Module 10- Supplements

Learning Objectives:

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

1. List the key micronutrient considerations for optimal fertility
2. Individually prescribe micronutrient supplements to your clients based on their unique needs
3. Appreciate the different types of folate and know how to determine which is best for your client
4. Respond to questions regarding alternative supplements for fertility in light of the available (or lack of) evidence

Fertility rates are improved with the use of a pre-natal supplement.[1] It is recommended that most women take a multivitamin *before* getting pregnant to help fill in nutritional gaps.

Micronutrient supplements

Folic acid

The neural tube is the baby's brain and spinal cord and is one of the first components to develop. Folate is essential for the development of the Neural Tube, so inadequate folate can be one of the main reasons for unsuccessful pregnancies. Folate, being a B group vitamin, is water soluble so requires regular replenishment. Insufficient dietary intake of folates for as short as 2-3 weeks has been reported to result in reduced blood concentrations of the vitamin.

It is recommended that all women planning to conceive take 400-500mcg folic acid for 3 months prior to conception.[2] Folic acid is commonly found in prenatal and preconception multivitamin supplements, but be aware that many of these multivitamins won't meet requirements for clients who have increased folate requirements. Women requiring higher doses of folic acid include those with certain folate-enzyme genotypes, previous pregnancies with neural tube defects, diabetes, malabsorption disorders, or obesity, or those who take antifolate medications or smoke, and those with partners who have a male partner who has a moderate risk of poor folate bioavailability.[3] [4] It is recommended that women with moderate risk take at least 1mg folic acid per day and recommended that women at high risk take up to 5mg folic acid per day for two months prior to conception.[5] [6] However, it is essential to be mindful. High levels of unmetabolized folic acid can mask B12 deficiencies (so women taking high doses of folic acid should consecutively take at least 2.6mcg vitamin B12 per day), and have been linked with increasing cancer risk, which is why the Upper Level for folate is set at 1mg per day. [7] [8]

Folate terminology

Folate – is the naturally occurring form of vitamin B9 (ie. Found in food).[9] It is also used as a generic name for a group of related compounds with similar nutritional properties, also known as vitamin B9. The best choice for most people.

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Folic acid – synthetic folate found in supplements and fortified foods. Only a small percentage of folic acid is converted to 5MTHF so can result in high levels of unmetabolized folic acid. However, it is cheap and helps to boost vitamin B9 levels for most people.

Folinic acid (5-formyl tetrahydrofolate) – the 'active' metabolite of folic acid. Supplementation with folinic acid alleviates the need for the enzyme dihydrofolate reductase (DHFR) and bypasses the deconjugation and reduction steps that are required with folic acid supplementation. Bioavailability of folinic acid appears to be high, with human absorption studies showing a bioavailability of 92%.[10]

5 methyltetrahydrofolate (5MTHF) – the 'active' form of folate. 'Folate' is converted to 5MTHF in the digestive system. Can also be purchased as a supplement, but is usually a lot more expensive than folic acid or folinic acid. Cheaper methylfolate supplements on the market may contain both the active 6S (otherwise known as the L- isomer) and the inactive 6R isomers of methylfolate which are less effective than using the pure active L- form.

Levomefolic acid/levomefolate – another term for 5MTHF

Activated folate – another term for 5MTHF

Methylated folate/methylfolate – another term for 5MTHF

MTHFR

When folate-rich foods are consumed, enzymes convert folate to folinic acid so it can be used by the body.[11] Some women carry a genetic mutation from only one parent that could decrease the activity of this enzyme (MDHF reductase). However, as they have the other set of genes without the mutation, they will generally not have any symptoms. Approximately 2-16% women will be homozygous, meaning that this mutation is inherited from both gene lines and this can cause a deficiency of the enzyme needed for appropriate folate absorption.

The enzyme methylenetetrahydrofolate reductase (MTHFR) directs folate species either to DNA synthesis or to homocysteine (Hcy) remethylation. The common MTHFR C677T polymorphism affects the activity of the enzyme and hence folate distribution. Under conditions of impaired folate status, the homozygous TT genotype has been regarded as harmful because it is associated with a high concentration of plasma total Hcy, which is identified as a risk factor for occlusive disease in the coronary, cerebral and peripheral arteries and for venous thrombosis, and has also been related to the occurrence of neural tube and other birth defects and pregnancy complications. Any period of rapid growth increases the need for healthy DNA production. Increased demand for the production of healthy DNA is huge during pregnancy due to the intense growth of the foetus.

It is thought these diseases result from:

1. Impaired DNA synthesis and repair
2. Changes in methylation that negatively change gene expression
3. If there is a mutated MTHFR gene, the availability of active methyl folate is decreased, then DNA production and gene expression cannot happen as abundantly as required for the growing baby

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4. This is when developmental disorders occur in offspring, such as neural tube defects, congenital heart disease, Down's Syndrome and cleft lip/palate

The MTHFR gene sits on Chromosome 1. There are two key variants commonly tested for MTHFR C677T and MTHFR A1298C.

MTHFR mutations

Heterozygous = 1 copy of the gene from either parent
Homozygous = 1 copy of the gene from each parent

MTHFR C677T Heterozygous = 40% loss of function
MTHFR C677T Homozygous = 70% loss of function
MTHFR A1298C Heterozygous = 20% loss of function
MTHFR A1298C Homozygous = 40% loss of function
MTHFR C677T & MTHFR A1298C heterozygous = compound heterozygous = 50% loss of function.

By taking standard folic acid supplements, the folic acid isn't converted to its active form and can result in high serum folate and low bioavailability of folate which may result in subfertility or Neural Tube Defects. Consequently, folinic acid or 5MTHF supplements are recommended in clients who have a poor intake of folate-rich foods and are homozygous for MTHFR C677T.

Iodine

Iodine deficiency has become a big issue over the past decade for women who are trying to conceive. Iodine is important for the development of the thyroid hormones. The thyroid gland regulates many metabolic processes, including growth and energy use. Iodine deficiency during early pregnancy can have serious consequences for the baby, such as stunted growth, diminished intelligence and retardation. In fact, it is the primary cause for preventable intellectual disability in children.

Iodine deficiency during pregnancy can result in abnormal function of the mother's thyroid and have a negative effect on the fetus' nervous system, increasing the risk of infant mortality.[2] Furthermore, a large observational study from the UK suggested that mild to moderate iodine deficiency in the first trimester of pregnancy may be associated with an adverse effect on child cognitive development.[12]

Iodine is sourced from a wide range of foods that come from the soil and sea. However, if soil is depleted of iodine, it impacts iodine levels of the food grown in it. Furthermore, iodine is particularly low in highly processed foods such as takeaway foods. To meet increased iodine needs during pregnancy, guidelines from Australia and the American Thyroid Association recommend that women planning to conceive take a supplement that contains 150mcg iodine per day.[13] Iodine supplements should not exceed a dose of 500mcg during pregnancy due to the increased risk of adverse effects to the foetus. Client's with Grave's disease should also be careful of taking excess iodine.[14]

Iron

Iron deficiency is believed to result in infertility.[15] Furthermore, during pregnancy a woman's plasma volume has been shown to increase by 50%, her red blood cell mass to increase by 18% and her haemoglobin mass to increase by 30% from average non-pregnant levels, resulting in a significant

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need for increased iron.[16] Iron deficiency during pregnancy can result in adverse outcomes, both for mother and baby, such as low birth weight and infant developmental delay (both motor and mental function).[17] Additionally, more severe symptoms of attention-deficit hyperactivity disorder (ADHD) may be present in children with iron-deficiency anaemia.[18] Yet, the evidence supporting the benefit of iron supplementation during pregnancy is mixed. Some countries (such as Canada) recommend routine iron supplementation during pregnancy (16-20mg/day), yet others (such as the UK and Australia) recommend iron supplementation only in the presence of anemia.[19] This is because iron supplements can result in gastrointestinal upsets, can impact absorption of other minerals and high serum ferritin levels have been associated with an increased risk of Gestational Diabetes.[20] [21] Consequently, it is recommended that a woman's iron status is optimised prior to conception. It is also important to note that large amounts of supplemental iron (greater than 25 mg) might also decrease zinc absorption (which is an essential nutrient for both fertility and pregnancy).[22] Taking iron supplements between meals helps decrease its effect on zinc absorption.

Serum ferritin is the best single diagnostic test for iron deficiency. A ferritin concentration below 15 µg /L for adults indicates iron deficiency. Supplementation should continue until iron stores are replenished and serum ferritin concentration is in the normal range; this usually takes 3-6 months. Supplemental iron is available in two forms: ferrous and ferric. Ferrous iron salts (ferrous fumarate, ferrous sulphate, and ferrous gluconate) are the best absorbed forms of iron supplements and usually contain 80-350mg ferrous iron salts (which converts to different amounts of iron depending upon the salt that it's combined with; however, iron is usually 30% of the salt). All oral iron supplements are non-haem and so adequate vitamin C levels are essential for adequate uptake.

Vitamin B12

Vitamin B_{12}, also known as cobalamin, is a water-soluble vitamin that plays a key role in the functioning of the brain and nervous system. It is also important in the metabolism and growth of cells. As mentioned above, high levels of unmetabolized folic acid can mask B12 deficiencies so women taking high doses of folic acid should consecutively take at least 2.6mcg vitamin B12 per day.[5]

Although B_{12} deficiency is not overly common in most women, it can cause anaemia and be particularly dangerous for those trying to fall pregnant or in the early stages of pregnancy. Studies suggest that low vitamin B12 levels are associated with infertility and developmental abnormalities.[23] Inadequate vitamin B_{12} can cause changes in blood that can increase the risk of abnormal egg development, ovulatory dysfunction as well as miscarriage.

Consequently, women at risk of B12 deficiency due to malabsorptive conditions (such as Crohn's disease or gastrointestinal surgery), diabetes, vegetarianism or poor diet have vitamin B12 levels tested and replaced as required.[24] [25]

Vitamin D

Vitamin D is a fat-soluble vitamin that is needed for the absorption of calcium. Daily requirements for vitamin D are around 800–1000 IU, but larger doses are needed for people who are already deficient.

The main source of Vitamin D is from exposure to UV sunlight and only a small amount (<10%) of daily Vitamin D requirements is obtained from dietary sources (~80-120IU/d). People who have

darker skin, have minimal sun exposure or who have excessive fat stores are at greater risk of deficiency.

Vitamin D receptors are distributed across various human tissues including ovaries, endometrium, placenta and the pituitary gland suggesting an active role of vitamin D in those tissues. As discussed earlier, there is accumulating evidence suggesting that vitamin D deficiency might be involved in the pathogenesis of insulin resistance and PCOS.[26] Moreover, vitamin D might influence steroidogenesis of sex hormones (estradiol and progesterone) in healthy women.[27] Vitamin D deficiency also has been reported to contribute to the pathogenesis of endometriosis due to its immunomodulatory and anti-inflammatory properties.[28] Although most studies support a role of vitamin D in the onset of these diseases (PCOS and endometriosis), randomized controlled trials to assess the efficacy of vitamin D supplementation have never been performed.

Studies investigating the association of vitamin D status with IVF outcomes reveal inconsistent results. In a study among 173 infertile women undergoing IVF, women with higher levels of 25(OH)D in serum and follicular fluid were significantly more likely to achieve clinical pregnancy following IVF.[29] Conversely, a study of Chinese women found that although lower serum vitamin D levels were associated with a lower fertilization rate, vitamin D level was not associated with an increased live birth rate following IVF.[30] However, most experts agree that vitamin D supplementation is a necessity, particularly in women suffering from obesity, insulin resistance or small ovarian reserve even though thus far research of vitamin D supplementation has not proven a significant difference in ovulation stimulation or embryo development.[31] It's interesting to note that UK guidelines recommend 10mcg (400IU) daily throughout pregnancy, and it's recommended that pregnant women should not consume greater than 4000IU on any one day. [32]

Vitamin B6

Vitamin B6 is believed to play an important role in fertility. A systematic review of over 90,000 healthy women found that those who had higher B6 levels were more likely to conceive.[33]

Furthermore, emerging research suggests that vitamin B6 supplements may play an important role in increasing cervical mucus.[34] Increased levels of cervical mucus play an important role in fertility as it provides an increased window of time for the sperm to survive in a woman's vagina.

Deficiency of vitamin B6 is most commonly seen in women who consume alcohol regularly, women who have taken the oral contraceptive pill for a long time, and women with thyroid disease.

Vitamin E

Vitamin E was discovered as an essential dietary factor for reproductive health in female rodents. Surprisingly, very little is known regarding human vitamin E status and reproductive health. In mice, α-tocopherol sufficiency is essential for placentation. α-TTP is expressed in the uterine wall of pregnant female mice and in the human placenta. Research in this field is of great importance because 96% of U.S. women do not meet vitamin E EAR.

Vitamin E (α-tocopherol) is an exogenous, lipid-soluble antioxidant molecule. It is thought to be a direct free radical scavenger by activating the intracellular antioxidant enzymes and saving the cell membranes from lipid peroxidation, which was demonstrated on sperm membrane components. Its antioxidant effect was concluded in cancer therapy, high-risk pregnancy and male infertility.

Research undertaken in Turkey showed that Vit E supplementation (500 IU/day) in unexplained infertile patients may have beneficial effects in improving the endometrial thickness during controlled ovarian stimulation and IUI cycles.[35] Another important result of this study was the higher implantation and ongoing pregnancy rates observed in the Vit E-administered group, even though the differences were not significant. These improvements again may be a result of the improving antioxidant effect of Vit E on the endometrial receptivity.

Related with the effect of Vitamin E on the endometrium, the anticoagulant effect may be another reason for the improvement in the thickness. This anticoagulant activity may increase the blood supply to the follicles and the proliferating granulosa cells so that may increase the estrogen production which may be one of the pathways to have a good endometrium. On the other hand, this anticoagulant effect may directly increase the endometrial blood flow that may improve endometrial development.

In cases with likely oxidative stress, such as in women with unexplained infertility, Vitamin E may improve the endometrial environment via its antioxidant effect.[36] It may also modulate the antiestrogenic effect of ovulation induction, and the problem of a thin endometrium in these cycles may be adjusted.

Selenium

Data pertaining to selenium status and female fertility and reproduction are sparse, with most studies focusing on the role of selenium in pregnancy. Only recently has some light been shed on its potential role in ovarian physiology.[37] The exact underlying molecular and biochemical mechanisms through which selenium modulate female reproduction are largely unknown, however selenium is a potent antioxidant, and recent studies suggest that the antioxidant effect may have an important role in both follicle growth and protection of embryonic tissues.[38] [39]

Choline

Choline is an essential nutrient that provides building materials for a range of different compounds that are used in a variety of different roles, however during pregnancy choline is an important nutrient for brain and spinal cord development. Adequate intake of this nutrient may help reduce the incidence of birth defects. Emerging research suggests that inadequate choline intake during pregnancy may also impact cognitive development in childhood (visual memory and processing speed) but further research is needed.[40]

Importantly, around 10-15% of the population have gene polymorphisms (SNPs) that reduce activity of key enzymes in the choline metabolism pathways. These individuals may have even higher dietary choline requirements.[41]

Research suggests that in pregnant women who have sufficient folic acid, increased intake of choline (amongst other nutrients) may offer additional risk reduction for neural tube defects.[42]

Omega 3

Studies show that adequate amounts of Omega-3 are beneficial for a range of health conditions, including improving fertility (both natural conception and IVF) as it can reduce oxidative stress to reproductive organs and therefore minimise damage to eggs.[43]

A recent US study analysing over 500 couples who were trying to conceive found that among couples in which both the man and women consumed at least eight servings of seafood per cycle, fecundity (fertility) was 61% higher verses couples in which both partners consumed less than one serving of seafood per cycle.[44] Specifically, 92% of couples who consumed at least two servings of seafood per week were pregnant by 12 months in the study versus 79% among couples consuming less.

The World Association of Perinatal Medicine Dietary Guidelines recommends at least 200mg DHA and/or EPA Omega 3 fats each day before and during pregnancy, which equates to two oily fish meals per week. Fish is the best source of omega 3 polyunsaturated fats, with oily fish such as salmon, trout, sardines and mackerel providing over 2000mg Omega 3 per 150g serve. Other types of fish (which aren't so oily) such as John dory, snapper, blue-eye trevalla and bass still provide more than 200mg Omega 3 fats per serve. Seafood, eggs and lean red meat are also a source of omega 3, containing over 30mg of Omega 3 oils per serve.

Zinc

Zinc is a basic building block for new cells, so ensuring the women get sufficient amounts is particularly important for the rapid cell growth that is needed for conception. Furthermore, zinc is also involved in immunity and insulin regulation, hence it plays an important role in fertility and pregnancy.

A study of 1060 Australian women found that those who had lower zinc levels took longer to conceive.[45] Another study of women undergoing IVF found that follicular fluid zinc levels were significantly higher ($P<0.001$) among participants who had undergone embryo transfer as compared to those who have not undergone embryo transfer, suggesting that higher zinc levels may optimise IVF outcomes.[46] One study also found a link between zinc levels and ovarian reserve.[47] Animal studies suggest that zinc deficiency disrupts oogenesis and meiotic division. [48]

As zinc is found primarily inside cells, blood tests for zinc are unreliable, which means there is no really good way to tell what a person's zinc stores are like. Plasma and urinary concentrations are probably the best indicators, however it is important to remember that results fluctuate widely. A comprehensive nutrition assessment considering a client's medical history and dietary intake is an important tool for determining zinc deficiency.[49] It is important to note that zinc absorption can be reduced in client's who undertake regular alcohol consumption, have malabsorptive conditions or have chronic liver disease.[50] Women following a vegetarian diet or who have a poor dietary intake may also be at risk of zinc deficiency.

In addition to considering the client's likelihood of zinc deficiency, it is also salient that interactions between zinc and copper be considered prior to administering zinc supplements as zinc and copper work against one another and compete for binding sites.[51] Supplements contain several forms of zinc, including zinc gluconate, zinc sulfate, and zinc acetate. [22] The percentage of elemental zinc varies by form. For example, approximately 23% of zinc sulfate consists of elemental zinc; thus, 220 mg of zinc sulfate contains 50 mg of elemental zinc. Research has not determined whether differences exist among forms of zinc in absorption, bioavailability, or tolerability. Most supplements provide 25-50mg elemental zinc which tends to be a typical dose used in practice; if prescribing a higher dose, consider if copper should be prescribed simultaneously to avoid deficiency.

Chromium

Chromium is an essential mineral that has an essential role in carbohydrate and lipid metabolism. Women with PCOS commonly have decreased chromium levels, which has been linked to insulin resistance.[52] One randomised control trial indicated improvements in insulin sensitivity after supplementation with chromium picolinate (200mcg/day for three months) compared to metformin among women with PCOS who were resistant to clomiphen citrate.[53] No significant difference was found in ovulation or pregnancy rates. No other studies have reported beneficial effects of chromium supplementation on reproductive hormones or ovulation.

Alternative Supplements

CoenzymeQ10

Coenzyme Q10 (also known as CoQ10 or ubiquinone) is fat soluble and has many functions in the body including energy production and antioxidant activity.

The body is able to produce coenzyme Q10, however the amount we produce declines with age. There is little human research into CoQ10 for egg quality. CoQ10 is essential for mitochondrial activity so plays an important role in age-related oocyte quality and quantity decline.[54] Young, healthy ovaries produce relatively high levels of CoQ10 and are able to efficiently uptake CoQ10 from external sources. Diminished expression of the enzymes responsible for CoQ10 production, *Pdss2* and *Coq6,* was observed in oocytes of older females in both mouse and human. The age-related decline in oocyte quality and quantity may potentially be reversed or reduced by the administration of CoQ10.[55] Although it is most likely that the ovaries are the most beneficial target of Co Q10 supplementation, it is also possible that granulosa/cumulus cells and/or the uterine environment may also benefit and thus contribute to the increased reproductive capacity of CoQ10-treated females.[56] Additionally, CoQ10 works as a powerful antioxidant by preventing the action of free radicals.

Food sources are varied but include red meat, fish and avocado. CoQ10 supplementation generally has few significant side effects, although excessive doses can cause nausea and vomiting. However, it may decrease effectiveness of warfarin and other anticoagulants and have interactions with statins and beta-blockers. The medical community is yet to reach a consensus about the recommended dose for egg quality, however one study used a dose of 600mg twice per day oil-based ubiquinone (ubiquinol) for two months so currently this is the most common recommendation.[57] [58] However, it is also essential to remember that dosing depends upon the type of CoQ10 used. Generally, CoQ10 dosing varies from 50mg to 600mg per day (spread across the day), however up to 1200mg is considered safe.

Melatonin

In recent years, the negative impact of oxidative stress on fertility has become widely recognised. Several studies have demonstrated its negative effect on the number and quality of retrieved oocytes and embryos following IVF. Melatonin, a pineal hormone that regulates circadian rhythms, has also been shown to exhibit unique oxygen scavenging abilities.[59] Some studies have suggested a role for melatonin in gamete biology. Clinical studies also suggest that melatonin supplementation in IVF may lead to better pregnancy rates.

In humans, the only data on cyclical melatonin changes comes from women undergoing ovarian stimulation. Levels of melatonin dip in the pre-ovulatory phase and peak in the luteal phase. This suggests that melatonin has variable effects depending on the menstrual phase. It is also well known that shift-workers are more likely than daytime workers to experience circadian disruption and longer menstrual cycles, more menorrhagia and dysmenorrhoea.[60] These results are corroborated by a very large cohort study, which also found that duration of shiftwork was modestly associated with menstrual cycle irregularity.[61] A Japanese study found that melatonin levels varied significantly between night and day shift workers, while LH and FSH levels did not, suggesting that the menstrual irregularity associated with shiftwork could be explained by melatonin fluctuations.[62] These findings are in line with central effects on the hypothalamic pituitary axis, being capable of modifying the release of gonadotrophins and GnRH. In fact, in very high doses, when combined with progesterone, melatonin has the ability to suppress ovulation in humans, possibly by interfering with LH release.[63] This may represent inhibition of ovulation during darker months designed to prevent the birth of offspring when resources are less abundant.

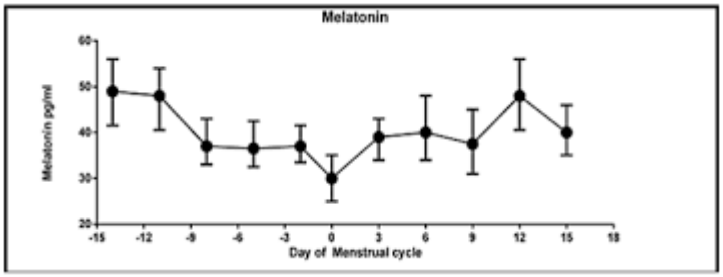

Figure 1: Relationship between melatonin cycle and menstrual cycle.[64]

Other human studies have been promising, but unfortunately, have also been challenged by design limitations.[65] Generally positive results may be seen with 3mg nocte of oral melatonin from day 3–5 of their cycle up until administration of the human chorionic gonadotrophin (HCG) trigger. It is recommended that doses greater than 5mg not be taken as a starting dose as it can disrupt the circadian rhythm.

Research demonstrated that women taking melatonin before their IVF cycle had 50% of their eggs successfully fertilized, compared to 23% of the eggs which had not received melatonin.[66] Following embryo transfer, 19% of women taking melatonin supplements became pregnant compared to 10% of women who didn't. Supporting these findings, a systematic review found melatonin supplementation during IVF increased pregnancy rate by 21%.[67]

Alpha-lipoic acid

Alpha-lipoic acid is an antioxidant that that body can produce naturally (in the mitochondria) but is also found in supplements and food (red meat, broccoli and tomatoes are excellent food sources). It's been gaining increased attention (particularly as a supplement) for its impacts on lowering blood glucose levels, reducing inflammation and weight loss (amongst other benefits) – which are beneficial for fertility.[68] [69] [70] It has particularly been gaining popularity for women with PCOS. For example, a case control study of forty-one women with PCOS found that on a combination of alpha-lipoic acid and d-chiro inositol, 76.7% women reported improved menstrual cyclicity and 40% women had ovulation restored.[71] A fascinating study of alpha-lipoic acid on non-obese women with

PCOS who had all previously undergone ICSI found a significant increase in grade 1 embryos after taking alpha-lipoic acid, however, there was no difference in fertilization rates.[72]

Though there is no set dosage, most evidence suggests that 300–800 mg is sufficient and safe, with anecdotally the most commonly prescribed dose being 600mg per day.[73] Research shows that adults can take up to 2,400 mg without harmful side effects.[74] Higher doses are not recommended, as there is no evidence that they provide extra benefits.[75] As few safety studies have been undertaken during pregnancy, it is recommended that it be ceased after a transfer. Supplementation with alpha-lipoic acid usually yields best results for women with PCOS when taken with myo-inositol as the two have a synergistic effect.[73] To date, even fewer studies have been undertaken on reproductive benefits for women without PCOS. Alpha-lipoic acid supplements are best taken on an empty stomach, as certain foods can lower the acid's bioavailability.

Inositols

Myo-inositol and D-chiro-inositol are involved in the insulin signalling pathways. More specifically, myo-inositol is involved in cellular glucose uptake and FSH signalling, and D-chiro-inositol is involved in glycogen synthesis and androgen production. Inositols occur naturally in fruit, grains and nuts. Current research indicates that these supplements may improve insulin sensitivity, menstrual regularity and ovulation rate among women with PCOS.[76]

It is important to note that the safety of inositols has not been adequately studied. For example, emerging evidence suggests that D-chiro-inositol treatment may be beneficial when administered in low doses, yet the progressive increase of its dosage has been associated with worsening oocyte quality.[77] [78] Furthermore, intestinal absorption of myo-inositol is reduced by the simultaneous administration of D-chiro-inositol since the two stereoisomers compete with each other for the same transporter that has similar affinity for each of them.[79] Clinical evidence has demonstrated that the 40 : 1 ratio (2g twice per day) between myo-inositol and D-chiro-inositol is the optimal combination to restore ovulation in PCOS women.[80] Common ratios in supplements tend to be 2000mg myo-inositol to 50mg D-chiro-inositol or 1100mg myo-inositol and 28mg D-chiro-inositol. Myo-inositol seems to be safe in doses up to 4,000mg per day even during pregnancy and up to 12,000mg per day before side effects commence.[81] Supplements are usually taken 15 minutes prior to meals.

L-Arginine

L-Arginine is (a non-essential amino acid) involved in protein synthesis. It also has antioxidant properties that aid in the inflammatory response and act against oxidative damage. A small study found that supplementation helped improve rates of pregnancy by 18%.[82] It is believed that it may help improve circulation to reproductive organs, that may enhance oocyte development and implantation. However, it is primarily used for increasing endometrial blood flow.[83] However, to date, there is no clear evidence of an increase in clinical pregnancy rates, although further research needs to be conducted.[84] However, one study suggested that L-arginine supplementation may be detrimental to embryo quality, so if used it should be commenced after egg collection, prior to transfer.[85] [86]

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Maca

Maca is most commonly consumed as a powered supplement added to smoothies and juices, however, can also be found in supplements. It was traditionally known as an aphrodisiac. Although it is a popular fertility supplement, there is very little evidence-based research, especially in females.[87]

Royal jelly

Royal jelly is made by nurse worker bees to feed to larvae in the first few days of their life. If larvae are fed royal jelly exclusively for a longer period, the larvae will actually develop into a queen bee, hence where the name 'royal' comes from. A queen bee lives exclusively on royal jelly and this allows her to lay up to 2,000 eggs per day. There are claims that the royal jelly can help balance out hormones in the bee to improve egg laying ability.

Royal jelly has been traditionally used to treat menopause symptoms by rebalancing the hormonal concentration in the blood, decreasing FSH and increasing the estrogen concentration.[88] Animal studies suggest that royal jelly may improve oocyte quality, so human studies are desperately needed.[89] Furthermore, royal jelly is rich in antioxidants (flavonoids, phenolic acids and terpenoids), may improve insulin sensitivity and has an anti-inflammatory effect.[90] [91] [92]

There are no recommended dosing guidelines as limited human studies have been undertaken, however studies tend to use between 50mg to 6000mg per day. Safety studies have not been undertaken during pregnancy, so it is recommended that it be ceased prior to an embryo transfer. Women who have an allergy to bees should also avoid these supplements.

Soy

Soy is rich in phytoestrogens, so it is not surprising that soy supplements are a popular adjunct. Evidence from human studies, while limited, has so far not shown little evidence of harm for females.[93]

One small study found that soy supplements improved ovulation.[94] In a prospective cohort of women undergoing IVF in the US, the odds of achieving a live birth during ART were 77% higher for women with the highest intake of soy isoflavones (mean: 12mg/d; range: 8–28mg/d) than for women who did not consume any soy products.[95] Similarly, isoflavone supplements (120mg/d of isoflavones) increased live birth rates (36.7% versus 13.6%) an RCT among couples undergoing infertility treatment with clomiphene citrate + timed intercourse.[96] Higher doses (1,500mg/d) have also been shown to increase endometrial thickness and ongoing pregnancy rates in women undergoing IUI (20.0% vs. 4.4%) and clinical pregnancy rates in women undergoing IVF (39.3% vs. 20.9%).[97]

A systematic review found that the amount of soy protein resulting in GI side-effects commenced at 20grams soy per day, and 40mg of pure isoflavones per day, although there was no clear dose relationship between the amount consumed and associated adverse events.[98] Effects of isoflavones depend on varied factors including the dose, duration of use, protein binding affinity, the individual's metabolism and intrinsic estrogenic state, as well as the source of the isoflavones.[99]

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