Module 2 – Optimising sperm health

Learning Objectives:

At the end of this module you should be able to:

1. Explain why sperm health is important and how paternal exposures can impact on the health of their offspring
2. Outline the process of spermatogenesis and list the factors that may impact on normal sperm production
3. List the most common causes of male factor infertility and identify cases when dietary management is likely to be beneficial
4. Understand the current evidence linking dietary intake to impaired sperm quality and other causes of male factor infertility
5. Identify key nutrients linked to improved sperm health in males and use the current evidence to apply this knowledge in practice

Role of sperm in foetal health

Studies in mice have also shown that paternal obesity can slow embryonic development before implantation, reduce the rate of implantation following embryo transfer and slow foetal development during gestation.[1] Interestingly, exposure of functionally mature sperm to reactive oxygen species (ROS) at levels similar to those induced by obesity, has also been shown to affect embryo growth and impair implantation.[2]

Studies that investigate the impact of sperm health on reproductive outcomes in humans are inherently challenging, particularly because couples share the same environment (e.g. place of residence, diet and lifestyle) and it can be difficult to differentiate the effect of individual parental exposures.[3] Also, as mechanistic studies are not always ethical or feasible in humans, relationships between exposures and outcomes are purely associative, so causation cannot be implied.

Despite these limitations, several recent studies have identified links between paternal nutrition, sperm quality and reproductive outcomes in humans that are consistent with results in animal models. In a case-control study conducted by Jayasena et al.[4] male partners (n=50) of women who had experienced recurrent miscarriage (RM) had two-fold higher levels of sperm DNA fragmentation and markedly increased levels of reactive oxygen species (ROS) in their semen. When compared to controls (n=63, healthy males with no known fertility issues), these men were also more likely to have a higher BMI, reduced sperm quality parameters and abnormal reproductive hormone profiles. In another study involving 651 couples undergoing IVF treatment, couples where the male partner had a BMI > 28 kg/m^2 experienced lower fertilisation rates, reduced good quality embryo rates and were less likely to achieve a clinical pregnancy when compared to couples where the male had a normal BMI[5]. Semen analysis also demonstrated that males with a higher BMI had increased DNA fragmentation rates and higher sperm ROS levels.[6]

Not all studies have identified associations between overweight and obesity and sperm quality or reproductive outcomes. Colaci et al.[6] found no relationship between BMI, embryo quality, clinical pregnancy rate or live-birth rates in couples undergoing *in vitro* fertilisation (IVF). However, they did observe a significant reduction in live-birth rate following intracytoplasmic sperm injection (ISCI) when the male partner was obese. Interestingly, a recent study found that obesity alone, without other comorbidities (deemed 'metabolically healthy'), did not affect semen quality parameters.[7] However, obesity, combined with impaired glucose tolerance and liver function (deemed 'metabolically unhealthy') was a strong predictor for reduced sperm count. Although this study was small and did not report other measures of metabolic fitness such as blood pressure, cholesterol and triglycerides, it suggests that improving an individual's metabolic health might be more significant that weight loss to improve reproductive outcomes in men.

Sperm health

Infertility in males

Sperm counts in males, regardless of their fertility status, have declined in many regions around the world by 50 to 60% in the past 40 years.[8] Consequently, infertility has been identified by the WHO organisation as a global public health issue. In infertile couples, male factors (either alone or in combination with female factors) account for 50% of all cases.[9] Alone, male factors account for approximately 20 to 30% of all cases. In terms of prevalence, male infertility in selected populations has been estimated to affect between 9% and 15.8% of males.[10] However, a recent evidence synthesis of male infertility commissioned by the World Health Organisation (WHO) concluded that it is not possible to determine the true prevalence of male infertility in the general population based on biases and flaws in the current literature .[10]

There are many different causes of infertility in males. It can be the result of congenital or acquired urogenital abnormalities, malignancy, infection, genetic factors, endocrine disorders, varicocele and immunological causes.[11] Approximately 30% of all cases of male factor fertility are idiopathic, with no identifiable cause found.[12] Lifestyle factors including obesity, stress, heavy alcohol consumption, smoking and illicit drug use, environmental exposures, inflammation and epigenetic mechanisms have all been identified as factors associated with idiopathic male infertility.[12]

Spermatogenesis and susceptibility to cellular insults

When considering male factor infertility and optimisation of sperm health, it is important to appreciate the steps involved in maturation of human sperm to understand how nutrition and other exposures can impact on this process. Spermatogenesis begins at puberty and is the process whereby male germ cells multiply, divide and mature into male gametes known as spermatozoa. The process begins in the seminiferous tubules of the testes and depends on a coordinated series of steps primarily under the control of testosterone that is produced by Leydig cells. The process involves three key stages, outlined in Figure 1. In the first stage, germ cells undergo mitosis to produce two daughter cells. One of these cells returns to the germ cell pool while the other, known as a primary spermatocyte, will proceed to stage two. The next stage involves two successive rounds of meiosis to produce four haploid spermatids that each contain 23 chromosomes. In the third stage, known as spermiogenesis, the spermatids undergo physical maturation into individual spermatozoa. At the end of this process, the mature sperm enter the lumen of the seminiferous tubule and make their way to the epididymis. Here they continue to develop functional maturity, including fertilisation ability and forward motility.

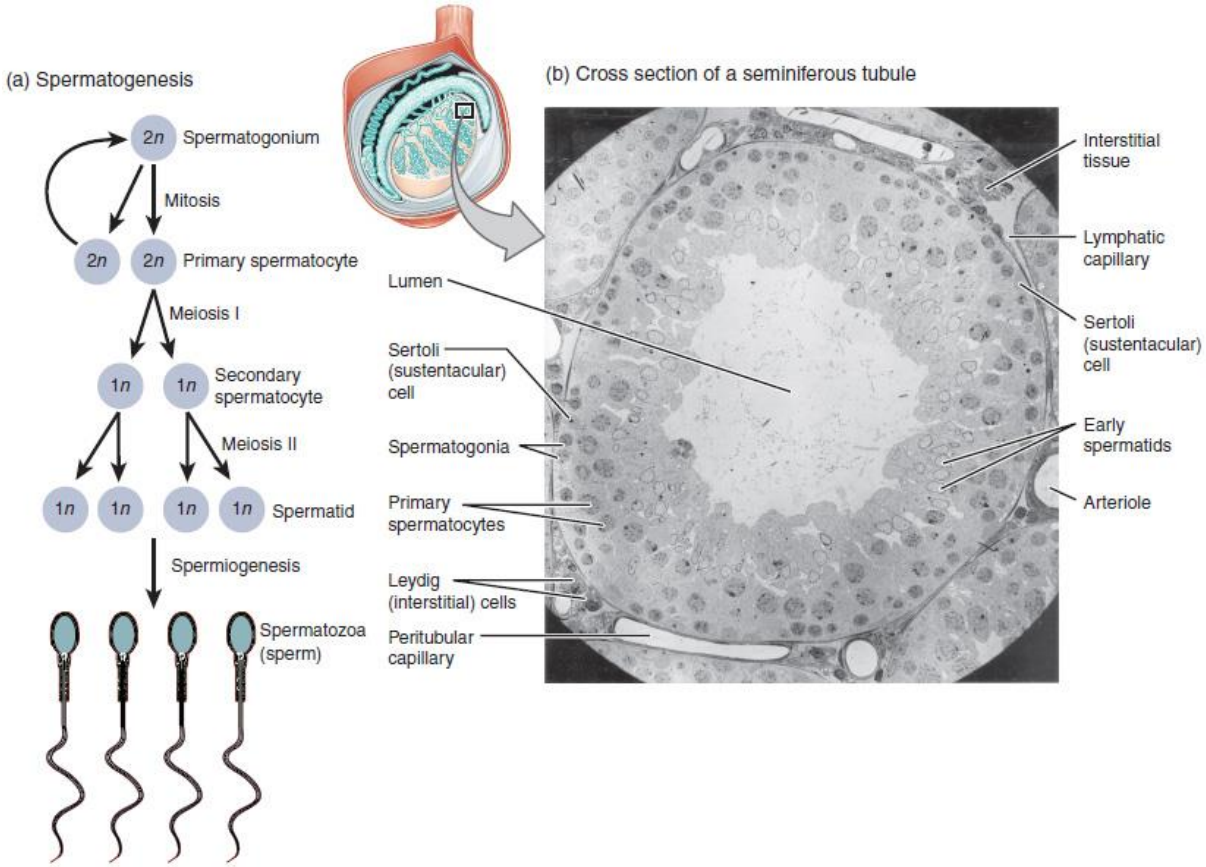

Figure 1: (a) An outline of the steps involved spermatogenesis. (b) An electron micrograph showing a cross-section of a seminiferous tubule. Spermatogonia are adjacent to the basement membrane. As spermatogenesis proceeds, cells at the different stages migrate towards the lumen of the tubule. Supporting cells including Sertoli and Leydig cells are also shown.

(Source: https://commons.wikimedia.org/wiki/File:Figure_28_01_04.jpg; OpenStax College / CC BY https://creativecommons.org/licenses/by/3.0)

The entire process of spermatogenesis takes approximately 74 days with mature spermatozoa spending an additional 12 days reaching functional maturity in the epididymis. It is also important to note that spermatogenesis is a highly redundant process with only about one-quarter of developed germ cells reaching the ejaculate.[13] Of the mature sperm that are potentially available for reproduction, a further 50% are malformed due to abnormalities acquired during spermiogenesis. Thus, of all the developed germ cells in testis, only about 12% have reproductive potential!

Although there are many complex steps involved in this process, some key changes that occur can be impacted by nutritional input. Firstly, the process of spermatogenesis involves successive steps of cell division and new DNA synthesis that require a constant supply of substrates.[14] Critical nutrients for these processes include folate, vitamin B12, vitamin B6, choline and amino acids.[15] Secondly, during spermiogenesis, most of the cytoplasmic contents are lost to reduce the bulk and weight of the mature sperm.[6] This renders sperm vulnerable to insults such as oxidative damage due to diminished cellular defence mechanisms.[6] During this phase, the fatty acid composition of the sperm membrane also changes incorporating more omega-3 polyunsaturated fatty acids (PUFA).[16] The high

concentration of long-chain PUFA in the mature sperm membrane also makes it more susceptible to lipid peroxidation by reactive oxygen species (ROS).[17]

Despite this vulnerability, mature sperm are normally protected from oxidative damage and other insults in the epididymis via the blood-epididymal barrier and the presence of different antioxidant enzymes that are associated with the epididymal epithelium.[18] However, in situations where high levels of ROS are produced (e.g. immature or abnormal spermatozoa resulting from inappropriate spermiogenesis), these antioxidant defence systems can become overwhelmed leading to an increased risk of sperm DNA damage and lipid peroxidation that further impair sperm quality. [18]

Measures of Sperm Health

Sperm has quantifiable attributes that allow sperm quality to be assessed when there are concerns regarding fertility. A typical sperm analysis provides information about the total number of spermatozoa (sperm count), ejaculate volume, sperm concentration and pH. Cellular characteristics are also examined including vitality, motility, morphology and leukocyte numbers.[19] Ideally, semen quality should be evaluated at least twice at different time-points. A diagnosis of infertility should not be made on semen characteristics alone but considered in conjunction with other clinical information. [19] (Terminology used to describe sperm quality anomalies are shown in Table 1).

Table 1: Definition of sperm quality anomalies detected using conventional semen analysis (adapted from Jungwirth et al., 2018)

Sperm Quality Anomaly	Definition
Normozoospermia	Normal
Oligozoospermia	< 15 million/ml (low sperm count)
Asthenozoospermia	< 32 % progressive motile spermatozoa (reduced sperm motility)
Teratozoospermia	< 4 % normal forms (abnormal morphology)
OAT Syndrome	All three variables are abnormal
Azoospermia	No sperm

In addition to semen characteristics, other measures are also used to assess sperm quality. Sperm DNA fragmentation may be examined in couples who have had three or more miscarriages (also known as recurrent miscarriage) or they have had several unsuccessful attempts at IVF. High levels of DNA fragmentation are usually indicative of oxidative stress and/or increased levels of activated leukocytes in sperm.[20] Activated leukocytes occur in the setting of infection or chronic inflammation and are a significant source of ROS production that can overwhelm the normal antioxidant defence systems present in seminal fluid. [26] Lifestyle and occupational exposures that have been shown to increase sperm DNA fragmentation include smoking, pesticides, testicular heat and obesity.[16] [20]

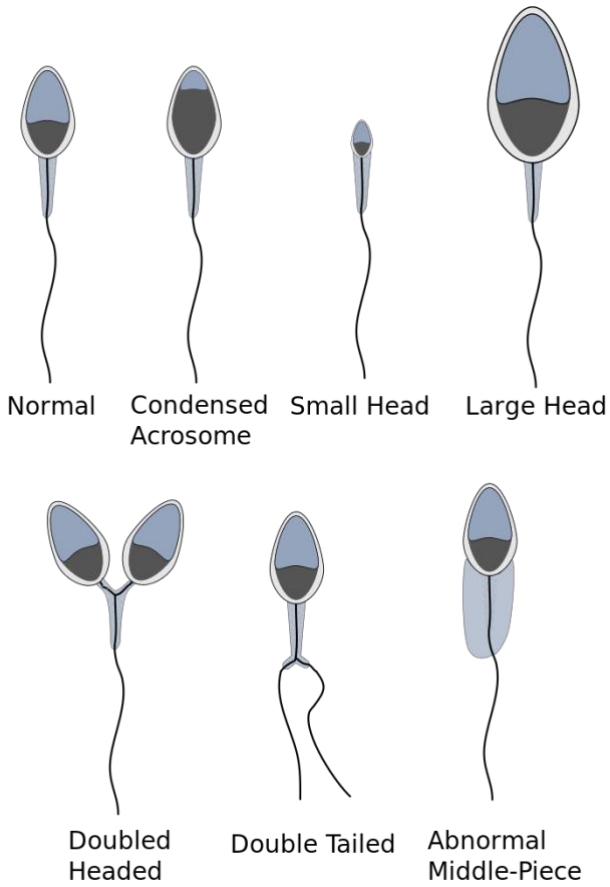

Figure 2: Normal and abnormal sperm

Diet and sperm health

Nutrition plays an important role in the normal physiological process of spermatogenesis but may also contribute to pathological events in the setting of nutritional deficiency and overnutrition. Thus, the relationship between dietary habits and sperm health is of great interest when considering modifiable factors to improve fertility.

Undernutrition

Few studies have examined the effects of undernutrition on sperm health. A meta-analysis involving 21 studies and 13077 men, Sermondade et al.[21] observed a J-shaped relationship between BMI and the risk of oligozoospermia and azoospermia. More recently, a study of 3966 Chinese sperm donors found that total sperm number, sperm concentration and total number of motile sperm were significantly reduced in men with a BMI < 18.5 kg/m^2 when compared to men with a normal BMI.[22] When individual nutrients are considered, studies have shown that iron deficiency anaemia, as well as deficiency in vitamins C, D, E and selenium, are also associated with reduced sperm quality and infertility in men. [23] [24] [25] [26] [27] However, caution must be taken when considering the clinical utility of these findings as they are based on limited studies with small numbers of participants.

Recommendations:

Men experiencing undernutrition should be assisted to gain weight with a nourishing, nutrient-rich diet. It is recommended that nutritional biochemistry be reviewed and supplemented as required.

Overnutrition and obesity

In contrast to undernutrition, a growing body of evidence has demonstrated clear links between obesity and sperm health in men. Several large population-based studies in men have shown that having a higher BMI increases the risk of infertility.[28] Furthermore, a linear relationship between infertility and increasing BMI exists, plateauing at a BMI of 32 – 35 kg/m^2.[15] Evidence suggests that obesity affects fertility in men via actions on multiple aspects of male reproductive function. In terms of androgen homeostasis, obesity has been shown to increase the production of circulating oestrogens in men, which in turn act on the hypothalamus and pituitary leading to a decrease in follicle stimulating hormone (FSH) and luteinising hormone (LH). [28] Reduced circulating FSH and LH levels, result in decreased testosterone synthesis by Leydig cells in the testes which has suppressive effects on spermatogenesis.[29]

Obesity has also been shown to influence sperm characteristics in some, but not all studies. In general, obesity seems to have the greatest impact on total sperm number and/or concentration with lesser effects on sperm motility and morphology. [28 16] Sperm DNA fragmentation has also been shown to be increased in the setting of obesity and this is thought to occur in response to the effects of systemic oxidative stress and inflammation associated with obesity. [28 30]

Recommendations:

The available evidence suggests that obese males trying to conceive should receive assistance to lose weight with a low saturated fat, nutritionally-complete, calorie-controlled eating plan.

Dietary factors that affect sperm health

Trans and Saturated Fats

Intake of both trans and saturated fats have been shown to have a negative impact on total sperm numbers and semen quality. In a recent systematic review, Ricci et al.[31] identified four studies that explored the effects of dietary fat on semen parameters. The studies, that included both infertile and healthy men, consistently demonstrated a negative association between trans and/or saturated fatty acid intake and either total sperm count, sperm concentration or both. Eslamian et al.[32] found a link between increased trans and saturated fatty acid intake and defects in sperm motility in a case-control study involving 342 men. However, it should be noted that cases in this study were men selected for asthenozoospermia so the findings might not be generalisable to infertility more generally.

In mechanistic studies, trans fatty acids have been found to be present in human sperm with higher levels linked to reduced sperm concentration.[33] Given that fatty acid metabolism in humans cannot introduce *trans* double bonds into a fatty acid chain, the presence of these fatty acids in sperm must be derived from dietary sources.

Recommendations:

Men seeking to improve fertility should therefore be encouraged to limit their intake of foods known to be high in trans fatty acids such as fried foods and baked goods. Aiming for a saturated fat intake of < 10 % of total energy intake also seems prudent.

Dairy

Milk supplied from commercial scale dairy farming is typically derived from pregnant cows. Thus, dairy products contribute a significant source of environmental oestrogen in the diet.[34] Given that oestrogen has been shown to supress testosterone production by reducing the secretion of gonadotropin hormones by the hypothalamus and pituitary, there has been considerable interest in dairy consumption as a potential risk factor for infertility in males. [20]

In the largest study conducted to date involving 189 male university students, total dairy intake was found to be inversely associated with sperm morphology.[35] When stratified for fat content, men in the upper quartiles for full-fat dairy consumption (2.0 to 7.5 servings per day) had significantly lower normal sperm morphology and progressive motility. No relationship between low-fat dairy intake and sperm quality parameters was found. Although this study was cross-sectional in design, data presented was adjusted for known confounders including age, race, smoking status, BMI, activity levels, energy intake and alcohol intake.

Other studies involving men from infertile couples have yielded contrasting findings. Mendiola et al. (2009) found no difference between whole milk and low-fat milk consumption in sub-fertile men with idiopathic OAT syndrome (cases) and men from infertile couples without male factor involvement (controls). Interestingly, skim-milk consumption was significantly higher in control subjects, however overall diet quality was also likely to be higher in this group with controls found to consume less processed meat and significantly more shellfish, raw vegetables and fruit when compared to sub-fertile men.[36] Similarly, Afeiche et al. found no relationship between sperm parameters and full-fat dairy intake in 155 men from infertile couples. However, low fat-dairy intake and in particular, low-fat milk intake in this cohort, was positively associated with sperm concentration and progressive motility. [35]

Only one study explored the impact of dairy intake on reproductive hormones. In the study of university students conducted by Afeiche et al. [35], FSH levels were found to have a significant positive relationship with total dairy intake (p=0.05). For all other hormones examined (LH, E2, Testosterone, Inhibin B and SHBG) no relationship with any other dairy intake parameters (total, high fat or low fat) were identified. Finally, a recent study by Xia et al.[37], found no impact of men's dairy intake (either total, high fat or low fat) on the outcomes of ART including fertilisation, implantation, clinical pregnancy and live birth rates. A key benefit of this study was the use of more direct measure of male fertility including fertilisation potential, and implantation, pregnancy and live birth rates.

Recommendations:

When taken together, the results suggest that any negative effect of dairy intake on sperm quality is more likely to be related to the saturated fat content of full-fat products. Low-fat dairy, particularly as part of a healthy diet pattern, does not appear to have deleterious effects on sperm quality and reproductive hormones.

Red/processed meat consumption

Hormonal growth promotants, which include both naturally occurring hormones such as oestrogen, progesterone and testosterone or their synthetic alternatives, are used around the world to promote growth in cattle prior to slaughter.[37] While their use is considered safe, it has been hypothesized that hormonal residues in high red meat consumers may have reproductive consequences.[20] In addition to hormonal residues, red meat, and particularly processed red meat products such as sausages, salami and bacon, are a significant source of saturated fat in high meat consumers.

In healthy young US men, increased processed meat intake was associated with a reduction in both total sperm count and sperm motility.[38] In the same study cohort, no association between sperm parameters and the intake of unprocessed meat was observed. In infertile men, Afeiche et al. found that processed meat intake was negatively associated with the percentage of sperm with normal morphology but no other markers of sperm quality. Unprocessed meat intake was also not related to any sperm quality measures in this population. In a study from Spain, Mendiola et al.[36] found that men with oligozoospermia and teratozoospermia had significantly higher intakes of processed red meat when compared to men with normozoospermia. Similar to other studies, no association between red meat consumption and sperm quality was found.

Recommendations:

Although studies on meat intake and sperm quality parameters are currently limited, collectively what has been found suggests that processed meat intake may have a negative impact on sperm quality in both fertile and infertile men. It also appears that unprocessed meat intake does not affect sperm quality in men suggesting that factors other than saturated fat content, such as high salt or the preservatives used in processing, may have a more detrimental effect on sperm quality. It is also interesting to note that the study from Spain was conducted after the European Union banned the presence of added hormones in their meat supply (either from farming or imports).[38] This also suggests that hormone residues in meat do not impact on fertility in men.

Fish consumption and mercury contamination

Fish consumption is particularly important for men experiencing infertility as it is an excellent source of long-chain omega-3 fatty acids, particularly DHA. However, fish in their natural environment consume plants and other organisms that can be contaminated with mercury. Methylmercury (MeHg) is a potent toxin that accumulates in the muscular tissue of fish and other marine animals. Eating mercury contaminated fish and other seafood is the most common source of MeHg exposure in humans.[39] As a result of its lipophilic nature, MeHg can readily cross cell membranes including the blood-testis barrier.

Studies conducted in mice demonstrated that exposure to MeHg via drinking water, reduced sperm count and overall testis volume.[40] In humans, the effects of MeHg on male reproductive outcomes have been less clear, possibly because studies have not controlled for fish intake in their participants. However, a recent study conducted by Mínguez-Alarcón et al. found that increasing exposure to mercury (measured in hair samples) was associated with higher sperm concentration, total sperm count and progressive motility.[41] After adjustment for fish intake, these relationships were no longer significant. The results of this study suggest that mercury, at the concentrations measured in this study, do not impact on sperm quality. It also appears that fish intake greater than

2 serves per week (the median observed in the highest quartile of hair mercury content) has beneficial effects on sperm quality and may offset any negative impact of mercury exposure.

Recommendations:

In line with these findings, men should be encouraged to consume fish at least twice a week and minimise consumption of high mercury fish such as orange roughy (sea perch), catfish, shark (flake), swordfish and marlin where possible. Suitable fish that should be encouraged due to their low mercury levels and high long-chain, omega-3 fatty acid content include salmon, mackerel, herring and sardines. Tinned tuna and salmon are also recommended.

Dietary patterns and weight loss

Only a few studies have explored the impact of dietary patterns on sperm health and reproductive outcomes in men. In a study from Spain involving 209 healthy young males, adherence to a Mediterranean dietary pattern was found to be positively associated with total sperm count. In the same study, adherence to a western diet pattern (characterised by high intakes of processed meats, French fries and snacks) in overweight or obese men was linked to lower sperm concentrations. Another recent study in Greece assessed adherence to a Mediterranean diet in 225 men seeking fertility treatment.[42] In this population, Mediterranean diet score was positively correlated with sperm concentrate on, total sperm count and motility. Finally, Vuijkovic et al.[43] explored the effects of two different dietary patterns in 161 Dutch men from men from sub-fertile couples. In their study, men who followed a 'Health Conscious' diet had lower levels of sperm DNA fragmentation when compared to men that consumed a traditional Dutch diet characterised by high intakes of meat and potatoes. When taken together, the results of these studies suggest that healthy diet patterns are associated with better semen quality.

There is also a lack of studies exploring the effects of weight loss on sperm quality and other measures of fertility in men. Mir et al.[44] recruited 105 men from infertile couples for a weight loss programme in India. The intervention lasted for 3 months and was based on healthy eating and daily exercise. After a 6 to 12 month follow-up period, mean BMI had reduced in the study participants (33.18 ± 5.06 v 30.43 ± 5.98 kg/m^2, $p<0.001$; pre v post, respectively) and this was associated with a significant increase in sperm quality parameters and improvement in the level of DNA fragmentation. The effect of weight loss on sperm quality and reproductive hormone levels has also been examined in men with severe obesity.[45] In this study, 43 men were recruited for a 14-week residential weight loss program involving healthy diet and exercise. Following the intervention, median weight loss was 15% of total body weight. This was associated with a significant increase in sperm count, semen volume, testosterone, SHBG and AMH. These authors also found that with greater weight loss, significant improvements in sperm count and morphology were also observed.

While these studies have highlighted the potential for improvements in sperm health with weight loss, the diet and exercise interventions were poorly defined in both studies and in the study conducted by Mir et al. no adjustment was made for known confounders such as age and smoking status.

Recommendations:

The available evidence suggests that healthy diet patterns, combined with exercise may be a suitable management approach to improve fertility in men.

Nutrients for sperm health

Omega 3 Fatty Acids

Interest in the benefits of omega-3 fatty acids for sperm health is not surprising given that they have anti-inflammatory and antioxidant properties and their abundance in the sperm cell membrane increases significantly as they mature. In particular, the DHA concentration increases five-fold relative to the amount present in the membrane of an immature germ cell. [22] While the exact functions of DHA in the mature sperm membrane are not known, it is thought to play an important role in the processes associated with fertilitsation. [23]

A recent systematic review identified two RCTs that evaluated the effect of DHA and EPA supplementation on sperm quality parameters in infertile men.[46] While the studies differed in their dose and treatment length, both found improvements in different markers of sperm health. In the longest study, supplementation with DHA + EPA (0.72 grams/d and 1.12 grams/d, respectively) for 32 weeks increased total sperm count and sperm concentration and led to improvements in motility and morphology. A recent RCT also examined the effect of walnut consumption, which are high in plant omega-3 fatty acids, on sperm health in young men.[47] After 12 weeks, men that consumed 75 grams walnuts per day saw improvements in sperm vitality, motility and morphology.

Recommendations:

The available evidence suggests that emphasis should be placed on diets that are rich in omega 3 fatty acids for sperm health. This includes foods such as fish but also plant-based omega 3 sources such as walnuts. Supplementation may be recommended for those not able to meet their requirements for omega 3 fatty acids, particularly DHA. To achieve equivalent dosing with a commercially available fish oil supplement (based on published studies), four high potency fish oil tablets would need to be taken daily for at least 3 months, and preferably up to 8 months, to have any impact on sperm quality.

Vitamin C and Vitamin E

Vitamin C and vitamin E both play important protective roles in mature sperm. Vitamin C is a ROS scavenger and has been shown to be the principal antioxidant in seminal plasma. [20] It also functions to reduce lipid peroxidation by recycling Vitamin E.[48] Vitamin E protects membrane lipids from ROS induced peroxidation, which is an established mechanism for increased DNA damage.

RCTs that have investigated the effect of vitamin C and vitamin E supplementation (either alone or in combination) on reproductive outcomes in men have been largely inconclusive. [46] The highest quality trial as assessed by Salas-Huetos et al., found that 8 weeks of combined supplementation of Vitamin C and Vitamin E (1000mg and 800mg per day, respectively) had no effect on sperm parameters or hormonal status in men.[49] Similarly, a study of infertile men from Italy found no effect of daily vitamin C and vitamin E (1000mg of each per day) for 8 weeks on sperm parameters [59]. However, these authors did see an improvement in sperm DNA fragmentation with supplementation, suggesting some benefit of short-term supplementation with vitamin C and vitamin E on sperm health.[50]

Recommendations:

While short-term supplementation with vitamin C and vitamin E have not been shown to improve sperm parameters in men, there may be some benefits on other measures of sperm health such as

DNA fragmentation which has been linked to recurrent miscarriage risk. Clients should be encouraged to increase their intake of vitamin C and vitamin E containing foods or consider supplementation if nutritional intake is inadequate. A dose of 1000 mg per day of both vitamin C and vitamin E for at least 2 months would be recommended in this instance.

Selenium

Selenium is an essential nutrient for spermatogenesis as it increases the activity of glutathione peroxidase-1, an important enzyme for reducing the damaging effects of hydrogen peroxide on spermatozoa in the epididymis. [46]

A recent systematic review and meta-analysis identified three studies that evaluated the effects of selenium supplementation on sperm parameters in healthy and infertile men. Results of the meta-analysis suggest that selenium supplementation between 100 to 300 µg/day for between 3 and 11 months is associated with significant improvements in sperm concentration, total motility and percentage of normal morphology. [46]

Recommendations:

The current RDI of selenium for men in Australia is 70 µg/day. Doses used in published studies were up to 4 times higher than the RDI suggesting that meeting requirements might not be sufficient to see improvements in sperm parameters in men experiencing infertility. Given that the upper limit of intake for selenium in males is 400µg per day, and the mean daily intake of selenium in Australian men is 110 µg, supplementation should be considered on a case by case scenario. Selenium rich foods that should be encouraged in males experiencing infertility include fish and nuts.

CoQ10

Coenzyme Q10, also known as ubiquinone, is an antioxidant molecule involved in the electron transport chain in mitochondria. CoQ10 has been hypothesised to reduce peroxide formation in seminal fluid, protecting the sperm membrane from lipid peroxidation and damage. [46]

Four RCTs have investigated the effects of CoQ10 supplementation on sperm quality. Salas-Huetos et al. found that studies less than 3 months duration in men with idiopathic fertility did not affect sperm quality. In contrast, studies where CoQ10 supplementation was continued for 6 months lead to significant improvements in total sperm count, concentration, motility and morphology were observed. [46] The dose used in these studies ranged between 200 to 300mg per day.

Recommendations:

Most individuals receive sufficient CoQ10 from their diet however foods that are rich in CoQ10 that should be encouraged include oily fish such as salmon and tuna, and wholegrains. [51] Supplementation may be useful if the diet is deemed inadequate. If supplementation is considered, it should be continued for at least 6 months to have any benefit on sperm quality parameters.

Folate

Folate is an essential nutrient for spermatogenesis serving as a substrate and co-factor for DNA synthesis and methylation reactions. [20] While the role of folic acid supplementation in women pre-conception to reduce neural tube defects in offspring is well established, less is known about the effect of suboptimal folate status on fertility and reproductive outcomes in men. [52] However, serum folate levels have been shown to be lower in men and women with obesity and this seems to parallel decreases in dietary folic acid intake. [53]

A limited number of RCTs have explored the effects of folate supplementation on sperm parameters in men. In the largest trial conducted to date involving both fertile and infertile males (n=193), six months of folic acid supplementation at a dose of 5 mg/day was associated with improvements in the percentage of sperm with normal morphology in men with infertility but not on other sperm parameters.[54] The same dose of folic acid also failed to improve semen parameters in infertile men in a study lasting 4 months.[55]

Recommendations:

There is insufficient evidence at this time supporting the use of high dose folic acid supplementation to improve fertility outcomes in men. However, given that folate is an essential nutrient for spermatogenesis clients experiencing infertility should be encouraged to consume foods rich in folate as part of a healthy diet. This includes leafy green vegetables, legumes, citrus fruits and fortified cereals and bread. Supplementation may be considered in men who have sperm with abnormal morphology, obese men and men who may be at risk of compromised absorption of folate (such as men who have mutations of the MTHFR gene, with who have had gastrointestinal surgery, men with Coeliac Disease etc).

Zinc

Zinc has multiple functions in supporting reproductive health in men. It is an essential nutrient for spermatogenesis via its function as a co-factor for different proteins and enzymes that are involved in sperm maturation. Zinc also has antioxidant actions and it is found at high concentrations in seminal fluid suggesting a role in protecting sperm from oxidative damage. Finally, zinc and folate work in synergy to support DNA synthesis, so several RCTs have also explored the combined effect of these two nutrients on sperm quality.[56]

Two RCTs have investigated the effects of zinc supplementation on measures of sperm quality. In one study, 220 mg/day of zinc for 4 months was associated with improvements in sperm chromatin integrity in infertile men[55], while 66 mg/day for 6 months improved sperm morphology in fertile men but not infertile men.[54] Studies exploring combined doses of folic acid and zinc (5mg/day folic acid + 66mg/day zinc) for 6 months saw improvements in sperm concentration and morphology but not on other sperm parameters.[54 57] Studies involving shorter intervention times (i.e. < 6 months) have not shown any effect of combined folic acid and zinc supplementation on sperm quality measures.

Recently, a large (n=2370) multi-centre randomised trial explored the effect of daily folic acid (5mg) and zinc (30mg) supplementation for 6 weeks in infertile men on conventional sperm parameters, sperm DNA fragmentation and reproductive outcomes such as clinical pregnancy, miscarriage and live birth rate.[56] Results from the study found no effect of the combined supplement on any of the primary and secondary outcomes.

Recommendations:

Results of the various studies do not support zinc supplementation either alone or in combination with folic acid to improve fertility in otherwise healthy men. Zinc is however vital for reproductive health and foods such as unprocessed meat (both red and white), fish, cereals and dairy should be encouraged to ensure adequate dietary intake. Zinc absorption can be affected in conditions such as Crohn's and coeliac disease, so supplementation may be considered in these men if dietary intake (14mg/day) is inadequate.

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