Malondialdehyde and Homocysteine Levels in Patients with Unexplained Female Infertility

ABSTRACT

Objectives: To assess association in between malondialdehyde and homocysteine in females with unexplained infertility.

Methods: A case control study.

Setting: Hospital based.

Patients: Fifty females diagnosed with unexplained infertility were matched with fifty normal healthy controls.

Intervention: Blood samples for malondialdehyde, a lipid peroxidation product and homocysteine measurements.

Results: Our study suggests that females with unexplained infertility have increase in malondialdehyde along with hyperhomocysteinemia when compared with normal healthy controls.

Conclusion: Determination of levels of malondialdehyde and homocysteine should be incorporated as one of the factors for ascertaining the cause of female unexplained infertility.

Keywords: Malondialdehyde, Homocysteine, Unexplained infertility female.

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INTRODUCTION

L-Homocysteine (Hcy) is an endogenous amino acid, containing a free thiol group, which in healthy cells is involved in methionine and cysteine synthesis/resynthesis. About 80% of Hcy is bound to albumin (via a disulphide bond) in the plasma, where as the remaining 20% exists as free disulphides. Genetic factors, smoking, hypertension, serum creatinine, total cholesterol and protein and nutritional factors such as vitamin B6, B12 and folate deficiency determine serum total homocysteine (tHcy) concentrations. Elevated circulating homocysteine or hyperhomocysteinemia (HHCY) is known to be associated with biotoxicity and has been underlined as an emerging risk factor for several diseases such as arterial and/or venous thrombosis1 and unexplained female infertility.2

In approximately 15 to 17% of couples, no reason for infertility is found and the infertility is defined as unexplained3 which is not a mere health problem but also a matter of social injustice and inequality.

Oxidative stress caused by the relentless formation of free radicals within an environment lacking proper antioxidant balance, is generated during oxidation of the free thiol group of Hcy. This mechanism is due to the binding of Hcy via a disulphide bridge with plasma proteins mainly albumin, or with other low-molecular plasma thiols or with a second Hcy molecule. Oxidation of Hcy may induce the subsequent oxidation of proteins, lipids and nucleic acids.4

This oxidative stress (OS) affect a variety of physiological processes such as folliculogenesis, oocyte maturation, endometrial cycle, luteolysis, implantation, and embryogenesis in the female reproductive tract thus influencing reproductive outcome.5,6

With this in mind it was thought worthwhile to evaluate and correlate the levels of malondialdehyde (MDA) a lipid peroxidation end product formed from reactive oxygen species (ROS) and homocysteine in females with unexplained infertility.

MATERIALS AND METHODS

A case control study approved by the Institutional Ethics Committee was carried out at NKP Salve Institute of Medical Sciences, Nagpur. Fifty females of unexplained infertility (group II) were included in the study. Unexplained infertility was diagnosed by the following criteria: Absence of male factor, i.e. normal semen analysis: Twenty million sperm per ml, ≥50% forward motility, and greater than 40% normal morphology (using World Health Organization Criteria, 1999); adequate ovulation using either a mid-luteal serum progesterone greater than 10 ng/ml, urine testing documenting the LH surge or serial transvaginal ultrasounds to monitor the development and rupture of a dominant ovarian follicle; normal FSH, LH, TSH, PRL; normal uterine cavity and patent tubes proved by hysterosalpingography or laparoscopy. These were age matched with 50 women
Homocysteine was measured by microplate enzyme immunoassay kit method of Biorad laboratories. For the measurement of homocysteine, all the specimens were transported to the laboratory within 30 minutes of collection. Thereafter, specimens were centrifuged for 5 to 7 minutes at 3000 rpm. The clear serum was transferred in a plastic vial and stored in refrigerator until analysis. Homocysteine was measured by microplate enzyme immunoassay kit method of Biorad laboratories.

Statistical analysis of difference was estimated using students ‘t’ test and correlation between variables was studied using pearson’s correlation coefficient test.

RESULTS

As depicted in Table 1, MDA and homocysteine are significantly increased (p < 0.001) in females with unexplained infertility. Correlation analysis between MDA and homocysteine reveals that there is a positive correlation (0.68, p < 0.001) in females with unexplained infertility.

DISCUSSION

Homocysteine, a sulfur containing amino acid is an essential intermediate in the transfer of activated methyl groups in the activated methyl cycle. Normally plasma Hcy levels are decreased during pregnancy. Our study demonstrates an increase in the level of Hcy in females with unexplained infertility. HHcy may occur due genetic defect in enzyme involved in homocysteine metabolism like tetrahydrofolate reductase (MTHFR) and other deficiency in vitamin cofactors like folate and vitamin B12. Under conditions of impaired folate status, the MTHFR 677 genotype encodes at thermolabile enzyme with reduced MTHFR activity and may cause moderate HHcy Since deficiency of MTHFR is rare and anemic patients were excluded from the study they being a cause for HHcy in infertility patients could be ruled out. Apart from the procoagulant effect of Hcy, i.e. inhibition of the protein C activation, antithrombin III and thrombomodulin, it is related to an enhanced pro oxidant activity. Hcy modulates glutathione peroxidase expression, nitric oxide bioavailability and endothelin – 1 production.

It triggers accumulation of the intracellular ROS including H2O2, O2-, and ‘OH through sulfur autooxidation. Moreover, sustained exposure to the endothelial cells to high levels of Hcy contribute to endothelial dysfunction. ROS oxygen species are known to modulate cellular functions resulting in a diseased cell. Our study suggests that ROS levels are increased in females with unexplained fertility. Research has revealed high levels of ROS in the peritoneal fluid specimen’s from women with unexplained infertility in contrast to fertile controls undergoing tubal ligation. Normally, ROS may act as key signaling molecules in physiological processes but in excess are also known to mediate pathological processes. Numerous mechanisms have been proposed for the induction of infertility by OS: damage to the DNA of the oocytes and spermatzoa leading to defective fertilization; in case fertilization is achieved OS induce an apoptosis resulting in embryo fragmentation, implantation failure, abortion and impaired implantation. Moreover, OS may induce luteal regression and an insufficient luteal hormonal support for the continuation of pregnancy.

Thus, from our study, Hcy and ROS may be involved in the pathogenesis of unexplained infertility. However, this being a case control study and both factors having a positive correlation it is difficult to assess whether Hcy or ROS singly or in association are responsible for the infertility.

Apart from the pivotal role of Hcy and ROS in infertility, ROS are said to be involved in the pathogenesis and Hcy has been described as an independent risk factor for cardiovascular disease. Endothelial cytotoxicity, lipid peroxidation, increased platelet adhesion, enhanced activation of the coagulation system and stimulation of vascular smooth muscle cell proliferation are the possible mechanisms which affect the vasculature.
Hence, apart from other investigations for ascertaining the cause of female unexplained infertility, analysis of biochemical parameters like Hcy and ROS assay should be incorporated. Also, since Hcy and ROS are modifiable predictors of overall mortality and mortality due to cardiovascular causes, the role of homocysteine-lowering therapy and antioxidant supplementation in the treatment of such patients needs to be revisited.

REFERENCES