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Chapter 7

Ovarian Reserve Markers: An Update

Harold Moreno-Ortiz, Iván Darío Acosta,
Elkin Lucena-Quevedo, Luis Alejandro Arias-Sosa,
Alix Eugenia Dallos-Báez, Maribel Forero-Castro and
Clara Esteban-Pérez

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Abstract

Ovarian reserve (OR) is defined as the pool of follicles available to provide eggs cells throughout the fertile age in each woman and define the potential of fertility to predict the reproductive lifespan of women. Several studies have focused on the clinical use in order to identify women with a decreased ovarian function and to improve the clinical approach to these patients. In this chapter we will describe different OR markers such as antimullerian hormone (AMH) and follicle stimulating hormone (FSH), count by ultrasound of antral follicles (AFC) and ovarian volume. The measure of OR markers has been reported as an effective test to predict a possible failure of reproductive capacity and important tool in the primary prevention of infertility and other related problems. Therefore, we will show the clinical use of these markers in both healthy and infertile women studies. Additionally, we describe the most recent and promising progress in the OR evaluation by construction of algorithms.

Keywords: ovarian reserve markers, infertility, potential of fertility

1. Introduction

Ovarian reserve (OR) is defined as the pool of follicles available to provide eggs cells throughout the fertile age in each woman [1, 2]. In reproductive medicine, OR reflects the potential of fertility and also predicts the length of reproductive lifespan on female patients [1, 2]. The evaluation of OR allows to identify cases of premature ovarian insufficiency and provide the opportunity to design programs for egg freezing preservation and egg donation. In addition,

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OR can predicts the success of the assisted reproductive techniques, oncofertility programs, and infertility counseling programs [3–5].

Some patients with spontaneous follicle depletion show a decrease of OR. A diminished OR (DOR) is related to the decline of the potential of female fertility that accompanies the normal ovarian aging [6].In some cases OR declines before 40 years which is a condition previously known as premature menopause, premature ovarian failure, or early menopause characterized by amenorrhea, hipoestrogenism, and elevated levels serum gonadotropins levels [6]. The decreasing of OR gives rise lower pregnancy rates, repetitive implantation failure, and high risk of miscarriages [3, 7–10]. The negative impact of DOR forces to organize early programs of detection that prevents numerous cases of woman infertility [6, 11, 12]. Additionally, early detection of DOR cases grants a better comprehension of the woman reproductive status to impede expensive assisted treatments and also generates strategies to ameliorate negative effects on emotional condition [6, 11, 12].

Today, the loss of fertility has been related with an increase use of assisted reproductive techniques (ART) [11]. One of the main factors is the delay of the motherhood to advanced age due to social, academic, familiar, economic, and demographic reasons [6, 13]. Unfortunately, mostly cases of advanced maternal age did not receive any medical advice in reproduction and they accept the age as a remarkable reference for fertility [6, 13]. It is known that the female age is not enough fact to determine and predict the individual fertility [6, 13]. Women have wide variations on their reproductive potential and the cessation of fertility can occur in an unexpected way [11, 14–18]. As a consequence, the use of predictive markers that reflects the reproductive status is remarkable and important [11, 14–18]. On the basis of fertility evaluation, health providers can improve plans for counseling for infertile patients and modify the management guides for prevention and promotion of sexual and reproductive health.

In clinical practice, the evaluation of OR can be assessed by blood markers and ultrasound markers. Antimullerian hormone, basal follicle-stimulating hormone, and basal estradiol are the blood markers whilst antral follicular count (AFC) and the ovarian volume are the ultrasound markers [13]. The use of above-mentioned markers permits the categorization and the assessment of fertility potential in female patients [14, 17] and brings the opportunity to design mathematical formulas for further evaluations for each patient.

2. Ovarian reserve

Ovarian reserve (OR) is defined as the pool of follicles available to provide eggs cells throughout the fertile age on female patients. The OR is considered as the biological and reproductive clock and it is a clinical term used to determine the capacity of the ovary to supply eggs for fertilization and resulting in a healthy and successful pregnancy [2].

OR is assured during the embryo development period starting with a cluster of 100 of primordial germinal cells (PGC) in the primary ectoderm (epiblast). In the third week of gestation, PGCs migrate from the primary ectoderm into the yolk sac wall and collect near the exit of the allantois and proliferate colonizing the gonadal ridge to develop the female gonad. At the 20th week of

gestation the proliferation of PGCs reaches 6–7 million of oogonias decreasing in a unexplained manner to 1 million of oogonias at the time of birth [19, 20]. The number of follicles continues to decrease and reaching approximately a number of 300000 - 500000 at the puberty time and later 25,000 follicles are identified at age of 35 years [19, 20]. Once the menopause time appears the number of follicles drops to 1000 at age of 51 years [19, 20].

Ovarian reserve assessment is the first step in determining the fertile potential of the ovary. In an effort to predict the status of OR, markers and tests described in the literature for OR evaluation includes: basal follicle-stimulating hormone (FSH), basal estradiol (measured on day 3 of the menstrual cycle), serum antimullerian hormone (AMH), and antral follicular count (AFC) assessed by transvaginal ultrasound [11, 21].

2.1. Ovarian reserve blood markers

Follicle-stimulating hormone (FSH) is a gonadotropin secreted by the anterior pituitary in response to gonadotropin release hormone (GnRH). FSH is responsible for growth and maturation of ovarian follicles and also for estrogen ovarian production [22]. Basal FSH is the most widely marker used for evaluation of OR. Regardless of age, high blood levels of FSH (>10 mUI/ml) at day 3 of the menstrual cycle are related with DOR and reduced fertility. However, there are some concerns about the use of FSH as marker of OR as result of inter and intramenstrual variations, the use of oral contraceptives, and some gynecological pathologies [11, 21].

Antimullerian Hormone (AMH) is a homodimeric glycoprotein secreted by granulose cells (GC) from the ovary. AMH blood levels reflects de overall amount of GC in the antral follicular pool. GCs surround early antral follicles and antral follicles, however AMH expression is found in follicles from primary follicles to 4-mm sized antral follicles [21]. In addition, AMH secreted by 5–8 mm-sized follicles is known to account for 60% of all blood AMH. The AMH level is not affected by the menstrual cycle and it is strongly correlated with the antral follicular count assessed with transvaginal ultrasound at day 1 of menstrual bleeding. AMH indirectly represents the ovarian reserve due to it is well-characterized throughout the female lifespan with increases levels in early childhood, a peak in the early 20s, and subsequently declines gradually with age toward menopause [21, 23–28]. Currently, the blood level of AMH is considered an effective and informative biomarker to evaluate fertility ovarian conditions.

2.2. Potential blood markers in ovarian reserve

Luteinizing hormone (LH) is a pituitary hormone that plays a critical role in folliculogenesis, follicular antrum formation, and development of the thecal vasculature. Additionally, LH is fundamental for supporting steroidogenesis via theca cells-LH receptors [22]. Whilst LH is essential for oocyte maturation, oocyte release, follicular rupture, and embryo implantation, follicles exposed to high concentrations of LH can compromise the normal oocyte development. Basal LH levels in blood rise during reproductive life and peak at the menopause. Although LH levels remain consistent throughout reproductive life, studies have found low predictive value as a marker of ovarian reserve [21]. Currently, in the clinical practice serum LH level is a non-routine marker for OR evaluation.

In the other hand, estradiol is an ovarian steroid involved in the regulation of the menstrual reproductive cycle. Blood levels of estradiol should be measured in the early follicular phase of the menstrual cycle to determine the status of OR [21]. Additionally, basal estradiol has been used to evaluate menopause cases, amenorrhea, and follicular response in ART cases [21]. However, published literature is still controversial in regards to its use of OR marker due to low predictive value and the differences in results from various studies [11, 21, 33]. Therefore, it is recommended that estradiol levels should not be used as an individual marker of OR but also with other markers such as AMH [11, 21, 29].

2.3. Ultrasound markers of OR

Antral Follicle count (AFC) is a conducted transvaginal ultrasound study that assesses the number of antral follicles during the early follicular period. Studies have confirmed that this method of evaluating OR is noninvasive and easy to perform [30]. The number of small antral follicles between 2 and 8 mm of size is closely related to the ovarian function. This number declines with age and the recognition of antral follicles has a significant predictive value in cases of OR conditions, ovarian aging, and reproductive lifespan status. Additionally, AFC is related to ovarian response in cases of controlled ovarian stimulation and it is strongly correlated with AMH levels [31, 32].

Ovarian volume is an indirect ultrasound marker that indicates the condition of individual OR. Calculation of ovarian volume is operator dependent, and has to be studied at the early days of the menstrual cycle [33, 34]. Ovarian volume is the result of follicular size, ovarian stroma and the vascular tissue. Likewise, ovarian volume is affected by age, gynecological conditions, and menstrual cycle phase leading to some limitations for this marker [35]. For this reason, some authors have proposed the use of antral follicular count and ovarian volume as strategy for further evaluation of OR [11, 35].

2.4. Evaluation of ovarian reserve markers in women with no reproductive failure

Research in the field of reproductive medicine is required and is important providing to infertility patients with answers about their behavior of OR markers to establish the fertility condition in normo-ovulatory women and identify patients with poor ovarian reserve. Bentzen et al. [36] described different markers of OR such as antimullerian hormone (AMH), AFC, and the ovarian volume in Danish patients throughout the natural ovarian aging. This research has identified the inverse relationship between age and the ovarian reserve markers showing an average decreasing of 5.6% of AMH levels, 4.4% of AFC, and 1.1% of ovarian volume each year [36]. In 2011 and 2016, two studies evaluated levels of AMH, FSH, and AFC and they found levels of AMH have a high predictive value for menopause individually, however the predictive capacity of AMH levels decrease with age requiring further studies [14, 16]. Different studies showed AMH levels and AFC are critical markers that reflect decreasing of reproductive capacity through the years and the high predictive value for evaluation of menopause [17]. Additionally, La Marca et al. and Grisendi et al. identified the reference levels for AMH, FSH, estradiol and AFC over the fertile life in healthy Italian women [2, 30, 37, 38].

Similarly, Rosen et al. [15] evaluated blood levels of AMH, FSH, estradiol, inhibin B and AFC in a North American population with no reproductive deficiencies. This study confirms that AMH and the AFC are the accurate noninvasive markers for ovarian reserve evaluation due to a significant progressive decline to age while FSH, estradiol and inhibin B did not exhibit significant correlation between age and ovarian reserve [15].

Du et al. [39] established the age-specific reference serum levels for AMH in healthy Chinese women and they found a positive correlation of AMH levels with AFC, testosterone, LH, progesterone, and prolactin levels but a negative correlation with FSH serum levels [39]. Similarly, Tehrani et al. [40] identified the age reference normograms for AMH in a large Iranian population to facilitate the individual clinic interpretation for assessment of ovarian reserve [40].

Okunola et al. [41] evaluated serum levels of AMH and FSH in fertile and subfertile women. They reported significant differences between groups of population related to low ovarian reserve in subfertile women and suggesting that early ovarian aging is associated to decreased number of follicles [41].

Additionally, studies of AMH levels in different ethnicity groups (Caucasians, Hispanics, Afro-Americans, and Asiatic) have shown significant variations. Bleil et al. [42] has shown that Hispanics and Chinese groups exhibit consistent low levels of AMH across all ages compared to Caucasian group supporting possibly a high risk of premature ovarian insufficiency. Similarly, African American group show low levels of AMH at younger ages but less reduction of AMH with advanced age [42], however further studies are needed to validate these results.

Kelsey et al. [33] established a normative validated model of ovarian volume using a systematic review in healthy women. This study found that the ovarian volume has a maximum peak (7.7 mL) at 20 years of age and smaller volumes thereafter leading to generate normal values and ranges for ovarian volume that help to clinicians in the evaluation of fertility conditions [33].

2.5. Evaluation of ovarian reserve markers in women with reproductive failure

Studies have shown the importance of the OR in the reproductive field because of its correlation with infertile patients [43, 44]. Furthermore, researches have been focused in the clinical use of OR to improve the possibility of pregnancy, delay maternity and prevent infertility in young women. Dayal et al. [45] studied the predictive capacity of AMH, FSH, LH, inhibin B, and estradiol with the evaluation of ovarian function from Indian infertile women. They found that AMH has strong correlation to ovarian reserve supporting the association between the number of follicles and AMH blood levels [45]. Similarly, Barbakadze et al. [13] evaluated the correlations between the markers used for OR evaluation such as AMH, FSH, and AFC in 112 infertile women. This study has shown that the use of AMH is best reliable marker for OR evaluation compared to FSH blood levels and the combination of AMH and AFC may improve the assessment of fertility conditions in patients with infertile factors [13].

Likewise, several studies have established reference values of markers as a tool for fertility counseling. Moon et al. [46] developed normograms for AMH, FSH and AFC to predict the ovarian response (number of retrieved oocytes) to the use of exogenous gonadotropins in IVF

cycles. Interestingly, they concluded that these normograms might be applied to both high and poor responders [46]. Likewise, Almog et al. [47] showed the data distribution and percentiles were constructed for AMH values of infertile women from Europe and North America [47]. Similarly, Castro et al. [48] developed AFC normograms in Brazilian infertile women as a reference guide to the clinician for individual evaluation in Latin American patients [48].

Interest in research on prediction of ovarian response in assisted reproductive techniques has increased in recent years. Lee et al. [49] studied variations of AMH FSH, LH hormones in Korean women. This study described that basal LH/FSH ratio and AMH level has a valuable clinical meaning as an important predictor of ovarian response in IVF patients [49]. Furthermore, Cohen et al. [10], Keane et al. [50], Zebitay et al. [51], Zheng et al. [52], Goswami et al. [53] and Spressão et al. [54] have shown the important clinical application of AMH and AFC in the fertility counseling on infertile women correlated with pregnancy rates, live birth rates, number of retrieved eggs, fertilization rates and embryo development rates [10, 50–54].

Satwik et al. [55] reported the use of specific markers such as AMH has high predictive value for poor ovarian response compared to age and FSH [55]. Similarly, Mutlu et al. [32] compared AMH, FSH, age, and AFC for prognosis of success in TRA. They found AFC and AMH have significant predictive value of poor ovarian response in IVF patients, however age has significant predictive value of live births [32].

2.6. Proposed algorithm for reproductive determination

Recently, integration of different ovarian reserve markers with high significant statistical value has been proposed by a math equation to calculate reproductive units in Hispanic healthy young women with no signs of reproductive failure [56].

Reproductive units (RU) = (AMH [ng/ml] × total AFC × Ovarian volume [cc])/Chronological age

Calculation of the RU reflects the individual reproductive condition as a tool to prevent reproductive failure from early ages through advanced maternal age. Additionally, RU allows to clinicians provide individual counseling of birth control programs, postpone maternity by egg freeze programs, determine possible ovarian response to exogenous gonadotropins in ART, and prognosis of pregnancy success [56].

3. Discussion and conclusions

Ovarian reserve (OR) is characterized by the number of eggs cells available to be fertilized throughout the female reproductive lifespan. OR is related with the capacity of female fertility suggesting that the clinical potential of measuring different biomarkers is a perfect tool to predict infertility cases. This has led to research to determine the high predictive value of different biomarkers and to increase treatment factors and to prevent new cases of infertility.

Recent studies have investigated biomarkers such as AMH levels and AFC considered first line tests for counseling patients who desire future fertility due to high predictive value. The relevance of FSH, LH, estradiol, ovarian volume, and inhibin B as biomarkers of OR is considered of low potential for clinical evaluation because predictive superiority of other metrics have emerged with robust studies. Nevertheless, recent studies have constructed algorithms to integrate different biomarkers and approach individualized and reliable evaluations to establish with confidence the risk factors of infertility.

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Conflict of interest

The authors have no conflict of interest.

Author details

Harold Moreno-Ortiz[1], Iván Darío Acosta[2], Elkin Lucena-Quevedo[1], Luis Alejandro Arias-Sosa[2], Alix Eugenia Dallos-Báez[2], Maribel Forero-Castro[2]* and Clara Esteban-Pérez[2]

*Address all correspondence to: maribel.forero@uptc.edu.co

1 Department of Reproductive Genetics, Fertility and Sterility Colombian Center (CECOLFES), Bogotá, Colombia

2 Escuela de Ciencias Biológicas, Grupo de Investigación en Ciencias Biomédicas (GICBUPTC). Universidad Pedagógica y Tecnológica de Colombia, Tunja, Colombia

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