

USE AND ABUSE OF COMBINATION OF ANTIESTROGEN AND ANTIOXIDANT TREATMENT FOR IDIOPATHIC MALE INFERTILITY

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Summary

Infertility is defined as the inability of the couple to conceive despite one year of frequent unprotected intercourse. In those couples male has a significant contribution to the infertility occurrence. However not all causes can be identified and so called idiopathic infertile. According to Horstein MD and Gibbons WE reported that the percentage of couples who experience infertile caused by unexplained infertility was 15%. The sperm parameter in infertile males usually has lower in concentration, motility, and morphology compared to fertile male. Various treatments have been used to surmount these problem including clomiphen citrate (CC) and antioxidant. Unfortunately by using both of modality did not indicate the increase of pregnancy rate. The purpose of this paper is to discuss about how CC and antioxidant combination have effect upon the sperm parameters and pregnancy rate improvement.

CC constitutes a mixture of two isomers which are enclomiphen and zuclophen. Like tamoxifen CC is a non steroidal triphenylethylene derivation, indicating both estrogen agonist and antagonist properties. In one side estrogenic agonist properties are generally manifest only in the moment of estrogen level is extremely low. On the other side CC able to act solely as a competitive estrogen antagonist. Various evident show that CC increase endogenous GnRH secretion from hypothalamus and gonadotropin (FSH, LH) from pituitary, thus increasing intra testicular testosterone, constituting a fundamental condition for spermatogenesis. As Hussein reported that CC administration for cases of non obstructive azoospermia allowed for both the appearance of sperm in ejaculate and in those patients were remain azoospermia, successful sperm retrieval for ICSI can be achieved. After 3 – 9 months of treatment using CC, 64.3% of patients manifested sperm in their

ejaculate. The mean of sperm density in this study was 3.8 million/mL, even the partner of one patient achieve spontaneous pregnancy. Meanwhile the ejaculate remainder of these patients contained sufficient sperm for IVF or ICSI. In addition according to double blind study was reported by Guay showed that treatment with CC during two months to impotent men with secondary hyphogonadism could increase LH, FSH, and Testosterone levels. These finding were also supported by meta-analysis from Cochrane, in which the CC administration could increase hormone concentration (FSH & Testosterone), sperm concentration, and motility significantly, but not significant for sperm morphology. On the other hand, even though the spontaneous pregnancy rate was increased by CC treatment but it is not significant. According to these data it can be conclude that CC treatment increase the quality of sperm parameters but not to spontaneous pregnancy rates. For this reason possibility of antioxidant treatment can be added as complementary.

Oxidant or free radical is an atom or a group of atom which has unpaired electron, thus very reactive and so called reactive oxygen species (ROS). ROS consist of oxygen superoxide ($O_2^{\cdot-}$), hydroxyl radical (OH^{\cdot}), peroxy radical (ROO^{\cdot}), and hydrogen peroxides (H_2O_2). To deter the ROS effect, body system has been naturally equipped with the biochemical buffer system namely primary antioxidant in order to make in balance between pro-oxidant and antioxidant. The balancing may be shifted to pro-oxidant when concentration of antioxidant is decreased or the production of ROS is increased. ROS in male reproductive tract can induce the damage of spermatozoa and decreasing quality of sperm parameter. In higher ROS concentration, natural antioxidant as scavenger is needed to neutralize oxidant effects. There are two types of natural antioxidant has been known, which are preventive antioxidant and chain breaking reaction. The preventive antioxidants are natural antioxidant which able to suppress or inhibit ROS production in initiation stage such as enzyme of catalase, peroxides, and glutathione peroxides has done. However the action of preventive antioxidant cannot clean up all the ROS but still left in low concentration, otherwise it will be increased when ROS from outside is also increase. Thus to

surmount of such ROS effect, chain breaking antioxidant is needed for ROS chain reaction chocking off in propagation phase. The natural antioxidant including in chain breakers are divided into two groups. The first group is water soluble antioxidant like as superoxide desmutase (SOD), uric acid, bilirubin, albumin, thiols, and vitamin C. Meanwhile vitamin E, carotenoid, ubiquinol, polyphenol (flavonoid), and caffeate phenetyl ester (CAPE) are fat soluble antioxidant. Antioxidant efficacy is very determined not only by chemistry properties and concentrations, but also by mobility and location of antioxidant in its micro environment. Accordingly vitamin E and other fat soluble antioxidant are very effective against ROS. Antioxidant treatments in male infertility considerably need in-depth thought about the primary sources of increasing ROS. However antioxidant can be treated directly to infertile male in whose the causes of infertility remained unknown, as well as to patients who were exposed by substance that cause the increase of ROS concentration, especially in spermiogeneis stage.

In the spermyogenesis stage 85% of nuclear histone to be replaced by protamine, in order to DNA tightly packaging and by which DNA will be resistant to oxidant attack. At the moment of histone replacement by protamine, temporary breaking of spermatozoa which is induced by topoisomerase II enzyme is needed, and will be recovered by the same enzyme. Abnormality of DNA packaging due to protamine deficient can induce DNA to be more vulnerable to oxidant attack and subsequently damaged easily. Thus treatment of appropriate antioxidant might prevent nuclear DNA damage during spermatogenesis, particularly in the stage of spermyogeneis. Based on such aforementioned data, the treatment combination of CC and antioxidant is make sense, but it is not including in misuse or abuse, providing the selection type and dose of antioxidant are appropriately.

Conclusion can be taken that CC treatment alone in infertile male or in combination with antioxidant is very beneficial.