

Short Communication

The Effect of Nutrition on Female and Male Fertility

Helena Jenzer* and Leila Sadeghi

Bern University of Applied Sciences, Health Division, R&D in Nutrition and Dietetics, Murtenstrasse 10, 3008 Bern, Switzerland

Fertility and Nutrition

A myriad of factors can influence fertility (and the lack thereof), which can for instance be impaired by environmental elements, including exposure to toxic substances, but also the maternal and paternal age at the time of conception, the parents' smoking habits and alcohol intake or genetic defects. The present publication will however focus on the role of nutrition in fertility, more specifically how a healthy nutrition can help combat infertility.

Female infertility mainly arising from nutritional, infective, or malformation causes affects 48 million women worldwide. Male infertility affects approximately 7% of all men and is caused mainly by deficiencies in semen quality, low sperm count or immotile sperm. In some cases, both the man and woman may be infertile or sub-fertile, and the couple's infertility arises from the combination of these conditions.

The World Health Organization defines infertility as a disease of the reproductive system when pregnancy cannot be achieved after 12 months or more of regular unprotected sexual intercourse, and if there is no other reason such as breastfeeding or postpartum amenorrhea. Primary infertility is infertility in a couple who have never had a child. Secondary infertility is failure to conceive following a previous pregnancy. Often there is no obvious underlying cause. Infertility can lead to considerable mental distress, which may worsen the prospect of conception and even develop to mental disease due to social pressures and personal grief.

It is widely accepted that manifest protein-energy malnutrition can have a negative impact on fertility. Thus, careful selection of nutrients possessing biochemical mechanisms fitting plausibly to the diagnosis, combined with lifestyle changes, increase the chances of conception. The impact of food is not restricted to the fertile phase of life and shall not end with conception. Fetal programming is a phenomenon known as epigenetic influence on the unborn child mainly in the first trimester of pregnancy. Methylation or absence of methylation of genes due to nutrition patterns such as hunger or deficiency of essential nutrients shows an increased risk of development of diseases such as obesity in later phases of life.[1]

Causes of Infertility

Genetic Factors / DNA Damage

Unrepaired DNA damage can induce miscarriage or malformation. Impacts on DNA are arising from environmental conditions such as cytotoxic xenobiotics, pesticides, silicones, asbestos, volatile organic solvents, pollution, as well as from lifestyle behavior such

as smoking, or from physical impacts such as radiation, fever or high testicular temperature. Tobacco smokers are 30-60% more likely to be infertile than non-smokers in both genders. Another heavy metal, cadmium, is chemically similar to zinc. It may replace zinc in the DNA polymerase and impede sperm production.

DNA may be altered from iatrogenic impact such as chemotherapy and adverse effect from cytotoxic medicines, anabolic steroids, cimetidine, spironolactone, phenytoin, sulfasalazine, nitrofurantoin and many more. Polymorphisms in folate pathway genes could be one reason for fertility complications in some women with unexplained infertility. Infertility caused by DNA defects on the Y chromosome is passed on from father to son. Single nucleotide polymorphisms (SNPs) and mutated genes are known among genes coding for bone proteins, fibroblast growth factors, FSH receptor, follitropin, gonadotropin releasing hormone, gonadotropin releasing hormone receptor, luteinizing hormone beta polypeptide, steroidogenic factor, prokineticin, prokineticin receptor, sex-determining region Y, et cetera. The syndromes arising from these genes and their expressed proteins are comprised in female infertility

- Hypergonadotrophic ovarian failure
- Ovarian dysfunction
- Primary ovarian failure
- Ovarian hyperstimulation
- Hypergonadotrophic hypogonadism
- Hypogonadotrophic hypogonadism
- pseudohermaphroditism
- Male-to-female reversal

***Corresponding author:** Bern University of Applied Sciences, Health Division, R&D in Nutrition and Dietetics, Murtenstrasse 10, 3008 Bern, Switzerland Tel:+41 31 848 45 57; E-Mail: helena.jenzer@bfh.ch

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- Kallmann syndrome
- Primary amenorrhea
- Normosmichypogonadotrophic hypogonadism

Abnormal Anatomical Structures, Non-Communicable Diseases and Metabolic Disorders

Diabetes mellitus, thyroid disorders, immunological disorders with auto-antibodies, adrenal disease with steroid metabolic disorders have to be stabilized if conception and pregnancy shall be successful. The hypothalamic-pituitary-gonads axis has to function properly. Hyperprolactinemia, Hypopituitarism, amenorrhea, primary and secondary anorexia, as well as obesity decrease or fully impede conception. Many unexplained infertility may be arising from immunological conditions. It may be that each partner is independently fertile but the couple cannot conceive together. A treatment with gammaglobulines may be a good choice to overcome immunological restrictions. Further option enhancing conception may be in-vitro fertilization [2], ovulation enhancing drugs such as clomiphene citrate, human menopausal gonadotropin, follicle-stimulating hormone, human chorionic gonadotropin, gonadotropin-releasing hormone analogs, et cetera.

Male infertility comprises blockage of the man's duct system, vas deferens obstruction, immotile sperm such as primary ciliary dyskinesia, or retrograde ejaculation. In females, fallopian tube or uterus malformations or scars, endometriosis, inability to ovulate, malformation of the eggs themselves, polycystic ovarian syndrome, or an excess of male hormones can represent insurmountable obstacles. Both overweight and underweight decrease the chance for successful pregnancy. For women aged 35, the conception chance is about 94% as compared to a younger age. For women aged 38, this chance is as low as 77% [3]. The effect of age upon men's fertility is less clear.

Acquired Infertility / Infections

Chlamydia trachomatis, neisseria gonorrhoea, cytomegalo, rubella and mumps virus, toxoplasma, *mycobacterium tuberculosis* (leading to pelvic inflammatory disease) and many more microorganisms have an impact on reproductive anatomical structures (e.g., orchitis, epididymitis), embryo or fetus, and thus lead to miscarriage or malformation. Bacterial or viral infections before and after conception need a thorough anti-infective treatment and active or passive immunization.

Nutritional And Dietetic Contribution To Fertility

Fertility enhancement by healthy foods implies the intake of nutrients containing building blocks for hormones, nucleic acids and other structures of the reproductive system, egg, sperm, and blood. In parallel, toxic and teratogenic medicines and foodstuff, as well as unhealthy lifestyles must be avoided or modified (e.g. smoking, caffeine, alcohol, Trans fats, psycho tropes such as hallucinogenic and euphoric drugs). This requires knowledge about ingredients and biochemical pathways.

Energy Metabolism

Monosaccharides are essential as a substrate of glycolysis,

anabolic metabolism and for energy production [4]. Mainly in pregnancy, when insulin resistance and gluconeogenesis induced by progesterone are imminent, carbohydrate and glucose intake must not exceed the concentration leading to gestational diabetes. Carbohydrates with a low glycemic index should be preferred.

Acetyl-CoA is formed as a substrate for the citrate cycle from glycolysis and from reserves arising from lipid and amino acid metabolism, and subsequently alimets oxidative phosphorylation and the respiratory chain. Apart from inorganic components, glucose, lactic acid, citrate, proteins, eicosapentaenoic [EPA], and docosahexaenoic acid [DHA], the content of fructose in semen is peculiar. Fructose can be formed from glucose or be provided from fruits.

Amino Acid Biosynthesis

Most amino acids can be biosynthesized. Branched ones such as valine or leucine are essential. Some such as arginine and glutamine become essential in times of severe illnesses or protein-energy-malnutrition due to lack of ATP, at least as soon as reserves from muscles, liver and albumin are exhausted. The citrate cycle is the most important pathway for amino acid biosynthesis (glutamate, arginine, proline, glutamine, aspartate, asparagine, methionine, threonine isoleucine, lysine), together with glycol sis from which alanine, tryptophan, phenylalanine, tyrosine, serine, cysteine, glycine, and histidine are formed.

Nucleic Acid Biosynthesis

DNA is biosynthesized from purine and pyrimidine nucleotides, as well as from ribose 5-phosphate. The biochemical pathways start all from glucose. In the first pathway, the citrate cycle branches at the α -ketoglutarate level to glutamate and glutamine, as well as at the oxaloacetate level to aspartate, thus delivering substrate essential for DNA biosynthesis. In the second pathway, ribose-5-phosphate is obtained from the pentose-phosphate cycle. These bricks together with one carbon bricks from tetrahydrofolic acid and methionine substrates are needed to biosynthesize nucleic acids.

Vitamins and Co-Factors / Ant oxidative Protection

Due to their function as apoproteins or co-factors of enzymes, vitamins and oligo elements are particularly important in metabolism. As their names implicate, vitamins are essential "amines for life" and have to be supplied with nutrition. Even vitamin D (cholecalciferol, calciferol), one of the lipophilic vitamins, which is synthesized in the skin under the influence of sunlight, is considered to be deficient frequently. Its recommended daily intake has been increased taking into considerations modern lifestyles and cultures leading to a lack of sun exposure and thus to cholecalciferol biosynthesis. As its physiological function is to enhance absorption of calcium, deficiency is linked to impaired bone metabolism and retarded growth. It is also associated with semen quality and with sperm count, motility and morphology [5,6]. Vitamin A deficiency, apart from being responsible for night blindness, inhibits sperm production, muscle and nervous function. Vitamin E is a group of several isomeric tocopherols which help counter oxidative stress. They are associated with sperm DNA damage and reduced sperm

motility. The predominant γ -Tocopherol has several roles in cell signaling processes and cell-to-cell communication. Vitamin K as essential co-enzyme in coagulation factor biosynthesis can be easily understood as being important for normal blood perfusion of all organs including gonads.

Vitamins of the B group are important co-enzymes in the glycolysis - citrate cycle - oxidative phosphorylation axis. Thiamine is co-enzyme of the pyruvate dehydrogenase, riboflavin in the monoamine oxidase and in the pyruvate dehydrogenase complex, niacin in lactate dehydrogenase, pyridoxal in glycogen phosphorylase, biotin in pyruvate carboxylase, pantothenate in CoA, and cobalamin in methylmalonyl mutase and in heme biosynthesis, also enabling endometrium lining in egg fertilization. Tetrahydrofolate arising from folate is implicated in the biosynthesis of the nucleic acid thymine and particularly important to prevent neural tube, heart, lips, limb and urinary tract defects in the embryo's development. In all these functions, electrons, acyl groups, aldehydes, CO_2 , methyls, or one carbon units are carried and transferred to the corresponding substrates.

Vitamin C (ascorbic acid) has multiple functions. It is co-enzyme in mixed functional oxidases and thus in detoxification of xenobiotics (phase-I-biotransformation). Other hydroxylation reactions dependent on vitamin C are those of prolin and lysine. Hydroxyprolin is a key amino acid in collagen and gives this protein its flexibility and elasticity. It is important for wound healing and repair processes. Further vitamin C functions are found in catecholamine-synthesis for neurotransmission, in bile acid and gluco-/mineralocorticoid biosynthesis from cholesterol, in tryptophan metabolism and in the synthesis of tetrahydrofolate from folic acid. As an antioxidant, ascorbic acid is easily oxidized itself to dehydroascorbic acid. This way, it prevents oxidative damages. The importance of ascorbic acid is often denied as benefits are frequently not evident. This can be explained by insufficient distribution to the sites where an action should be obtained.

Oxidation reactions depend on oxygen as one of the reaction partners. Not only oxygen itself but mainly reduced oxygen-derived species and radicals such as per hydroxyl and hydroxyl radicals are highly reactive. Hydroxyl radicals can be formed in a Fenton-like reaction whenever metals with partially occupied d-orbitals such as iron or copper react with hydrogen peroxide [7]. Antioxidants are able to scavenge these electron rich molecules. This means that they have to be able to retain the afflux of electrons. This can be achieved due to unsaturated partial structures such as double bonds or aromatic ring systems. In addition to vitamins A and E, examples of antioxidants in food are polyunsaturated fatty acids such as flavonoids (including rutin, quercetin, et cetera), anthocyanidines, or resveratrol from red and blue berries [8].

There are more substrates also referred to as pseudo-vitamins which are considered being precious. Examples are carnitin ("vitamin B11" or "vitamin T" for cross-membrane transport of fatty acids into mitochondria), polyunsaturated fatty acids ("vitamin F" as antioxidant), flavonoids ("vitamin P" as antioxidant), or coenzyme

Q10 ("vitamin Q" as antioxidant protecting mainly egg and sperm DNA).

Several metals are co-factors [4]. e.g. in hexokinase (Mg^{2+}), urease (Ni^{2+}), nitrate reductase (Mo), glutathione peroxidase (Se) [9], or superoxide dismutase (Mn^{2+}). Zn^{2+} is a co-factor in as many as 300 enzymes, e.g. carbonic anhydrase, metalloprotease or carboxypeptidase important for repairing and remodeling processes in wound healing, in the prevention of miscarriage as well as in sperm count boosting. Selenium deficiency is associated with infertility in genders, miscarriage, preeclampsia, fetal growth restriction, preterm labor, and gestational diabetes [4].

Nutrients With Potential For Fertility Support

High scores in increasing fertility and conception are registered following diets with less trans fats and carbohydrates, but more protein, fiber, iron, and multivitamin preparations. A lower body mass index (BMI) favors diet success as compared to higher BMIs. Enough but not excessive physical exercise, as well as not riding or biking, are positively correlated to diet success. Whole milk and dairy products from whole milk seem to be more suitable than low-fat dairy products.

Concisely, providing substrates to help the metabolism remain in the anabolic state will be adequate to warrant wish for conception, to support wound healing, and to practice disease-preventing lifestyles. An anabolic state does not signify that cell death cannot occur. Creation of new cells and elimination of debris after programmed cell death (apoptosis) is well equilibrated. However, enough and a proper selection of substrates is needed to avoid that reserves are withdrawn from blood, muscles and liver. Providing these substrates means preventing risks from depleting own energy and bricks' stores.

Best substrates for enhancing fertility in both genders will be

- Meat
- Liver
- Fish and vegetable oils rich in ω -3 fatty acids (mainly eicosapentaenoic [EPA] and docosahexaenoic acid [DHA]) [10]
- Whole milk and dairy products from whole milk
- Eggs
- Carbohydrates in amounts adapted to the energy needs and with low glycemic indexes
- Vegetables such as various beans, asparagus, and spinach
- Whole grains rich in fiber
- Nuts
- Fruits
- Table salt containing iodine and fluorine
- Mineral water

Many foods are to be avoided [11,12,13]. Food should be well-

balanced and free from herbicides and pesticides, as well as not containing xenobiotics, which are widely used for food production, and processing, and which are recognized as foreign by the cytochrome P450 isoenzyme and P-glycoprotein systems. Although these isoenzymes and efflux transporters in liver and in the GI tract are highly effective, they should not be exhausted by a massive afflux of xenobiotics. Allergens should be strictly avoided. It is still a matter of debate if soy is friend or foe. It contains precious polyunsaturated fatty acids. However, some flavonoids from soy are effective aromatase inhibitors due to a partial structural similarity with physiological estrogens. If soy has an impact on hormone metabolism is a question of abundance and concentration as in pharmacology and toxicology, where toxic effects become manifest after exceeding the therapeutic band width [14]. Similar understudied issues are the correlation of red meat consumption and endometriosis, or the risk of high arginine intake. Arginine liberates nitrogen monoxide (NO) formerly known as the endothelial derived relaxing factor which dilates vessels and thus increases perfusion of tissues with blood, bringing with it oxygen and substrates. Arginine in amounts between 12g and 18g has been widely used in urology to favor mainly male fertility. Such amounts however are difficult to reach with common nutrition, even with diet rich in nuts. Locally injected preparations containing arginine and zinc are used to sterilize young male dogs without orchietomy as an alternative to surgical neutering. The effect is a chemical testicle disruption due to the liberation of high amounts of NO. These local concentrations are not reached with common nutritional arginine amounts. The same is true for the debate of arginine in connection with oncology. Although arginine is angiogenic, it has not been proven to enhance tumor growth. Tumor growth depends mainly on direct energy production from glycolysis, in contrast to normal cell energy production by the citrate cycle and oxidative phosphorylation. Thus, arginine in tumor tissue is not the most critical issue.

Super Food

Maca (from Peru), royal jelly (the food fed to the queen bee), bee propolis (an immune system stimulant) and bee pollen (contains 50% more protein than beef and is rich in every vitamin and mineral), spirulina, wheat grass, barley grass and leafy green vegetables are considered to be fertility super foods.

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