The Promising Biomarker for Multiple Clinical Situations

Biomarkers have achieved broad logical and clinical attention in diverse disciplines such as screening, diagnosis, prognosis, recurrence prediction and therapeutic monitoring of diseases in modern medicine. Due to lack of direct access to the function of reproductive organs and their malfunction especially in women, most of data are received through application of sensitive and specific biomarkers. These biomarkers have been developed and validated over time. An ideal and specific biomarker should be non-invasive, easy to detect, inexpensive with acceptable precision and reliability and able to detect early onset of changes in associated organ. Anti-mullerian hormone (AMH), also known as mullerian inhibiting substance (MIS) is a biomarker indicative of above features. AMH, discovered in 1947 by Alfred Jost, is a dimeric glycoprotein member of TGF-β superfamily. It is known for its primary role in Mullerian duct regression in embryonic genital tract. Sertoli cells and granulosa cells are the main sources of AMH production in male and female gonads, respectively. The AMH secretion starts from 36 weeks of pregnancy in preantral and early antral follicles smaller than 4 *mm*. It reaches peak levels after puberty and steadily decreases until menopause. Development of antral follicles leads to the decrease in AMH and finally stops its secretion in follicles larger than 8 *mm* and atretic follicles. AMH levels are stable during the menstrual cycle. However, its level declines during pregnancy due to placental inhibition of ovaries and increases rapidly after delivery (1).

It is well known that AMH is a key factor in regulation of ovarian function during folliculogenesis and oocyte maturation. The beginning of the development of primordial follicles and sensitivity of granulosa cells to FSH are regulated through AMH. The outcome of its activity on follicles leads to drive a large number of developing follicles to atresia process and finally selection of a graafian follicle in each cycle (1).

Regarding the role of AMH in folliculogenesis and ovarian function, at present, it is applied as an excellent biomarker for assessing a broad range of physiologic and pathologic conditions of female fertility. AMH is a candidate biomarker for PCOS diagnosis. Impaired oocyte maturation in these patients leads to accumulation of large number of pre-antral and small antral follicles that subsequently raise serum levels of AMH. Increased level of AMH in PCOS has strong correlation with the *Rotterdam diagnostic criteria*. Serum AMH may be used as a marker to identify candidates of PCOS and normal ovulatory women for *in vitro* maturation program (2).

The serum AMH level has a close correlation with oocyte and embryo quality and blastocyst formation rate in IVF/ICSI cycles; however, live birth rate and clinical pregnancy rate have only correlation with AMH concentration in follicular fluid. Serum level of AMH is a valuable marker for prediction of oocytes number retrieved after stimulation cycles in aged women. The cut-off of 1.0 *ng/ml* can be used to predict poor responder patients. This cut-off level can be useful to predict the probability of embryo transfer, without predictive value for clinical pregnancy. Receiver operating characteristic (ROC) analyses showed that different cut-off for serum levels of AMH are good predictors of oocytes numbers retrieved in controlled ovarian stimulation cycles (3).

Serum AMH is a sensitive biomarker for monitoring cancer chemotherapy and gonadotoxic treatment on ovarian follicular reserve of young women. It is a good indicator for comparison and determination of gonadotoxicity in different chemotherapy regimens (4). AMH is also proposed as a therapeutic agent for endometriosis. AMH is expressed in normal endometrium and suggested to negatively regulate cellular viability via paracrine function. Recent data indicates that AMH will be the frontline hormone for treatment of endometriosis in future; therefore, it will reduce high recurrence rates of current surgical and medical treatments strategies (5). However, several other new clinical applications are suggested for AMH such as a tumor marker of granulosa cell tumor, diagnosis of precocious puberty, delayed onset of puberty, anorchidism, intersex disorders and control of spermatogenesis (1). Therefore, AMH is the most excellent marker of ovarian reserve in different clinical conditions (especially infertility), in prediction of reproductive lifespan, ovarian dysfunction (PCOS) and ovarian damages of cancer therapy or surgical treatment. Despite the above benefits, AMH measurement has broad variation in different storage and handling conditions. Therefore, improved assay validity and standardization, reference preparation and compatibility with international guideline for laboratories are critical tasks to maximize the clinical utility of this promising biomarker in future.

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