Review Article

NUTRITION-THERAPY IN THE MANAGEMENT OF INFERTILITY

ABSTRACT

Besides aging, a number of non-modifiable lifestyle-related factors such as smoking, elevated consumption of caffeine and alcohol, stress, agonist sports, chronic exposure to environmental pollutants, and other nutritional habits exert a negative impact on both man and woman's fertility. In particular, metabolic disorders including diabetes, obesity and hyperlipidemia commonly associated to hypercaloric diets are suspected to affect fertility either by direct damage to oocyte/spermatocyte health and differentiation, or by indirect interference with the pituitary-hypothalamic axis, resulting in dysfunctional oogenesis/spermatogenesis. Obese women show decreased insulin sensitivity determining persistent hyperinsulinemia, which may be involved in the pathogenesis of Polycystic OvarySyndrome. Thus, the reduced insulin secretion induced by dietary adjustments is an attractive non-pharmacological treatment to prevent infertility, and a Mediterranean diet aimed at maintaining normal body mass may be effective in the preservation of ovarian health and physiology. Furthermore, in relation to the oxidative stress as a co-factor of defective oocyte/spermatocyte maturation, an appropriate intake of proteins, antioxidants and methyl-donor supplements (1-Carbon Cycle) may decrease the bioavailability of toxic oxidants resulting in the protection of oocyte as well as spermatocyte maturation.

Keywords: Infertility, nutrition, lifestyle.

1.0 INTRODUCTION

Infertility is a major problem in modern society and recurs in as much as 20–30% of the fertile female population [1]. The American Society of Reproductive Medicine (ASRM) defines infertility as the failure to conceive after one or more years of attempts of natural fertilization. According to World Health Organization (WHO), about 80 million women world-wide have been affected to date, with a prevalence of ~50% of all women in developing countries [2]. Besides a number of gynecological and systemic diseases affecting an individual's fertility, lifestyle factors and environmental conditions such as stressful jobs, unbalanced nutrition and unhealthy diet concur to interfere with reproduction safety in both women and men. Therefore, abnormal body weight and energy supply in terms of restrictions, as well as dietary enrichment in carbohydrates, fatty acids, proteins, vitamins and minerals all exert a detrimental impact on both ovulatory function and normal spermatogenesis. In addition to the negative interference with the safety of gametes, several nutrients of major diets also affect the implantation of a normal embryo. This review revises how several lifestyles and rough nutritional regimens may interact with the reproductive health in women and how adequate nutritional support may improve fertility.

1.1 Major Lifestyle Factors Affecting Fertility

A number of lifestyle-related factors, such as obesity, smoking, intense sporting activity, alcohol consumption, drug addiction or abuse of other substances, have been shown to have an adverse influence on both male and female fertility [2]. To date, most infertility is usually treatable with major procedures belonging to the Assisted Reproductive Technology (ART) methods. However, the normalization of those factors could probably restore normal oocyte maturation and prevent the adoption of these procedures [3]. Therefore, the major factors influencing infertility are listed below.

1.1.1 Age

Besides lifestyle factors, woman's age is a major factor influencing the spontaneous probability of conception that already starts to decrease by 25–30 years of age. Given the age-correlated deterioration of the ovarian reserve and oocyte quality, it is expected that the global trend of postponing maternity will result in increasing involuntary childlessness. The improvement of oocyte vitrification resulting in pregnancy and live birth rate increases comparable to using fresh oocytes, which has offered a chance to cryopreserved oocytes for upcoming practice, presenting women with the possibility to delay their motherhood [4].

1.1.2 Tobacco Smoking, Coffee and Alcohol Abuse

Tobacco smoking markedly affects the reproductive health of both men and women, albeit acting in different ways. Heavy alcohol consumption indirectly affects the fertility when associated with nutritional or secondary health disorders [5].

In females, smoking is associated with a rapid decline of ovarian reserves, delayed conception and heightened risk of spontaneous miscarriage, as well as a lower success rate from ART, while in males the percentage of normal semen morphology and motility is significantly reduced [5]. The influence of alcohol intake on reproductive outcomes has already been investigated in several studies, yet it is still impossible to demonstrate a significant correlation between alcohol intake and oocyte maturation and fertilization in females, and between male alcohol consumption and the rate of lost pregnancies [6]. Ferroni and co-workers [7] evaluated the impact of these lifestyle factors on *in vitro* fertilization (IVF) outcomes in 351 couples attending the PIVET Medical Center in Western Australia. Considering the quantity of collected oocytes, fertilization rates, pregnancy, and pregnancy loss, the multiple regression analysis showed that smoking strongly damages the quality of gametes in both sexes resulting in a reduction of ovarian reserve in women, and in a significant decrease in density, count, mobility and morphology of sperm in men. On the contrary, female alcohol consumption did not show any correlation with fertility parameters, while in males, it even showed a positive effect on fertilization rate in the cohort with an associated consumption of fruit and vegetables [6]. In addition, evidence suggests that high intake of caffeine has a potential dose-response association resulting in both a longer time for conception and increased risk of pregnancy loss [8].

Therefore, based on the available evidences, there is an important impact of tobacco smoking on IVF clinical outcomes. However, the link between alcohol consumption and infertility needs to be well explored.

1.1.3 Stress

A stressful life, particularly in hard-working women, may contribute to infertility since symptoms related to anxiety and depression are described as more frequent in infertile than fertile females. These features concur to produce a condition of psychological stress that may alter the physiological oocyte maturation [9]. In a meta-analysis performed on 2,202 patients, Purewal and contributors [10] demonstrated that a favorable success of ART treatments leading to a higher rate of conception is obtainable in the absence of depression and anxious mental

states. Furthermore, it has been described that stress management by periodic relaxing training is helpful in decreasing the psychological distress in infertile women and may result in increased conception rates [11].

1.1.4 Nutrition Styles and Body Weight

Reproductive performance has been shown to be influenced by foods and type of nutrition. An unbalanced caloric and protein intake due to incorrect food consumption, responsible for severe under- or over-weight, leads to alterations of the ovarian function with subsequent increase in infertility. Several studies exploring the effect on fertility of various dietary habits are based on data from extended studies including 116,678 females in the Nurses'Health Study II that defined the reduced risk of fertility due to ovulatory disorder in women whose food regimen included low glycemic content and limited intake of nutrients [12]. Variations of the body weight in terms of overweight, obesity or severe underweight associated to alterations of the energy balance are also suspected to produce ovulatory disorders. To this regard, it has been reported that the time to conceive is longer in women with body mass index (BMI) superior to 25 kg/m^2 or inferior to 19 kg/m^2, and that both overweight and obesity are significantly related with reduced pregnancy rate, increased supplies of gonadotrophins and higher miscarriage rate [12]. High BMI is also associated with adverse pregnancy outcomes such as gestational diabetes, hypertension and premature births and unbalanced diets with a prevalence of carbohydrates, fatty-acids, proteins or vitamins and micronutrients. Moreover, nutritional factors may influence not only oocyte maturation, but also quality of embryos and efficiency of implantation [13]. However, more information regarding the role of nutrition in procreation is needed to provide guidelines devoted to nutritional management of infertile women.

1.1.5 Environmental Pollutants

The Occupational Safety and Health Administration (OSHA) postulated that long-lasting exposure to chemical agents such as organic solvents, heavy metals, aromatic amines, pesticides and vegetal toxins is related to reduced fertility and improved predisposition to occasional or recurrent miscarriages. Furthermore, environmental pollutants, determining the formation of DNA adducts and a basic sites construction can induce DNA modifications in gametes and embryos by introducing genetic mutations once unrepaired [14].

2.0 NUTRITIONAL DISORDERS

A normal reproductive performance requires a healthy nutrition since malnourished males and females are reported as major infertile populations in developing countries while, eating in excess, fast food consumption, hyper-caloric dietary regimens and obesity, concur to infertility in well-developed and western societies. Particularly in women, abnormal nutrition may permanently affect oocyte maturation, and a better understanding of the molecular events deranged in malnourished people would provide solutions for restoring normal reproductive functions [14].

2.1 Malnutrition

Deficient food intake, inadequate alimentary regimes, strong dietary restrictions and a general lack of nutrients result in loss of both body weight and physical performance, delayed puberty, lengthening of the post-partum interval to conception, lower gonadotropin secretion levels with alterations of the physiological ovarian cyclicity and increased infertility. Poor intake of proteins, micro and macro-minerals and vitamins has be reported to be associated with reduction in reproductive performance since the altered energy balance is directly correlated to the reduced ovulatory maturation in women [15]. Thus, inadequate nutrition is closely linked to female reproductive pathophysiology. This is confirmed by the fact that both bulimia nervosa and anorexia, namely two pathologic conditions affecting 5% of womenin childbearing age, are indisputable causes of amenorrhea, infertility and miscarriages [16].

2.2 Overweight and Obesity

Overweight and obesity are diffused pathological conditions during the woman's reproductive age, with an incidence up to 20–25% among patients consulting for infertility. WHO estimates that 9% to 25% of females in industrialized countries are obese and at greater risk of generating obese children, particularly when affected by gestational diabetes [15]. Through insulin resistance (IR) and high levels of insulin and androgens, the adipose tissue is responsible for ovulatory disorders in disposed patients and anovulation associated to obesity is responsible for higher risk of miscarriages and infertility [15]. Management of anovulation in obese women includes diet and exercise in parallel with standard methodologies of ovulation induction.

In patients without ovulatory disorders, overweight and obesity extend the time to conceive, decrease the outcome of infertility treatment and increase the rates of gestational diabetes, hypertension, cesarean section, overweight newborns, perinatal mortality and morbidity. A

number of nutritional and clinical studies have confirmed that the Mediterranean Dietary (Med. Diet) patterns and regular physical activity in overweight women significantly reduce unsuccessful attempts to conceive and improve the efficacy of ART pregnancy programs. Therefore, the evaluation of lifestyle habits and the modification of unhealthy behaviors by appropriate assistance or with specific management, such as acid folic supplementation, must be systematic in females attempting to conceive [13].

2.3 Polycystic Ovary Syndrome (PCOS)

PCOS is a recurrent reproductive endocrinological disorder that affects up to 20% of women of reproductive age globally [17]. Basic diagnostic criteria for PCOS include at least two of the following criteria: oligo-anovulation, hyper-androgenism and ultrasound-ascertained polycystic morphology of one ovary (minimum 12 follicles of 2–9mm in diameter or $\geq$10 cm^3 ovarian volume) [17]. The IR and hyperinsulinemia play asignificant role in the development of PCOS and contribute to the development of metabolic syndrome (MS) [18]. However, the mechanism by which hyperinsulinemia and hyper-androgenism are responsible for the deregulation of ovarian function is unclear. Experimental data showed that through its receptor, insulin has specific activities on steroidogenesis by stimulating the cells of the theca to over secrete androgens and improving the responsiveness of ovaries to the luteinizing hormone (LH) for the androgen production [19]. The insulin-like growth factor-I receptor (IGF-IR) could also be involved in the mechanism of hyper-androgenism induced by hyperinsulinemia that is observed in PCOS patients. In fact, when bound to IGF-IR, the insulin activates β-subunit tyrosine kinase activity by amplifying the normal IGF-I signal [20]. Moreover, the insulin-like growth factor binding proteins (IGFBPs) are involved in the systemic and local regulation of IGF activity by both IGF-I and IGF-II with high affinity. These complexes thus lead to a reduction in the hepatic secretion of insulin growth-factor binding protein-I (IGFBP-I) and a consequent bioavailability of IGF-I, with the final effect of enhancing the androgen production by both interstitial and stromal cells of the theca [20]. Previous studies have established that patients affected by PCOS with BMI in the highest quartile ($\geq$30 Kg/m^2) have a very high risk of developing MS [21]. PCOS is the major cause of infertility due to ovulatory disorders, although the anovulation mechanisms are unclear. The anovulation is characterized by an apparent arrest of antral follicle development at the 5–10 mm developmental stage thus implying a failure in entering the cycle pre-ovulatory phase. Under specific conditions, however, the spontaneous ovulation may also

occasionally occur, and the disorder can be reverted in most cases by increasing the Follicle stimulating hormone (FSH) serum levels.

Metformin is the most commonly used insulin-sensitizing drug to treat PCOS due to its ability to increase insulin sensitivity, reduce hepatic gluconeogenesis, as well as to inhibit hepatic uptake of lactate and alanine, and to increase the conversion of pyruvate to alanine. The molecular pathway triggered by Metformin is today partially unclear. Several studies have identified multiple potential mechanisms of action such as the inhibition of the mitochondrial respiratory chain and glycerophosphate dehydrogenase, hyperactivation of AMP-activated protein kinase (AMPK) or cyclic adenosine monophosphate (cAMP), inhibition of glucagon and deregulation of gut microbiota [22]. These mechanisms, together or individually, result in an increase of oocyte maturation and a favorable effect on infertility in PCOS.

2.4 Metabolic Syndrome (MS)

MS is a very common disease in Western countries and includes multiple endocrine disturbances, such as overweight, altered levels of hepatocytolysis, arterial hypertension, obesity, dyslipidemia, and insulin resistance. MS is a major social health problem, particularly in developed nations such as the United States but also in Europe, with a prevalence of 20 and 30%, respectively [22]. Although not completely assessed, several factors have been implicated and primarily include the hypercaloric diet in association with deregulated dietary habits, sedentary lifestyles, increased age and augmented BMI. MS is also suspected to play a definite role in carcinogenesis, particularly in the gastrointestinal tract. Several studies have demonstrated that females with MS, inadequate metabolic control and primary or secondary amenorrhea showed low levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), associated with a lack of residual insulin secretion [23]. Such studies have demonstrated abnormalities of GnRH pulse generator, as well as a decrease in numbers and amplitude of LH pulses in patients with diabetes and amenorrhea compared to patients with normal menstrual cycles. On the other hand, insulin resistance, hyperinsulinemia and related metabolic abnormalities in MS may exert a role in the progress of the PCOS [24]. Interestingly, all therapeutic approaches used for the correction of insulin homeostasis in obese and MS patients, such as Thiazolidinediones, Metformin, lifestyle modification for weight reduction or bariatric surgery have been proven to produce restoring effects on ovulation and hyper-androgenemia [25] (figure 1).

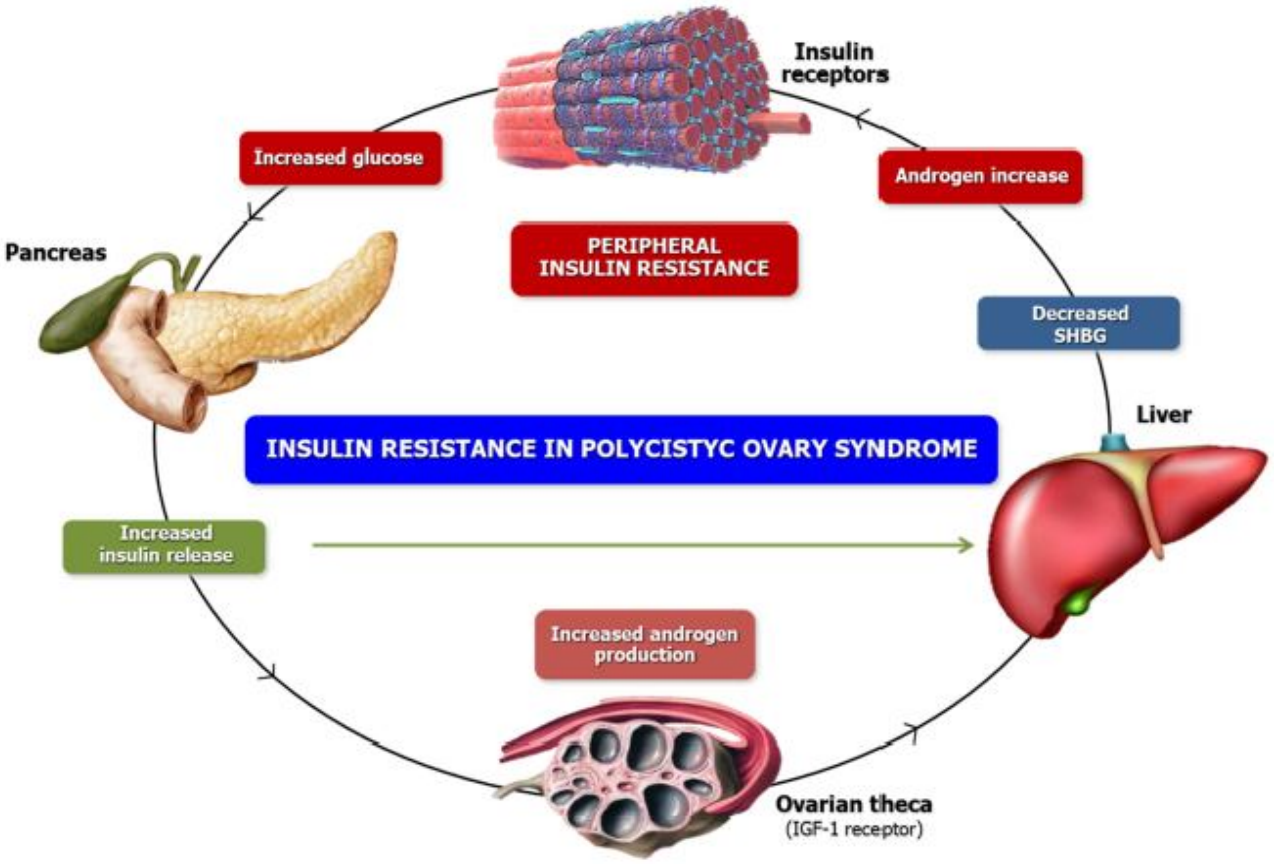

Figure 1: Mechanism of Hyperandrogenism[5].

Similar to the high bio-availability of androgens, high insulin concentrations inhibit sex hormone-binding globulin (SHBG) production. However, the combined activity of insulin and androgens reduces the SHGB concentrations yielding increased free androgen levels which aggravate the underlying insulin resistance (figure 1). These conditions ultimately foster a self-propagating positive feed-back loop that increases in severity over time. On the other side, insulin stimulates ovarian androgen production acting via insulin receptors on theca/interstitial cells in ovarian stroma. At high levels, insulin also binds to IGF-1 receptors or possible hybrid receptors, which are structurally similar and use a similar signaling mechanism (figure 1) [5].

3.0 HEALTHY NUTRITION FOR A HEALTHY OVULATION

Nutrition plays a major role in enhancing the reproductive efficiency both in women and men, and contrarily to the detrimental role of body weight, the effect of the diet in female fertility is not well-defined. However, the interaction between nutrition and fertility appears critical for the reproductive performance and the relationship between ovulatory disorders and metabolic

diseases such as diabetes and/or galactosemia suggests that dietary factors exert etiological role in some variants of infertility [13]. The role of different nutrients that could have an impact on female fertility is summarized below.

3.1 Proteins

The role of protein intake on reproduction is complex and it is still unclear how the source or the amount of protein consumption may affect the ovulatory function or women's fertility. However, it is well-known that protein intake has been associated with a deregulation of the steroidogenesis in women affected by PCOS, likely by reducing hyperinsulinemia.

To this regard, Mumford *et al*. [26] demonstrated that in healthy women, a protein-rich diet, particularly of animal source, is significantly associated with lower testosterone levels, thus highlighting the potential correlation between protein intake and androgen synthesis. Furthermore, in a cohort of healthy women, Chavarro and coworkers [27] showed that the consumption of animal or vegetable proteins was associated with increased or lower risk of ovulatory and infertility respectively. This correlation is statistically significant in women older than 32 years but the underlying mechanisms remain unclear.

3.2 Carbohydrates

To date it is still not well-established whether carbohydrate consumption could have an effect on ovulatory function and in general on fertility in healthy women. In a population of 17,544 women, Chavarro and coworkers [27] further showed that the chronic intake of carbohydrates was positively associated with ovulatory disorders. In this context, restored ovulatory function and fertility were observed in healthy women with PCOS by improving glucose homeostasis. Thus, it is possible that several ovulatory disorders are caused by the effects of carbohydrate intake on glucose metabolism [28]. Therefore, a higher dietary glycemic load appears related with elevated fasting glucose levels, hyperinsulinemia and insulin resistance, that are responsible for a higher release of free IGF-I and androgens ultimately resulting in endocrine disturbance and oocyte maturative defects [29].

3.3 Lipids

The impact of fats on reproduction in women is an actual focus of investigative research. Dietary fatty acids and cholesterol intakes are theorized to affect fertility and pregnancy outcomes, likely through the increased production of prostaglandins and steroids [30]. However, few data are available about the relationship between fat intake, androgen levels and ovulation. Mumford and

collaborators observed in a group of 259 regularly menstruating women that the total fat intakes of polyunsaturated fatty acids (PUFA) were not associated with higher testosterone levels, but rather with progesterone elevations promoting a decreased risk of anovulation [31]. Therefore, their results suggest a weak role for fatty acids, specifically PUFAs, in androgen synthesis, although future studies are needed to answer the question of whether or not alterations in androgen synthesis may consistently affect the female fertility [31].

3.4 Antioxidants

Oxidative Stress (OS) and the resulting variation of the DNA methylation are capable of impacting reproductive capacity. OS develops from a bodily imbalance between the anti-oxidant protection and free radical release [32]. Therefore, since diet is a source of exogenous oligo-elements and vitamins, current clinical practice suggests integrating the diet with some nutritional supplements that are capable to reverse this imbalance, inducing the control of the OS and improving fertility [33]. Among several existing antioxidants, Glutathione is a natural compound with a strong detoxifying activity, which maintains the redox state of the cell by limiting the production of free radicals. Other antioxidants include the Lipoic acid, Vitamin E, Vitamin C and Coenzyme Q10 (CoQ10), whose deficiency or altered concentrations, alone or in combination, may definitely impair the function of the whole detoxifying system [34].

The effect of a regular intake of ascorbic acid has been widely described in literature, showing that its consumption during pregnancy could stimulate the human placental/trophoblastic steroidogenesis that physiologically supports gestation [35]. Infact, it has also been reported that among women with frequent spontaneous abortions dependent on a luteal phase defect, the blood levels of this antioxidant were lower than in females with better reproductive outcomes [32].

However, although there are many studies supporting the influence of the antioxidants intake on the reproductive capacity, less is known about their action on menstrual function [36]. A report from the BioCycle Study described a positive correlation between OS and endogenous estradiol (E2) and it explained the intricate relationship between reproductive hormone levels (such as estrogen and progesterone) and biomarkers of oxidative stress and antioxidants during the menstrual cycle. Nonetheless, further trials are necessary to investigate the action of antioxidants on organisms in order to improve the reproductive outcome.

3.5 Folates

It is well-known that pre-conception folic acid supplementation (400 µg per day) both improves folate and decreases homocysteine (Hcy) levels in follicular fluid. Supplementation with folic acid, or multivitamins containing folic acid, has been associated to better embryo quality, improved chances of pregnancy and reduced risk of ovulatory infertility [34]. Folates are a group of inter-convertible coenzymes that play fundamental roles in DNA synthesis, methylation and protein synthesis. In fact, folate deficiency may alter these synthetic processes, resulting in Hcy accumulation and consequent excessive OS and methylation reactions. The DNA methylation is an epigenetic mechanism, able to modify the expression of specific genes without changing the DNA sequence. Also, methylation alters the physical accessibility to the nucleic acids by molecular complexes responsible for gene expression and, therefore, may modify or suppress the gene function. This process is involved in numerous molecular events such as gene transcription, embryonic development, X chromosome inactivation, genomic imprinting and chromosome stability, and the methylation profile is maintained during cell division. Thus, the relative information is transmitted to the daughter cells independently of the DNA sequence [34].

Three enzymes, namely methylene tetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and methionine synthase reductase (MTRR) exert a major role in both Hcy and folate metabolic pathways, and the activity of these enzymes is regulated by the concentration of folate. Hcy is metabolized into methionine via the 1-CC. From Hcy, Cysteine can be produced via the cystathionine beta synthase pathway (CBS), a source of the 1-CC, and can be utilized for the synthesis of glutathione and hypotaurine. However, in the oocyte and the early embryo the CBS pathway is not expressed [33]. To prevent some birth defects, a supplementation with folic acid is recommended during the preconception period and during the first trimester of pregnancy (figure 2).

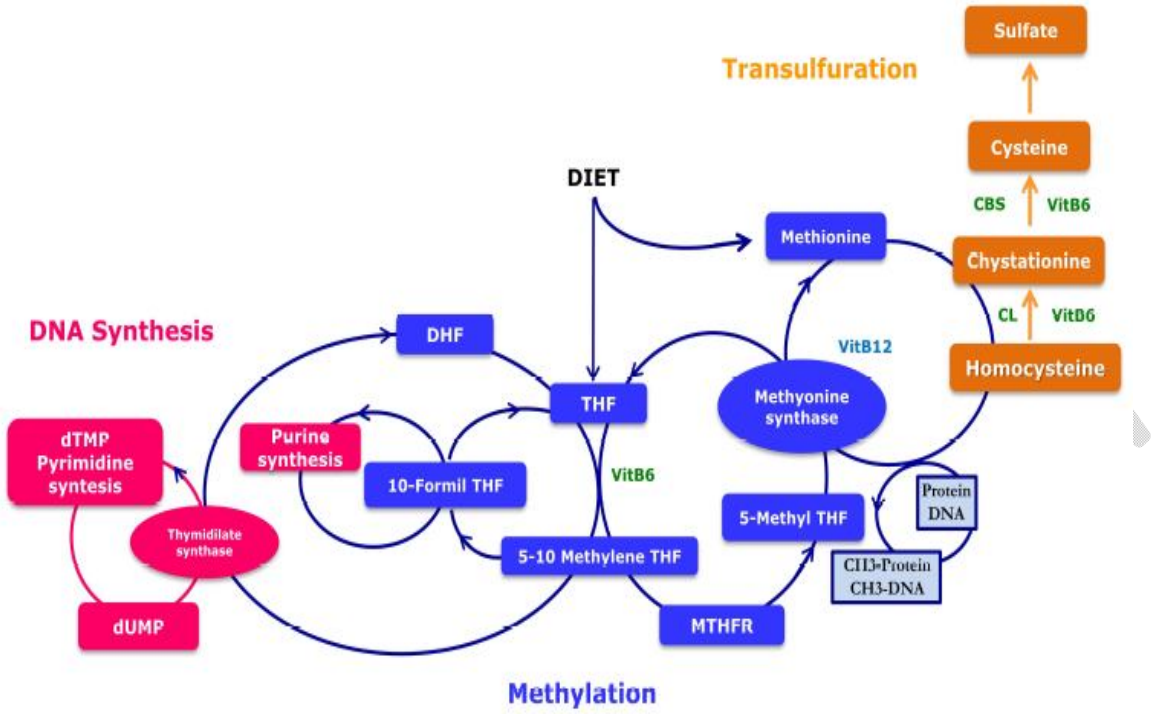

Figure 2: Metabolism of folates [5].

Folic acid cycle involves the recycling of homocysteine to methionine and contains the methyl tetrahydrofolate receptor (MTHFR) necessary for the formation of 5-THF. MTHFR catalyzes the reduction of methylen tetrahydrofolate (5,10-methylen-THF) to methyl (5-methyl THF) by donating a methylgroup (figure 2). MS can catalyze the transfer of the methyl group from 5-methyl THF to homocysteine, which generates methionine and THF. The cystathionine-beta synthase pathway allows the formation of cysteine from homocysteine, that is a precursor of glutathione and hypotaurine (figure 2). Impaired methylation will thus lead to a number of major genetic health problems such as cystic fibrosis.

4.0 HOW TO IMPROVE FEMALE FERTILITY WITH A PROPER DIETARY REGIMEN AND ORAL SUPPLEMENTATION

Several ovulatory disorders are directly linked to metabolic pathologies such as diabetes and galactosemia, suggesting that dietary factors may play an etiological role in some types of infertility.

4.1 The Oral Supplementation against the Endocrine Disruptors

Animal studies have demonstrated that an appropriate dietary assumption of methyl donor supplements can reduce the effects of environmental endocrine-disrupting chemicals (EDCs). EDCs are usually components of cosmetics and “domestic use” products. They induce abnormal effects on methylation profiles and regulatory epigenetic mechanisms in their trans-generational transmission. In animal models, plastic products such as Bisphenol A (BPA), Di(2-Ethylhexyl)phthalate (DEHP), and Dibutyl phthalate (DBP) induce trans-generational reproductive and metabolic pathologies. The relation between EDCs, OS, and DNA methylation abnormalities is now well-recognized, namely EDCs generate OS through estrogen receptors and peroxisome proliferator-activated receptors [37].

BPA has a strong structural similarity with Diethylstilbestrol and E2. Human epidemiological studies have recently highlighted the presence of BPA, parabens, and other organic pollutants in the urine or serum of women who have difficulty conceiving and/or suffer early menopause. Experiments with mice have shown that methyl donor supplements (support of the 1-CC) affect gene expression and counteract the hypomethylation effects of BPA. As already mentioned above, the 1-CC is involved in the methylation processes, by recycling Hyc, and the generation of endogenous antioxidants such as glutathione and hypotaurine, as well as CoQ10, capable of modulating epigenetic settings in association with Vitamins B2 and B3 [5].

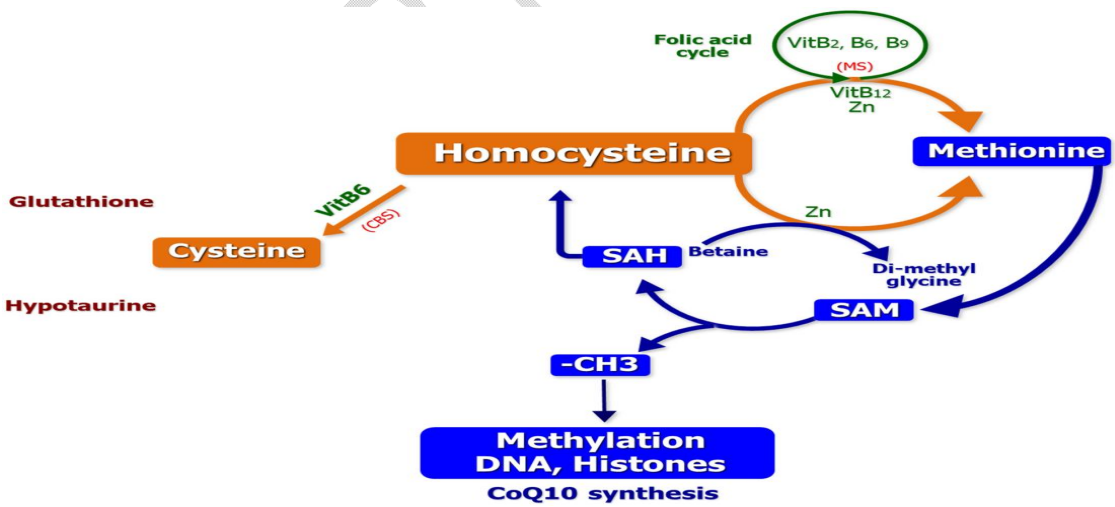

Figure 3: The one carbon cycle: contribution to methylation process and genesis of major antioxidant molecules [5].

5.0 CONCLUSION

Infertility is a global medical and social condition caused by various pathophysiological alterations. In a remarkable number of cases, the pathogenesis is not clearly defined, determining indecision concerning the most appropriate treatment choices. While in developing countries, this condition is related to preventive, diagnostic and therapeutic inadequacy, multiple ovarian endocrine dysfunctions in industrialized nations are apparently associated with improper life-styles. In this context, IR appears as a major pathogenic mechanism impairing the physiology of ovulatory functions, while an adequate intake of monounsaturated fatty acids from vegetables may be effective in the prevention of female infertility. Adequate intake of antioxidants also supports female reproductive functions since the dietary supplements containing folic acid, β-carotene, Vitamin C and E, and an adequate nutritional support of the 1-CC are efficient in shortening the time to conception. Therefore, a correct balance of proteins, carbohydrates, lipids, antioxidant and folate in the daily diet provides essential benefit for an optimal male and female reproductive health and reduces the risk of infertility.

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