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Nutrimiromics: A Possible Answer for Premature Ovarian Failure

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Abstract

Nutrimiromics studies the effect of dietary factors on modulation of miRNA expression which leads to disease development. Studies have confirmed their role in immune modulation and their ability to get transferred themselves in other tissues where they influence tissue specific functions. These functions are conducted by means of their transfer in extracellular vesicles such as exosomes. Exosomes deliver their contents such as miRNAs to recipient cells. Micronutrients/Dietary trace elements are essential components for various biological processes. Dietary deficiency of trace elements has shown to alter various reproductive functions including folliculogenesis. Altered folliculogenesis causing oocyte atresia is the major etiopathological change ultimately leading to premature ovarian failure (POF). POF is a primary ovarian defect with symptoms of absent menarche or cessation of menstruation, infertility and symptoms of physiological menopause due to low estrogen levels before the age of 40 years. Dietary trace elements alter miRNA expression and disease processes. As the trace elements are essential for folliculogenesis, their association with ovarian failure is highly suggested.

Keywords: Nutrimiromics, Folliculogenesis, Trace elements

Introduction

Premature ovarian failure (POF) is a primary ovarian defect with symptoms of absent menarche or cessation of menstruation, infertility and symptoms of physiological menopause due to low estrogen levels before the age of 40 years. Fertility is already compromised by the time clinical manifestations of hormonal decline are yet to appear [1]. The etiology of POF remains idiopathic in most cases and the treatment options are lacking.

POF is a potential area of high yield research. Normal ovarian function is integral to reproduction in females. Ovarian development is a highly regulated phenomenon involving complex interactions between somatic cells and germ cells. The phenomenon is regulated by multiple gene expression that itself is regulated by miRNAs. The occurrence small RNAs including miRNA in ovary is supported by the fact that studies knocking down their function leads to dysfunction in folliculogenesis, ovulation and infertility [2,3].

Fertility is a key component of reproductive health. Infertility has become a global health issue. Prevalence of infertility in female is estimated to be 15% in India [4]. Infertility in POF is caused by decreased oocyte reserve due to accelerated follicular and oocyte/granulosa cell atresia or decreased ovarian reserve since birth. POF constitutes roughly 1% cases of infertility in females [5]. Despite of multiple etiologies suggested such as genetic, metabolic, infections, autoimmune etc., POF remains idiopathic and untreated in most cases [6]. In India, POF remains almost unexplored. POF is usually diagnosed at the terminal stage (FSH levels ≥40 IU/L) of the disease by which time large numbers of women have lost their fertility potential and are usually suffering from menopausal symptoms. The routine tests fail to detect POF at earlier stages where chances of fertility improvement may persist. Moreover, treatment options are lacking in POF. Therefore, search on early diagnostic markers and treatment options is utmost important.

Nutrimiromics deals with influence of dietary factors on modulation of miRNA expression which leads to disease development. The origin and function of miRNA is a field of latest research. Few studies have confirmed their role in immune modulation and their ability to get transferred themselves in other tissues where they influence tissue specific functions [7]. These functions are conducted by means of their transfer in extracellular vesicles such as exosomes. Exosomes deliver their contents such as miRNAs to recipient cells [8]. One of the most abundant molecules present in exosomes are microRNAs (miRNAs) which are small (~22-nt) non-coding, single-stranded RNAs and considered critical for cell proliferation, cell differentiation, cell death and tumorigenesis. miRNAs are small (~22-nt) non-coding, single-stranded RNAs occur both intraand extracellularly and are important for various cellular events such as cell proliferation and differentiation, apoptosis, and immune regulation [9]. miRNAs regulate gene expression by catalyzing mRNA cleavage or repressing mRNA translation [10]. Different microRNA profiles have been implicated in disease pathogenesis such as neurological disorders (Parkinsons, Alzheimers), cancers and recently in infertility [11-14]. It has been shown in various studies that miRNAs can be regulated by dietary factors [15,16].

When follicular cells are supplemented with the follicular fluid in culture, they can take up follicular fluid miRNAs thereby allowing miRNAs to signal through fluid to facilitate reproductive maturation [17]. One of the gene implicated in POF is NOBOX (Newborne Ovary Homeobox gene). It has been found that miR-196a has a regulatory effect on NOBOX expression [18]. miR-132, 212 were found to be responsive to ovarian LH/hCG secretion [19]. Other miRNAs regulating ovarian function are miR-210 (pre-ovulatory folliculogenesis regulation), miR-146a,139 (granulosa cell apoptosis pathway) [20-22].

Extracellular vesicles (EVs) or exosomes are the main channels of intercellular communication. EVs produced by cells are of three main types, according to their size and biogenesis: exosomes, microvesicles (MVs), and apoptotic bodies. Exosomes form intracellular multivesicular bodies which fuse to the plasma membrane and are secreted as vesicles measuring 0.04-0.1 μm [23,24]. EVs deliver their contents both miRNAs and mRNAs to recipient cells. One of the most abundant molecules present in exosomes are microRNAs (miRNAs)

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which are considered critical for cell proliferation, cell differentiation, cell death and tumorigenesis. Exosomal miRNAs are channels for cell-cell communication and are potential easy-access biomarkers [25]. Exosomal miRNAs has been identified in follicular fluid. Very recently potential role of exosomal miR-144-5p in treatment of ovarian failure has been tried in animal model of chemotherapy induced POF [26].

Studying effect of nutrients on miRNA expression related to disease conditions is a vital area to search for the effect of nutrients on miRNA modulation and influence on disease development. Micronutrients are as essential to human health as the other dietary nutrients. Micronutrients/Dietary trace elements are essential components for various biological processes such as hormone production, metabolism, nerve conduction etc. Physical and mental stress and environmental pollution alters our requirement of the micronutrients. Therefore, studying their deficiency levels is important to understand pathophysiology of various diseases. Dietary deficiency of trace elements has shown to alter various reproductive functions [27]. As these are also essential for folliculogenesis (iron, zinc, selenium, copper, iodine, etc.), their association with ovarian failure is highly suggested. Dietary trace elements alter miRNA expression and disease processes [28]. Diet modification in modulating the risk of diseases or as therapeutic intervention is definitely highly promising and potential approach. Role of micronutrients via nutrimiromics in POF has not been studied in detail. Therefore, it may be suggested that dietary trace elements (vitamins and minerals) modulate expression of exosomal miRNAs regulating ovarian function. Altered expression of exosomal miRNAs due to decreased dietary mineral and vitamins levels may affect ovarian function and leads to POF. But this hypothesis is proved only by conducting studies in large number for validation.

Conclusion

Regulation of ovarian function by micronutrients through exosomal miRNAs is a potential research area. Nutrimiromics holds future prospects in therapeutics based on micronutrient mediated effects on folliculogenesis.

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