More recent studies evaluating supplementation with Zn and folic acid (FA) by Azizollahi et al. [94] has shown to improve semen parameters. Unfortunately, there was no uniform measurements of dosing or participant selection across studies which makes comparison is difficult. Wong et al. [95] found a significant increase in sperm count of 74% when supplementing with 5 mg/day FA and 66 mg Zn/day for 26 weeks. Dosages of 5 mg FA/day are at the very upper limit of the lowest observed adverse effect level (LOAEL) in those without vitamin B12 deficiency [100] and significantly higher than the UK reference nutrient intake (RNI) for folic acid of 200 ug/day for adult men [101]. Conversely, another study found a small but not significant difference in sperm count when supplementing with FA and Zn, which may be due to the lower dose of 22 mg of Zn/day for 16 weeks [96]. Dosing of Zn was significantly higher in the studies by Omu et al. [98]; Omu et al. [99] at 500 mg per day compared to the studies of Zn combined with folic acid supplementation. Such a high dosage of 500 mg/day is classed as toxic and may lead to acute Zinc toxicity and poisoning [102]. The European Food Safety Authority (EFSA) reported an absence of adverse effects at dosages of less than 50 mg/day and therefore recommended a tolerable safe upper limit of 25 mg/day for adult men [97].

4.3.5. Vitamin E

Vitamin E is the collective name given to the complexed group of compounds known as tocopherols. There are four saturated analogues known as tocopherols and four unsaturated analogues known as tocotrienols [103]. Vitamin E is known to inhibit lipid peroxidation and reactive oxygen species formation [104]. Vitamin E has been shown in RCT's to significantly reduce oxidative damage to the lipid cellular membrane of the sperm cells and subsequently increase sperm motility in sub-fertile men [105]. In addition to this, vitamin E has also been shown to significantly improve DNA fragmentation, reduce reactive oxygen species (ROS) in seminal fluid and improve semen parameters [106]. An RCT of a 2-month intervention demonstrated that supplementation with 1 g of vitamin C and 1 g of vitamin E daily showed a significant improvement in levels of DNA fragmentation and therefore, improving the DNA integrity of the sperm cell [107].

4.3.6. L-Carnitine

Carnitine is an amino acid and is found to be in high concentrations throughout the structure of the testes and the epididymis and the spermatozoa [108]. Carnitine is involved in a wide range of physiological processes, thought to play many important functions in semen cells including maturation of the sperm [109], initiation of motility [110] and protecting sperm chromatin from oxidative damage [111,112]. Carnitine has been studied extensively for the impact on semen and fertility parameters, predominantly in those diagnosed with idiopathic oligoasthenozoospermia [113]. A systematic review and meta-analysis by Shang et al. [114] of 7 RCT's, totaling 751 participants concluded that L-Carnitine supplementation significantly improves motility and morphology of semen as well as significantly improving the rate of spontaneous pregnancy compared to controls. L-Carnitine has been shown in double-blind, placebo controlled RCT to significantly improve semen parameters including DNA fragmentation, motility and sperm concentration [115]. The majority of studies that have shown L-Carnitine or L-acetyl-Carnitine to effective in improving semen parameters were at dosages of between 2000 mg–3000 mg per day for 24 weeks [110,116]. The Cochrane review by Smits et al. [80] concluded that there may be a benefit where dosages of L-acetyl-Carnitine are at 1000 mg or above.

4.4. Environmental Impacts on Male Fertility

4.4.1. Testicular Heat Exposure

Keeping the testes cool and avoiding overheating of the testes is advisable, which may happen as a result of being seated for long periods. Heat exposure to the testes may be a contributory factor in the incidence of male infertility [117]. Normal scrotal temperatures are approximately 34 °C, whereas sitting with the legs together raises the average scrotal temperature to 36 °C [118]. In a small study of 9 men, their scrotal temperatures increased by between 1.7–2.2 °C when they were seated compared to when they were walking. This study was limited by the cohort size and also did not seek to determine causation of infertility through increased scrotal temperature [119]. Evidence for this is limited and mostly draws on data from animal studies or associations from observational studies rather than higher quality evidence. It is likely that there are not more RCT's investigating this subject because it would not be ethical to knowingly cause damage to the participants sperm, therefore correlations can be drawn between heat exposure and sperm quality, but causation could not be determined. One RCT was found, which found that heat exposure to the testes caused severe but reversible reductions in sperm quality and motility [120].

4.4.2. Mobile Phones and Device Radiation

Over recent years there have been a growing number of studies investigating the link between declining sperm health and exposure to environmental toxins including chemicals, plastics and radiation. Several studies have found a link between mobile phone radiation and increased levels of DNA fragmentation [121] and a reduction in semen parameters. However, the methodology for this study tested the mobile phone in talk mode as opposed to standby mode, at a distance of 5 cm from the semen sample which is not representative of real-world use when talking on the phone. A systematic review and meta-analysis by Adams et al. [122] analyzed data from ten studies with a combined 1492 samples investigating the effect of mobile phone radiation on semen parameters. The authors concluded that exposure to mobile phone radiation significantly reduces semen motility and viability but does not impact sperm concentration. Data on the use of laptops on sperm health is a little sparser, with the first study that could be found being published in 2012. The authors found that exposure to a WIFI connected laptop for 4 h demonstrated a significant reduction in progressive motility and a significant increase in seminal DNA fragmentation [123]. Unfortunately, this study had several methodological flaws that were described by Mortazavi et al. [124]. In a comprehensive review of the literature by Kesari, Agarwal & Henkel, [125] the authors concluded that radiation emitting devices or devices connected to WIFI networks produce deleterious effects on the testes, which may affect sperm count, morphology, motility, and increased DNA damage to sperm and an increase in ROS. The authors noted that the exact mechanism of action is yet to be determined and further studies are needed to determine the link.

4.4.3. Environmental Contaminants and Endocrine Disrupting Chemicals

Bisphenol A (BPA) is used in the process of plastics manufacturing to make particularly strong and durable plastics and has been linked to reproductive dysfunction in both men and women due to its ability to bind and interact with estrogenic, androgenic and thyroid hormone receptors [126]. Cariati et al. [127] reported that BPA is able to disrupt a host of hormones associated with male reproduction and sperm cell maturation including testosterone, luteinizing hormone (LH), pregnenolone, 5-dehydroepiandrosterone (DHEA) and DHT 5 α -dihydrotestosterone (DHT) which resulted in a decrease in sperm count, concentration, motility, and normal forms. In animal models, foetal exposure to BPA has been shown to disrupt testicular development, testosterone production and subsequently spermatogenesis in later life [128]. The toxic effects of BPA are reported to be higher in males than females possibly due to differences in androgen related enzyme activity [129]. BPA is commonly found in food packaging and several studies have reported that BPA is able to leach from plastic containers, bottles and liners of cans into food and beverages,

although the European food safety authority (EFSA) concluded that the amount leached was below safe limits [130]. Many products are now marketed and sold as BPA free after concerns were raised regarding its safety [131]. Unfortunately, in plastics manufacturing BPA is often substituted with other types of Bisphenols such as Bisphenol F (BPF) or Bisphenol S (BPS, which have been shown to have the same hormone disrupting abilities as BPA [132].

4.4.4. Phthalates

Phthalates are fat-soluble synthetic chemicals known for their ability to soften plastic [131]. Phthalates are used in flexible vinyl plastics which are used across many different industry sectors including food processing, pharmaceuticals, cosmetics, personal care products, flooring and wall coverings [133]. The impact of phthalates on male reproductive function is well studied, with in excess of 900 results returned evaluating Phthalates and semen, with the majority of data coming from animal studies. Because of the limited number of human studies, the mechanism of action remains unclear as to how Phthalates impact on fertility in humans [134], with much of the data coming from epidemiological and observational studies. However, there is an undeniable link between urinary Phthalate metabolites and impaired reproductive function in males [135]. The effect of Phthalates on males is an emerging area of research, Phthalate's exposure on the foetus of boys when in utero is associated with a shortened anogenital distance (AGD), and the prevalence genital birth defects such as hypospadias and cryptorchidism [136]. In animal studies, a shortened AGD from in utero phthalates exposure is associated with testicular dysgenesis syndrome (TDS) which includes undescended testes, reduced testes weight and impaired semen production [137]. Historical evidence for the association of phthalate exposure and male reproductive impairment is limited, however a comprehensive systematic review by Radke et al. [138] concluded that there was sufficient robust evidence to link general, non-occupational exposure to phthalates with decreased AGD, decreased testosterone and increased time to pregnancy for phthalates, di(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP).

4.4.5. Pesticides

The term pesticides covers a broad range of agricultural chemicals including pesticides, herbicides, insecticides and fungicides in which its production dates back to 1952 [139]. Pesticides may interfere with several systems directly related to reproduction [140]. Data from 1061 couples was collected where the male partners were directly exposed to pesticides and found that there was a significant increase in male infertility and spontaneous abortion. There was also a significant increase in still births, neonatal deaths and congenital defects [141]. In a 2016 review of environmental contaminants and spermatogenesis the authors highlighted that exposure to pesticides through dietary, occupational or environmental toxins have been shown to disrupt hormones and spermatogenesis [142]. The mechanisms by which pesticides interfere with male reproductive function remain unclear. It is known that pesticide exposure can lead hormone disruption, germ cell apoptosis, testicular shrinkage and decreased spermatogenesis [143].

5. Conclusions

It has been shown that positive nutrition and lifestyle changes can significantly improve semen parameters, independent of supplementation [66,144]. Moreover, dietary modification or supplementation with antioxidants such as vitamin C, vitamin E, coenzyme Q10, selenium, carnitine and zinc [20] has been shown to improve markers of male fertility and reduce markers of seminal oxidative damage [145,146]. Additionally, a Mediterranean style diet is associated with higher quality sperm counts [19,69], yet there is no formal guidance in many countries on nutrition and lifestyle measures to improve semen parameters beyond maintaining a healthy weight, avoiding high alcohol intake and smoking cessation. Losing weight is beneficial in terms of normalizing endocrine profiles but at present it is

not possible to determine if this is the effect of weight loss alone, or the combined effect of weight loss alongside other dietary improvement, for example swapping to a lower calorie diet with more fruits and vegetables may increase the availability of antioxidants (and a reduction in ROS). Further research is therefore needed to understand the role of the many potential confounding factors. However, given the profound psychosocial impacts of infertility and associated financial cost of assisted reproduction, nutritional and lifestyle pre-conception guidelines should be issued to patients who are having trouble conceiving and personalised nutrition support should be considered. Hence, preconceptual guidelines for men have been developed from findings of this review (see Table 2). These new guidelines are based upon a Mediterranean diet high in omega 3 fatty acids, antioxidants, vitamins and minimally processed foods and minimising exposure to environmental pollutants and radiation. Health care providers are encouraged to consider the potential of multidisciplinary practice embracing allied health professionals and nutrition and lifestyle therapies in the management of sub-fertile and infertile males and consider using the proposed preconceptual-care guidelines as a basis for developing personalised nutrition care for infertile and sub-fertile men.

Table 2. Proposed Nutrition and Lifestyle Preconceptual Guidelines for Men.

<ul style="list-style-type: none"> • Aim to be a healthy weight with a BMI in normal ranges (19–25), so keep active as this can help you maintain a healthy weight.
<ul style="list-style-type: none"> • Avoid trans fats in foods whilst eating sufficient healthy polyunsaturated fats such as the omega 3 oils. Trans fats are often in processed foods and baked produce such as pastries and cakes. Omega 3 fats are found in oily fish such as salmon, trout and sardines as well as in walnuts and flaxseeds. Men should avoid following a low-fat diet, as fats are important for hormone synthesis (including testosterone) and metabolism.
<ul style="list-style-type: none"> • A traditional Mediterranean style diet is recommended including plenty of fruits, vegetables, beans, pulses, fish and nuts. Green vegetables are particularly important as they contain folate which has a role in DNA/RNA replication and the production of sperm. Colourful fruits and vegetables such as berries and tomatoes are also important as they contain antioxidants which can help protect sperm from damage. Walnuts, Brazil nuts, almond and pumpkin seeds as these contain many minerals such as zinc which is important for sperm production and healthy fats which can also be beneficial for sperm.
<ul style="list-style-type: none"> • Try to avoid cola based fizzy drinks and high intake of caffeine in coffee or tea. A moderate intake (e.g., 1–2 cups of coffee a day is recommended).
<ul style="list-style-type: none"> • It is recommended that moderate to heavy alcohol consumption is avoided, modest consumption within the safe limits is recommended. Seek professional help if you are finding this difficult.
<ul style="list-style-type: none"> • If you smoke, consult smoking cessation services or support and make a plan to stop smoking.
<ul style="list-style-type: none"> • Avoid tight underwear and activities that heat up the testes for long periods such as saunas and very hot baths as excess heat is not beneficial for sperm.
<ul style="list-style-type: none"> • Avoid laptops on laps and mobile phones in pockets as this can also heat up the testes and there is some evidence the radiation can affect sperm quality.
<ul style="list-style-type: none"> • If plastics are used at home for food or drink storage opt for containers made from glass or stainless steel. Plastics are known to be endocrine disrupting chemicals (e.g., BPA, BPF, BPS) that can affect both men and women.
<ul style="list-style-type: none"> • Wash and peel fruits and vegetables to remove any pesticide residues.
<ul style="list-style-type: none"> • A multivitamin and mineral supplement containing folic acid, zinc, and antioxidant nutrients such as selenium and vitamin E maybe useful to support attempts to conceive as it can help improve semen parameters. Co Q10 may also be useful, but the recommended dosage is 200–400 mg a day. Nutritional supplementation should be discussed with a Nutritional Therapist, Doctor, Pharmacist or Allied Health Professional, who should assess any interactions with any prescribed medication.

Table 2. *Cont.*

- Avoid making food an additional stressor at this time, it is still important to enjoy food and manage your overall well-being and stress levels. Remember healthy food provides the fuel for your brain and body and that unhealthy diets are associated with the development of many weight and health problems longer term e.g., diabetes type 2, cardiovascular disease and obesity, which is known to influence levels of hormones in men.

Note: These have been produced from this review.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/dietetics1030016/s1>, Table S1: Details of included studies allocated to theme.

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