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Appropriate growth profile



Symmetrical IUGR



Asymmetrical IUGR



Prediction of IUGR by  
Down syndrome screening  
biomarker in first trimester

# Nutraceuticals and infertility

**SANJAY AGRAWAL**

## Definition

According to the definition of the World Health Organization, a couple is considered infertile if no spontaneous pregnancy has been achieved in spite of "exposure to the risk of pregnancy" during at least 12 months. A male factor is detected in nearly half of the infertile couples, in 65% a problem is present in the female partner, and in approximately 10% no obvious abnormalities are found. Hence, in one out of every 4 couples both the male and the female partner simultaneously present fertility-impairing pathology

## Mechanisms of Sperm Dysfunction and Female Infertility

The membrane of normal spermatozoa contains a high concentration of the long chain poly-unsaturated fatty acid (PUFA) of the omega-3 group, docosahexaenoid acid (DHA; 22:6w3; also called cervonic acid). This procures a high fluidity to the membrane's phospholipids. The cell membrane of poor-quality spermatozoa of patients with varicocele, male accessory gland infection, or idiopathic infertility, contains less DHA, and displays lower fluidity. This is due to inadequate nutritional intake of omega-3 fatty acids, and to higher oxidative load registered among infertile men as compared to fertile controls. Consequently, the capacity of spermatozoa to undergo induced acrosome reaction and to fuse with the oocyte is diminished, explaining their

poor fertilizing potential. Sperm concentration and motility were inversely related to the nutritional intake of the long-chain PUFA's Eicosapentaenoid acid (EPA) and DHA, but positively correlated with the ingestion of the short-chain omega-3 PUFA alfa-linolenic acid (ALA; 18:3w3). Testicular tissue contains an exceptionally high concentration of the enzymes elongase and desaturase, and mice that were "knocked out" for delta-6-desaturase were infertile with maturation arrest of spermatogenesis. It seems logical to assume that the long-chain PUFAs cannot pass through the blood-testis barrier, whereas the shortchain ALA can do so. The latter is then metabolised into the long-chain PUFAs within the cells of Sertoli thanks to the abundant elongase and desaturase. Therefore, providing an extra amount of ALA to infertile men seems indicated, which is given as linseed- or flaxseed-oil. Also, vitamin B6 and zinc should be added, since these are co-factors for the elongase and the desaturase enzymes. Eicosapentaenoid acid and the extract of the bark of the Mediterranean pine tree (Pycnogenol®, Korphag, Geneva, Switzerland) reduce the damage caused by IL-6 to the oocytes and to the Fallopian tubes, through the inhibition of the NF-κB, of the cyclooxygenases 1 and 2 (COX 1&2), and of the 5-lipoxygenase. Both EPA, given as fish oil, and Pycnogenol® were shown to be beneficial for infertile female patients. The oxidative/anti-oxidant balance can be estimated in blood by measuring the lagtime before extracted LDL-

cholesterol is oxidised when exposed to copper. The lag-time was on an average 25% shorter in blood of infertile men than in fertile controls, indicating that there was oxidative overload in the former. Oxidative stress not only damages the phospholipid composition of the cell membrane containing a high concentration of PUFAs, but it also inhibits the function of the mitochondria. These are situated at the midpiece of the spermatozoa and generate adenosine triphosphate (ATP). ATP is transported via micro-channels to the flagellum where the protein called Dynein contracts, inducing sperm movement. Similarly, the mitochondria in the oocytes are necessary for energy production, and during embryogenesis. The mitochondria produce ATP through the Krebs cycle using the long-chain PUFAs (EPA, DHA) as substrate. The latter are transported from the cytoplasm into the mitochondrial matrix through binding to acetyl-carnitine-CoA. Oxidative overload impairs mitochondrial function and reduces sperm motility, and it may disturb cell division during embryogenesis. Complementary treatment with a strong anti-oxidant Astaxanthin, the carotenoid from the algae *Hematococcus pluvialis*, improves sperm motility, and so does the supplementation with L-(acetyl)-carnitine and PUFA. Since ATP production in the Krebs cycle generates reactive oxygen species, the mitochondrial anti-oxidant co-enzyme Ubiquinone Q10 should also be supplemented. Oxidative overload affects DNA integrity by oxidising guanine into 8-hydroxy-

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2-deoxyguanosine (8-OH-2dG). During cell replication, the latter will not bind to cytosine, which guanine normally should do, but to thymine, causing transition mutagenesis. Sperm of infertile men commonly contains a high concentration of 8-OH-2dG, which is dramatically reduced by oral anti-oxidant treatment. Stress is a common phenomenon among infertile couples, and it is well-known to induce ovulation disturbances through hypothalamopituitary deregulation. Also, stress exerts direct mutagenic effect on gametes, while the efficiency of the repair protein p53 is inhibited. The phyto-adaptogen extracted from *Lepidium meyenii* (MACA) activates the production of the stress suppressing heat-shock protein P70, and can improve fertility in experimental animals. Also, in men *Lepidium meyenii* was reported to improve sperm quality.

### **Fertility Treatments**

The treatments discussed below are supports that assist a woman's body to attain a state of highest fertility. It is neither surprising nor new that, when provided with adequate nutritional and environmental support, the body can achieve a state of excellent health; enhancing fertility. Until then, patients who have difficulty in conceiving are advised to take as many steps toward health as necessary to prepare their bodies for reproduction.

### **Nutritional and Lifestyle Factors**

A number of strategies can be used to address certain female health conditions. Incorporation of all factors is important for achieving overall reproductive health; regardless of the diagnostic "label" a patient has been given. In particular, females will need

to work on a variety of factors to optimize their fertility. It is also important that woman who wishes to use nutraceutical and botanical regimens be strongly advised to work closely with a physician because some supplements taken to improve fertility may alter the fetal environment.

### **Dietary Deficiencies**

Regardless of research studies on the benefits of specific supplements for enhancing fertility, there is no substitute for a healthy diet. The foundation of good health has always been the proper care and feeding of the human body. Diet, in both women and men, has a profound effect on fertility; what is (and what is not) put into the body can affect the multiple things that must go right for conception to occur (or not occur).

Interestingly, the human body almost seems to have a built-in mechanism to prevent conception to the degree a person is undernourished or over stressed. Certainly, pregnancy occurs often in undernourished individuals, yet, this tendency is thought-provoking at the very least.

Indeed, food is the best medicine and avoiding contaminated food is equally important as proper diet and nutrition. Consumption of therapeutic foods and correctly prescribed supplements can help offset less-controllable environmental factors.

### **Fertility Promoting Lifestyle Factors**

Help your patients improve their fertility by advising them to:

- Maintain an optimal diet, including varied sources of nutrition
- Avoid environmental chemicals at work, home, and in food sources Eliminate or avoid caffeine prior to conception

- Avoid drastic weight loss and dieting at least 6 months prior to conception.

### **Environmental Contaminants**

Increasing evidence relates the effects of environmental exposure to chemicals, radiation, and infections on germ cells, fertilized eggs, and on hormonal balance to implantation and development. Passive environmental exposures to pollutants are common, from workplace chemicals, to products in the air from manufacturing facilities, to urban water supplies with supposedly "acceptable" levels of contaminants.

Environmental chemicals that affect fertility are also in many people's food if they do not consume foods from organic farms or derived from similar production means. Second-hand cigarette smoke presents a problem because cadmium, a toxic metal in smoke, is absorbed in the body and is known to have negative effects on fertility, as well as other components of cigarette smoke.

It is easy to become overwhelmed by the numerous ways in which the world has become increasingly in conducive to optimal fertility levels; patients must be trained to be diligent in protecting themselves without becoming overwhelmed.

### **Alcohol**

Research has proven that alcohol affects the fertility of women and men adversely and that fertility can be improved when alcohol is eliminated from the diet. The strong link between alcohol consumption by a pregnant mother and the incidence of fetal-alcohol syndrome provides strong evidence for alcohol avoidance during pregnancy; however research now points to the importance of



avoiding alcohol prenatally as well, in order to boost fertility.

### **Caffeine**

Caffeine, while not the most detrimental of dietary incursions, does apparently have a rather negative effect on fertility. In fact, there is strong evidence that avoidance of caffeine is important for women who are trying to conceive. One study indicated that consumption of more than 2 cups of coffee per day may lead to adverse effects on fertility, especially among women with fallopian-tube disease and endometriosis.

Other studies have shown interesting evidence associating caffeine consumption with delayed conception. Hatch and associates discerned that women who consumed >300 mg of caffeine per day had a 27-percent lower chance of achieving conception while woman who consumed <300 mg per day of caffeine had a 10-percent lower chance of conception compared to women who consumed no caffeine. Studies have also shown a decreased incidence of miscarriage in women who avoid caffeine during pregnancy.

Sources of caffeine other than coffee include green and black tea, soft drinks, cocoa, chocolate, and some over-the-counter supplementation with medicines. Elimination of caffeine, even though the supplementation with these vitamins may ensure fertility and healthy pregnancy in a number of ways.

### **Folic Acid**

Folic acid is well-known as a necessary nutrient for preventing neural-tube defects in fetuses. The vitamin can also be used to maintain proper cervix health by preventing cellular oxidative damage. Folic acid acts as a

chemo preventive agent that interferes with the activity of human papilloma virus infection (a leading cause of abnormalities that are revealed by Papanicolaou smears) and of cervical cancer.

### **B-Vitamins**

B-vitamin deficits may be relatively common today as a result of certain medications (oral contraceptives) or lifestyle factors (inadequate intake of vegetables and fruits). Inadequate B-vitamin levels may predispose a person to depression, carpal tunnel syndrome, and most importantly, altered hormone levels.<sup>16</sup> What is more, it is interesting to note the therapeutic ability of vitamin B6 and folic acid to prevent and treat morning sickness; it appears that women who ingest inadequate amounts of these vitamins tend to experience more illness during the course of pregnancy.

### **Vitamin C**

Known for its multiple health effects, vitamin C has been shown to assist certain populations of women to achieve pregnancy. An older study showed that women taking a fertility agent (clomiphene) with no results were then able to have a menstrual period and ovulate following 400 mg of vitamin C supplementation.

Another study, using laboratory animals as models, showed that animals which were given vitamins C and E experienced a decrease in age-related reduction in their ovulation rates; that is, the animals were able to ovulate more frequently when given the supplements compared to other animals of similar age who were not given the supplements.<sup>18</sup> Although direct implications for human fertility cannot be assumed on the basis of this study, it does suggest implications for age-associated infertility in humans.

### **Iron**

Iron, which is important for erythropoiesis, may prove to be an important preconception nutrient for women who are trying to conceive. One report noted that women with lower levels of iron could improve their fertility by taking iron supplements. physiologically; this makes sense, because women with insufficient amounts of iron will not be able to respond to the high demand for this nutrient once conception has been achieved. It is important to note that, prior to taking iron, women should be tested to determine the actual (ferritin) and apparent (complete blood count) levels of iron in their bodies. It is also important to be aware if a woman is taking a multivitamin mineral supplement because many of these contain required amounts of iron and additional supplementation may be contraindicated.

### **Multivitamins - Minerals**

Prenatal vitamins, as their name suggests, should be taken during pregnancy and prior to it. Multivitamin/mineral supplements promote general health and supply the body with the nutrients it needs as well as those needed for a new, developing life.

A study that evaluated multivitamin supplementation during a 28-day preconception period demonstrated a significantly increased rate of conception among women that took a test supplement pre conceptually compared to women who took placebo during the same time period; this difference was a 5-percent decreased time to achieve conception for the women who took the test supplement.

In addition, the same research team noted a significantly higher occurrence of multiple births among the women in

the supplement treated group compared to women in the placebo group as well as the entire population from which the study groups were taken. Multivitamin supplementation seems to increase chances for successful conception when taken during preconception; supplementation should begin 3-6 months prior to conception, if possible.

### Botanical Medicines and Fertility

When utilizing herbal medicine to treat medical conditions, including infertility, it is important to note that herbal medicine, when used in traditional practice, embodies the concept of natural medicines. Herbal medicines are not necessarily meant to treat specific health problems directly but rather to support the body or organ systems to regain physiologic, functional control over a body system that needs fine-tuning. Many herbal medicines can be used to help women to become pregnant, based upon patients' individual symptoms and designed to nourish each patient's body allowing it to be at its healthiest.

#### Puncture Vine

Puncture vine (*Tribulus terrestris*) is useful for helping the body produce productive ovulatory cycles. A concentrated form of tribulus, standardized to 45 percent steroidal saponin content used in a clinical study, assisted women in achieving ovulatory cycles when the test preparation was administered at 250-500mg, 3 times per day, for 3 months.

#### Chaste Berry

Chaste berry (*Vitex agnus-castus*) appears to have prolactin inhibiting effects, among others, and has been used for women who are sterile as a result of secondary amenorrhea and luteal insufficiency. The herb seems to

normalize luteal-phase defects and may increase the chances of becoming pregnant for women with relative progesterone deficiency.

For women with hyperprolactinemia, vitex was shown to suppress prolactin release, lengthen luteal phases, and improve progesterone synthesis after 3 months of treatment.

In another study, 120 women with polymenorrhea, oligomenorrhea, and corpus luteum insufficiency were treated with a standardized extract of vitex for 6 months. Sixty (60) percent of these women had sought conception preparation assistance previously. During the study, the women's progesterone levels were increased from an average of 6.4 ng/mL to 9.3 ng/mL while 64 percent of the women's cycles became normalized and 29 percent of the women became pregnant.

#### Two Chinese Herbal Preparations

Shakuyaku-Kanzo-To, a Chinese botanical combination of extracts from *Paeoniae radix* and *Glycyrrhizae radix* has been used to lower elevated testosterone levels in a number of settings. When this preparation was given to subjects at a dose of 10 mg per day for 28 weeks, women with elevated circulating levels of androgens had significant lowering of testosterone. Six (6) of the 7 subjects in this study began ovulating regularly and 2 of them were able to conceive.

Zhibai Dihuang, another Chinese formula (comprised of the herbs *Anemarrhena*, *Phellodendron*, and *Rhemannia*) and given in pill form, has shown promise for helping couples with anti-sperm and/or antizona pellucida antibodies. Infertile couples were treated with this formula; following treatment antibody conversion

to negative was at 81.3 percent of the infertile couple subjects in the study. Moreover, in the 19 months following the study, all 8 previously immunologically infertile couples were able to conceive, and the women's antibody status remained negative throughout their pregnancies.

#### Conclusions

This paper provided information on a short list of female-specific, reproductive-focused botanical and nutritional medicines that may be used to help woman become pregnant via regulation of reproductive organ function.

Botanical medicines offer an opportunity to treat each woman as an individual to address her specific cause of infertility. This approach serves patients best, especially when dealing with multiple confounders, such as those that occur in infertility.

Lifestyle factors are "fertile ground" for addressing numerous causes of infertility. One can examine each woman's diet, place of work, home environment, and other lifestyle choices to give her options for achieving adequate nutrition. A balanced and varied diet is essential and optimal amounts of the key supplements are also important for helping women achieve conception. This is vital in addition to examining other avenues for addressing infertility fully to help woman prepare their bodies for the miracle of conception. ❖

Both traditional and cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) can increase the risk of acute myocardial infarction.

- The BMJ