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Editorial – Modern approach to the infertile male: the use of andrositol® test (myo-inositol in diagnostics)

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Infertility is a critical and widespread problem affecting 15% of couples worldwide. For about one in five infertile couples the problem lies solely in the male partner[1]. Male fertility is a complex process and can be impaired by different medical treatments and health issues such as varicocele, genital and urinary infections, ejaculation issues, environmental factors (pesticides, light pollution, hormones), lifestyle etc. Furthermore, the presence of high levels of seminal reactive oxygen species (ROS) has been implicated as a cause of male infertility[2]. Excessive ROS production in the semen has been reported in up to 20-40% of infertile men[3]. They are produced by sperm cells and seminal leukocytes, and may interfere with sperm function through the induction of toxic fatty acid peroxides and peroxidation of sperm lipid membranes[4,5]. Although high levels of ROS are detrimental to human spermatozoa, they are also involved in the physiological sperm functions such as the acrosome reaction and capacitation[6]. Man's fertility generally relies on the quantity and quality of his sperm. The fertilizing capacity of spermatozoa is evaluated through the analysis of seminal fluid according to the World Health Organization criteria, including semen volume, sperm concentration, total motility, sperm morphology, viscosity and the total number of spermatozoa[7]. However, the assessment of these parameters determines only partially the sperm quality and the spermatozoa health. For this reason, it is of primary importance to identify functional deficits that may impair the fertilizing capacity. This editorial draws attention to the diagnostic evaluation of male infertility. As a matter of fact, several scientific studies have shown that the mitochondrial membrane potential (MMP) is an important parameter that should be considered in order to identify the "real" normospermia[8,9]. In spermatozoa, the key site of ATP production in oxidative phosphorylation is the inner mitochondrial membrane, where is required a chemiosmotic proton gradient usually translated into MMP[10]. In diagnostics, the efficiency of the mitochondrion is measured by the assessment of the MMP. A high MMP is directly correlated to a greater fertilizing capacity and a higher chance of getting good quality embryos and more likely achieving a pregnancy[8]. For this reason, it is important to report some different studies that have highlighted the correlation between myo-inositol and a high MMP[11]. Myo-inositol is the most prevalent of the nine stereoisomers of inositol(s) found in many foods and human cells[12]. It is present in high concentrations within the seminal fluid[13] and, at testicular level, it is produced by the Sertoli and epididymal epithelial cells[14]. More precisely, high levels of myo-inositol are found in the seminal fluid along the epididymis and vas deferens[15]. Myo-inositol is a precursor of second messengers in the cellular signal-transduction pathways and regulates the calcium intracellular concentration in sperm plasma membrane, mitochondria and acrosome. This suggests the need for inositol to trigger the metabolic processes necessary for fertilization[16]; indeed, deficiency of myo-inositol is associated to a reduced sperm count. Moreover, two-hours incubation of pathological or normal semen samples with 2 mg/ml of myo-inositol has shown to improve progressive sperm motility and mitochondria efficiency[17,18]. Its addition allows the recovery of a greater number of sperm after swim-up in either normospermic or oligoasthenoteratozoospermic patients[19]. *In vitro* studies have also demonstrated how myo-inositol is capable of reducing the seminal fluid viscosity (either normal and pathological) and increasing the sperm motility[17,18]. In fact, besides inducing a normalization of mitochondrial cristae, myo-inositol maintains a high MMP[17,18]. MMP can now be measured through the andrositol® test (Patent number 2764361, Lo.Li. Pharma, Rome, Italy), which distinguishes the seminal fluid of different patients in three categories: low, medium and high responders. Patients identified as "low responders" would have a high MMP, whereas "high responders" have a low MMP. A semen sample classified as medium or high responder contains an under-

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performing mitochondrion, and therefore requires further evaluation by the specialist. Indeed, such classification depends on the functionality of mitochondria and hence the sperm ability to fertilize and obtain physiologically a pregnancy. Furthermore, this test is used for predicting the success of a human spermatozoa treatment with inositol for increasing their vitality. The benefit of this innovative test is the straight identification of early seminal alterations in patients of which the semen analysis, according to the WHO criteria, might be considered normal.

Conclusions

This novel diagnostic test opens new prospects for men's infertility. This valuable approach might be associated to standard analyses that may still fail to detect subtle sperm defects present in patients with male factor infertility. It is a sperm quality test that can be used as a non-invasive method to estimate the sperm functionality and the potential to achieve a pregnancy.

Conflict of interest

The authors declare no conflicts of interest.

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