Nutrients and infertility: an alternative perspective

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Abstract. – Background: Different gonadotrophin preparations or different protocols of ovulation induction are powerless to determine a significantly increase in oocyte quality in the majority of aged patients or in patients with repeated failed in vitro fertilization-embryo transfer (IVF-ET) cycles.

Information Sources: Papers published on journal focused on nutraceutical and human reproduction.

Evidences: It is questionable if various molecules that are positively associated with higher oocyte competence, higher fertilization rate and embryo development could be supplemented to infertile patients with the aim to partly reduce the frequency of unsuccessful IVF.

Perspectives: Aim of this short review is mainly to focus the attention on potentially positive effects in female fertility of few, well established substances, that could be suggested as a dietary supplement.

Key Words: Nutrition, Follicular fluid, Oocytes quality, IVF-ET outcome.

Introduction

There is an arising interest on vitamins, minerals, antioxidants and phyto-nutrients in both gynecological and obstetric fields, while in reproductive medicine attention is above all focused on hormonal treatment.

In fact different ovarian stimulation protocols for in vitro fertilization (IVF) are being developed to obtain elevated number of oocytes at retrieval with the aim to increase success rates.

Nevertheless, live birth rates per cycle range between 30-40% in women <37 years of age undergoing their first IVF cycle, with significantly worst outcome in repeated cycles or when age >38 years or other negative prognostic factors (i.e. endometriosis or premature ovarian failure) are present.

It is well established that oocyte quality determines the embryo’s developmental potential after fertilization.

Variety of factors play a role in oocyte competence including environmental conditions, oocyte interactions with cumulus cells (CC) and follicular fluids (FF) and various chemical components.

Human exposures to environmental contaminants in air, water, food, and consumer products may result in adverse effects included impaired development and function of the reproductive tract and permanently altered gene expression, leading to metabolic and hormonal disorders, reduced fertility and fecundity1.

It is open to question if in the ovarian micro-environment the lack of some substances or the excess of other molecules could positively or negatively affect oocytes development. Thus, it is questionable if dietary supplementation with detailed molecules could somehow positively influence follicle growth and oocytes maturation in infertile patients.

Aim of this short review is primarily to argue about the importance in female fertility of few, well established nutrients, summarizing results of different papers where substances were considered as positive or negative factors in determining IVF outcome.

Reactive Oxygen Species and Antioxidant Treatment

Oxidative stress may induce DNA damage and trigger apoptosis. In fact, severely hypoxic follicles contain oocytes with a high frequency of abnormalities of the meiotic spindle, with subsequent increased probability of aneuploidy in the embryo2.

Both selenium3 and melatonin4,5 exert antioxidant effects, potentially preserving oocytes from high reactive oxygen species (ROS) levels.
Selenium levels and glutathione peroxidase (GSHPx) activity seems to be significant for the evaluation of the follicular milieu. In fact patients with unexplained infertility had significantly decreased follicular selenium levels as compared with those with tubal infertility or male factor, while tobacco smoking resulted in significantly diminished follicular GSHPx activity.

In patients who failed to become pregnant with a low fertilization rate ($\leq 50\%$) in the previous IVF-ET cycle, the addition of 3 mg per day of melatonin improved fertilization rate if compared to the previous attempt.

Melatonin and its metabolites are powerful antioxidants. Human preovulatory follicular fluid (FF) contains higher concentrations of melatonin than plasma, and melatonin receptors are present in ovarian granulosa cells.

A large amount of scientific evidence supports a local role of melatonin in the human reproductive processes. The indole indeed has potential roles in the pathophysiology of endometriosis, polycystic ovary syndrome (PCOS), and premature ovarian failure (POF).

**Homocysteine and Folic Acid Treatment**

Homocysteine (HCY) is an amino acid being a methionin catabolite and its concentration in follicular fluid is negatively related to oocyte maturity.

Mild to moderate hyperhomocysteinemia is associated with detrimental effects on reproductive outcome, while, in patients undergoing IVF-ET procedure, high levels of homocysteine (HCY) in the follicle negatively affects oocytes quality6,7.

Even in PCOS patients undergoing assisted reproduction, concentrations of HCY in follicular fluid on the day of Ovum Pick Up may be a useful marker for fertilization rate, being inversely related to oocyte and embryo quality8.

The oral administration of folic acid lowers HCY follicular fluid and serum concentrations, protecting follicular growth against excess of oxidative stress HCY-caused, with positive effects on number of mature oocytes at ovum retrieval.

**Myo-inositol and Aspartic Acid**

Myo-inositol (MYO)9 and D-aspartic-acid (D-Asp)10 concentrations in FF are positively related with percentage of good morphology, mature oocytes, and fertilization rate.

The levels of MYO in FF were positively correlated with the amount of estradiol in their corresponding FF samples and also correlated with embryo quality.

In human follicular fluid, D-aspartic acid is present at a relatively higher concentration in younger women than in older patients and there appears to be a relationship between the concentration of d-Asp and fertility outcome parameters.

In addition MYO has been extensively investigated and its helpful role in PCOS11, as a natural insulin sensitizer-agent, well established.

Furthermore MYO is positively involved in physiological triggering of oocyte maturation12,13.

**Thyroid Disease, Implantation Defects and Selenium Treatment**

Recent evidence suggests that thyroid anomalies14, can compromise the success of implantation.

In fact, thyroid sub-clinical abnormalities are more prevalent in women experiencing IVF failure15,16. In patients with sub-clinical hypothyroidism the use of thyroid replacement therapy during pregnancy was found to be successful in reducing miscarriages, confirming that a mild thyroid insufficiency can lead to spontaneous abortion. Therefore, it can be speculated that the presence of an underlying thyroid abnormality could have an adverse effect upon implantation, compromising the success of IVF treatment.

Among all human tissues, the thyroid gland contains the largest amounts of selenium and is involved in several aspects of thyroid homeostasis.

For this reason selenium supplementation seems to be effective in preventing a mild thyroid dysfunctions restoring physiological activity17.

**Conclusion**

This brief commentary want to open a debate on the opportunity to introduce other molecules in the approach to infertile patients undergoing gonadotrophin ovulation induction.

Ideally, all of these molecules represent only a fraction of different elements that could be nutritional supplemented with a relatively small risk of excess complications, far outweighed by the substantial prospect of further IVF failure.
Potentially these compounds could get to ovarian district and locally exert a valuable storage and an useful aspect.

Each single molecule could exert a potential benefit in different phenotypes of infertile patients (i.e. aged patients, PCOS or poor responder patients).

For this reason it should be widely investigated if a dietary supplementation of single, specific molecules during ovulation induction with standard gonadotrophin protocols could benefit for oocytes maturation in particular childbearing patients, in some measure reducing the unsuccessful rates of IVF.

References


