

# Preparing for pregnancy and a healthy baby

## - How diet and food supplements can help

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Within the last decades there has been a trend for subfertile couples to present relatively early at fertility centers for medical assistance. On the one hand, this is due to an increased awareness of women about age-related decline of oocyte number and quality and on the other hand, it is related to earlier testing of the male partner, with semen analyses often revealing male fertility issues. Even young people suffer from diseases linked to our modern civilisation and need to take medication on a regular basis, resulting in safety concerns regarding pregnancy. A sedentary lifestyle with a lack of exercise, unfavourable nutritional habits, and poor-quality food puts stress on our organisms, impacting the normal menstrual cycle.

Pollutants can act as endocrine disruptors, impairing healthy hormonal balance in men and women and decreasing fertility. While 30 years ago, we were able to demonstrate that exposure to chlorinated hydrocarbons and heavy metals had a clear link to fertility disorders in women and men [1-3], today's generation is reviewed with regard to the stresses of so-called plasticizers. Increased metabolites of phthalates and bisphenol A in the urine are associated with poorer fertilization, pregnancy rate and baby-take-home rate [4-6].

For health care from the very beginning, it may be useful to precede the active fertility therapy with a phase of detoxification, e.g. by applying a fasting cure, a herbal tea cure, supportive treatment of liver

and intestinal function. It is ideal if the couple decides to take such a cure together [7].

### Preconceptional nutrition

At least 3 months before conception, the diet should be revised and optimized. If it hasn't happened yet, now is the perfect time to quit smoking, because it takes a long time for the body to get rid of toxins. This applies both to the woman and her partner. Alcohol consumption should be reduced or even better avoided altogether, as it can overwhelm the antioxidant capacity of the cells.

Underweight women should be motivated and supported to gain weight. Good ovulation and an undisturbed pregnancy benefit from an optimal fat content.

Animal studies show that maternal obesity poses a health risk not only for the next generation, but may impact health up to the F3 generation. Mice were fed a high-fat/high-sugar diet and compared to a control group with normal diet: the oocytes in the diet group had fewer mitochondria, less ATP, less citrate, even if the following generations were fed normally. If an antioxidant was added to the IVF medium, the unfavorable effect could be prevented. From this, the researchers concluded that obese women with desire to have children should take antioxidants [8]. However, micronutrients are no substitute for nutritional advice and lifestyle change!

Overweight and obese women should not take a crash cure and then get pregnant quickly. Our experience shows that an optimized diet will automatically improve metabolic function and lead to slow weight loss, increasing the patients' prognosis for spontaneous pregnancy significantly [9]. To achieve this, an average weight loss of 5 % is sufficient!

Men who are overweight or obese have lower semen quality than those with normal weight. This is particularly true when they are affected by metabolic syndrome. In these patients, changes to lifestyle and nutrition alone can boost sperm motility [10].

The diet should be plant-focused with a high proportion of complex carbohydrates (whole grains, legumes, vegetables, fruits), preferably locally and organically farmed. Fast food, soft drinks and food with industrial sugar should be avoided.

Add certified organic meat once or twice a week, and fish once a week at most. From an ecological point of view and considering the strong exposure to environmental toxins, fish can also be dispensed with, however, important omega-3 fatty acids should then be supplemented.

It is recommendable to reduce consumption of dairy products from cattle, as factory farming has led to increased hormone concentrations and other undesirable substances in milk. Dairy products from goats or sheep sometimes present as an alternative.

Particularly strict dietary recommendations apply to women with myomas, endometriosis or polycystic ovaries (PCO). Foods containing many endocrine disruptors (dairy products) and many inflammation-promoting substances (meat, milk) or that load sugar metabolism (monosaccharides) need to be reduced [11].

Epidemiological studies on the nutritional situation of the population on the one hand and agricultural composition studies of fruit and vegetables from today's industrialized agriculture on the other hand unfortunately give cause for concern that even under optimal nutritional conditions the need for micronutrients and antioxidants cannot always be covered.

#### Supportive micronutrient therapy for fertility patients

For the past five years, supportive micronutrient therapy has been enjoying increasing popularity in reproductive medicine, a trend which is reflected by numerous studies on different vital substances carried out all over the world. Relying on assisted reproductive techniques alone is often not sufficient to result in fast success. Supplements and antioxidants can help to increase chances for natural or assisted conception.



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While due to its frequently idiopathic nature, pathological semen analysis of the male partner often had to be accepted as incurable in previous years, it can now be an indication for orthomolecular therapy that has been shown to be promising in vitro or in animal experiments. After 3 or a maximum of 6 months, success or failure of this approach can objectively be measured without invasive surgery applying semen analysis. Please find below the most important findings on micronutrient therapy summarized separately for men and women.

#### How to improve male fertility with micronutrients

Today, when assessing semen quality it's not sufficient anymore to only evaluate sperm count, motility, and morphology. In 30 to 80 % of subfertile men, increased stress markers are detected in seminal fluid [12]. A sign of oxidative stress in pathological semen analysis are increased levels of malondialdehyde and decreased levels of glutathione [13]. At the same time, **selenium, zinc, and**

**coenzyme Q 10** are frequently below and iron above normal levels [14]. Various studies have investigated the impact of 3-6 months of antioxidant-treatment on the semen quality of subfertile men either using single substances or combinations. Quite a few of the studies were placebo-controlled and featured a sufficient number of patients. On the downside, study populations varied significantly with respect to nationality, age, diagnostic methods, laboratory results and also the antioxidants used were heterogenous, making it difficult to establish general recommendations for treatment.

**Coenzyme Q 10** in a dosage of 200 mg ubiquinol per day given for half a year led to a significant improvement of semen quality in patients with oligo-asthenoteratozoospermia (OAT) as compared to a placebo controlled group [15].

In combination with other antioxidants like **vitamin E or C**, lower dosages were effective as well.

In another study, the combination of an antioxidant (vitamin E 400 mg/day) with an anti-estrogen (Clomiphen 25 mg/day) for a duration of 3 to 6 months, resulted in significant improvement of semen quality of patients with oligoasthenozoospermia [16].

Motility of sperms is associated with the level of vitamin D in blood [17, 18]. However, studies investigating the effects of supplementation with vitamin D were inconclusive [19].

Myo-inositol is important for sperm development, acrosome reaction, and fertilization.

Supplemented alone or in combination with vitamins/trace elements it can result in improved sperm parameters [20, 21]. Its effects are particularly significant in men with metabolic syndrome.

New, systematic reviews with positive outcomes are available for folic acid and zinc [22], as well as DHA [23]. Therefore, treatment with these vital substances can be considered as well. However, a big, randomised US-study with more than 2.000 couples undergoing fertility treatment found no effect on semen quality or pregnancy rates after paternal supplementation with folic acid (5 mg) and zinc (30 mg) versus placebo [24] (yet it may be worth to consider that in this study, only 20 % of men had pathological semen quality). L-carnitine, L-arginine, acetylcysteine are other substances that have been tested in vitro and used in food supplements for improvement of male fertility.

Dosages are usually rather low and side effects are not to be expected. Even in cases of severe OAT-syndrome it is worth a try to add a suitable supplementation to lifestyle changes for a duration of 6 months. In many cases, semen quality can benefit significantly [25].

A Cochrane review from 2019 assessed 61 studies on antioxidant treatment encompassing 6264 infertile men: While a universal remedy could not be found and study quality was limited, there were seven small randomised studies finding improved pregnancy rates [26]. Fertility experts have developed a product as food for special medical purposes that reflects current scientific knowledge and may maintain male fertility and improve pathological semen quality (Fertilovit® Mplus, Gonadosan).

#### How to improve female fertility with micronutrients

After hormonal contraception, supplementing various micronutrients is mandatory, as hormones are veritable vitamin thieves. All **B-vitamins, magnesium, zinc, vitamin C and iodine** are excreted or consumed in higher quantities than usual. A first choice is a product that is the first on the European market to counterbalance these nutrient deficits (Resilovit®, Gonadosan).

Even though it is well known that women who are supplied well with micronutrients have a lower risk of fertility issues than women with deficiencies, it is still not common to test for status of important vitamins and minerals. When it was recently done at a big Italian IVF center [27], out of 269 women (average age 37 years), only 69% had normal homocysteine levels and only 44 % normal B12-concentrations.

Only 12 % had folate levels in erythrocytes that were optimal to prevent neural tube defects.

After a meta-analysis, the Canadian Medical Association proposed as early as 2015 that all women in their reproductive years should take a multivitamin with 0,4 mg folic acid. If medical history hints to an increased risk of neural tube malformations, an additional 4 mg of folate are recommended [28]. It should be noted that folate supply does not seem to have an impact on time to pregnancy [29].

A few reviews, amongst others from German authors, did not support a benefit of orthomolecular support for fertility. As it was the case in the studies on male fertility discussed before, study-populations and micronutrients used were so heterogenous that a final assessment is difficult.

#### Micronutrients for special patient groups

PCOS  
PCOS (polycystic ovarian syndrome) is a disorder that is caused by multiple factors. Genetics, environmental impacts during pregnancy, childhood, and adolescence, as well as lifestyle factors can play a role. 168 women with PCO, hyperandrogenemia and cycle disorders were compared to 168 women without PCO. Women with PCO consumed significantly more fat, took up more calories, had less exercise, and altogether lower awareness of a healthy lifestyle (controlled for age and BMI) [31].

Several studies show unequivocally that women with PCOS and low vitamin D levels have a significantly poorer ovulation rate and life birth rate [32].



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In an IVF-study, 305 PCOS patients were randomised into 4 groups: normal vitamin D values, normal values after vitamin D supplementation, and too low levels without or despite vitamin D supplementation. Evaluation revealed that women with normal vitamin D levels had significantly better embryo quality than women with low vitamin D values [33].

Women with low vitamin D levels showed improvements of various metabolic and fertility parameters after 2 months of therapy with 50.000 IU vitamin D per week [34]. Optimum vitamin D levels were identified as good prognostic parameter in a different study, with life birth rates highest for 25-OH-vitamin D above 45 ng/ml [35].

Another interesting micronutrient for PCOS patients is myo-inositol, which can help to lower androgen levels and improve insulin resistance. It alters gene expression of granulosa cells and improves oocyte and embryo quality [36]. A randomised study showed that women taking myo-inositol needed less FSH for follicle stimulation and had better pregnancy rates [37]. In another study, myo-inositol and melatonin were given from the first day of the cycle until 14 days after embryo-transfer: oocyte quality and embryo quality improved significantly [38].

In another randomised study, in which 60 PCOS patients received metformin (500 mg) only and 60 others metformin plus myo-inositol (600 mg), the combination group had a life birth rate of 55 % compared to 26% in the metformin only group [39].

D-chiro-inositol is another stereoisomer of inositols and also has a strong impact on sugar metabolism. The combination of myo-inositol and D-chiro-inositol is recommended as a first line treatment for overweight women with PCOS. The effects on sugar metabolism, endocrine balance and embryo development complement each other. Significantly higher pregnancy rates and less hyperstimulation have been described. Recommended dosages vary. Good success was reported for a relatively high dosage of 500 mg myo-inositol and 150 mg D-chiro-inositol twice daily [40]. Other authors go for lower dosages and myo-inositol plus D-chiro-inositol in a proportion of 40:1 [41].

A combination of these two inositols with antioxidants and vitamins was beneficial for normal and overweight PCOS-patients

with respect to cycle regulation, diminishment of hirsutism and improvement of insulin sensitivity [42]. The first European product to include all these relevant components has been developed by fertility experts: **Fertilovit® F PCOS (Gonadosan)**. Some components are rather low-dosed, so it can be recommended to add some single nutrients as needed, e.g. in cases of very low vitamin D levels.

### Endometriosis

Important aspects in endometriosis are inflammation with increased oxidative stress levels. A diet low in foods from animal origin, high in vegetables and fruit, whole-grain product and oils that contribute to a normalization of omega-6 to omega-3 ratio protects from endometriosis and improves endometriosis-related pain [43, 44]. Randomised studies with single antioxidants (vitamin C, E) for women undergoing IVF treatment have not been successful, but resulted in less pain [43, 45]. Supplementing vitamin D could not improve pregnancy rates either [46], even though deficits of vitamin D in blood should be counteracted as well. There is a lack of good studies looking at combinations of micronutrients. Given the pathomechanisms of endometriosis, combinations of micronutrients could be an appropriate approach as e.g. **Fertilovit® F Endo** (Gonadosan), which contains N-acetyl-L-cysteine, highly-dosed folic acid, omega-3-fatty acids, vitamins and minerals to cover the increased demand.

### Idiopathic subfertility

It has been proposed that the idiopathic female infertility may be associated with disturbed oxidative balance in ovaries. While vitamin D level did not impact pregnancy rate, a vitamin deficiency was associated with an increased risk of early pregnancy loss. In follicular fluid of women

with idiopathic sterility, significantly lower concentrations of melatonin and elevated stress markers were measured in comparison to fertile women. In a randomised study including 30 women with idiopathic sterility, it was tested whether the daily administration of melatonin (3 or 6 mg in the evening) for 40 days until oocyte puncture made a difference [47]. Indeed, the melatonin concentration in follicular fluid increased significantly and stress markers fell to the level of fertile women. Rates of fertilization and pregnancy increased. This therapeutic approach should be validated in a bigger patient population.

### How to improve success rates of IVF treatments

In 2017, a systematic literature review regarding micronutrient therapy in IVF was published [48]. Five studies with 467 participants complied with criteria. Even though therapies were very heterogenous, pregnancy rates and live birth rates were convincingly better in micronutrient groups as compared to control groups. For single substances, the best evidence was found for vitamin D and coenzyme Q10. Q10 improves mitochondrial activity, acts as an antioxidant to protect lipids and DNA from oxidation and thus inhibits oxidative damage to oocytes and the embryo [49]. This is particularly visible in patients of advanced age.

An Italian group of scientists compared two IVF cycles in women aged above 39, one of which was preceded by 3 months of antioxidant therapy [50]. After antioxidant therapy, the quality of oocytes was significantly improved and follicular fluid offered optimum protection.

In cell culture of oocytes and embryos, a range of different antioxidants has been tested as

additives in vitro. For certain dosages in specific growth stages and culture media, effects improving IVF could be shown, for example for Q10, biotin, vitamin C, melatonin and others [51]. However, it can be tricky to find the right amount of reactive oxygen species needed for embryo development.

### Conclusion

In fertility treatment, it is important to take one step after the other. That means, as health care provider it is advisable to assess anamnestically and by lab tests whether there are environmental stress or micronutrient deficits.

Given today's nutritional conditions, 3 – 6 months of supplementation in addition to lifestyle changes can be recommended in any case. This not only enhances the chance for spontaneous pregnancy, but also increases success of IVF, if it becomes necessary. Intestinal health should be considered as well and microbiome improved with prebiotics and probiotics [52].

While studies on supplementation of vitamin D are inconsistent, it has been validated that fertilization rate is highest for optimum vitamin D levels. 25-OH-vitamin D concentrations between 40 and 70 ng/ml are to be aimed for.

In addition to usual antioxidants, B-vitamins including folate (measurement of folate in erythrocytes), choline and vitamin B12 (measurement of holotranscobalamin) should be supplemented.

Magnesium (measurement in whole blood) is almost always deficient, the same is true for iodine and omega-3 PUFAs. Myo-inositol has been shown to be an important supplement for women and men, but consistent recommendations for dosage are not available yet.

Data regarding improvement of fertility in PCOS after supplementation is convincing. In idiopathic subfertility and women of advanced age, antioxidants can improve ovarian function. In men with normal or slightly limited semen quality, assessment of antioxidant status in seminal fluid is common practice.

Meanwhile, a variety of supplements for improvement of male and female fertility are offered online. I recommend to get an overview of products, their components, dosages and galenics in order to be able to advise your patients an option that is suitable individually for them. Prefer products free from preservatives, colorants, food additives, and artificial sweeteners. Otherwise, taking dietary supplements may cause more harm than benefit.

The **Fertilovit®** range of products (**Gonadosan**), which has been developed by fertility experts, corresponds to the current state of knowledge and offers indication-adjusted preparations for men and women planning for pregnancy. **Special products are available for patients with thyroid autoimmunity, endometriosis, PCOS, and mature patients (age 35+) with decreasing oocyte quality.**

**Keywords:** preconception, micro-nutrients, fertility, endometriosis, PCO

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