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Review Article

Follicle Selection in Mares: 90 Years from Observation to Theory

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ABSTRACT

The day of selection of the ovulatory follicle was first observed in any species by an equine practitioner during transrectal palpation in 1926. It was not until 1997 that ultrasonic imaging demonstrated the nature of selection. A wave-stimulating follicle stimulating hormone (FSH) surge reaches a peak on about day 13 postovulation when the growing follicles are about 13 mm. The FSH declines initially from secretion of inhibin by the multiple growing follicles. After about 2 days, estradiol is secreted by the future dominant follicle (DF) and synergistically contributes to a continuing FSH decline. On about day 16, the two largest follicles have grown to 23 and 20 mm, respectively, and begin to deviate in growth. The deviation process begins a day before diameter deviation as indicated in the future DF by (1) an increase in intrafollicular estradiol, inhibin-A, insulin-like growth factor 1 (IGF1), and vascular endothelial growth factor (VEGF) and (2) changes in echotexture and increased blood flow in the wall of the future DF. The IGF1 increases the sensitivity of the cells of the future DF to the reduced FSH, and VEGF presumably increases the vascular perfusion of the DF wall. The future DF is thus prepared to be the only follicle able to respond to the reduced levels of FSH. Ablation of various follicles at expected deviation indicates that several follicles have dominance capacity. And so, 90 years after the original observation of selection it can be proposed that the deviation process represents the theory of follicle selection in mares.

1. Introduction

One of the enduring and well-defined mysteries in equine reproductive biology is the selection of a future dominant follicle (DF) from a pool or wave of many follicles [1,2]. The ovulatory or primary follicular wave in mares is characterized by emergence of follicles at 6.0 mm on about day 10 (day 0 = ovulation) followed by a common-growth phase until day 16 [2,3]. The two largest follicles grow approximately in parallel and begin to deviate in diameter at the end of the common-growth phase. Deviation is characterized by continued growth rate of the largest follicle to become the DF or ovulatory follicle and a reduction in growth rate of the second-largest follicle to become the largest subordinate follicle (SF). Diameter deviation occurs when the future DF and SF are 22.5 mm and 20.0 mm, respectively, and is a manifestation of follicle selection.

The first, although elementary, observation of follicle selection in any species was a result of transrectal palpation by an equine practitioner in the 1920s [4]. It was noted that several 20- to 30-mm follicles were present before estrus, but during estrus (length, 7 days [5]), only one or two chosen follicles increased to a preovulatory diameter of 50 mm. Two years later, another clinical report confirmed the observation [6]. However, it was not until the 1970s that transrectal palpation studies began to better characterize the dynamics of follicle selection in mares [7,8].

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In the 1980s, transrectal ultrasonic imaging was introduced for examining the reproductive tract of mares [9]. This noninvasive approach allowed characterization of equine follicle dynamics throughout the estrous cycle [10] eventually including the monitoring of individually identified antral follicles from examination to examination [11]. Hundreds of research reports have since been published on some aspect of follicle selection in mares and other monovular species (cattle, women). An influx of equine reports was published in 2002–2004 involving (1) the development of transvaginal ultrasound techniques for sampling or injecting a test substance into a specific follicle followed by later sampling or determining whether the follicle became a DF or SF, (2) transrectal color-Doppler ultrasound for assessing ovarian and follicular blood flow, and (3) the use of experimental or induced deviation to compare timelines among systemic and intrafollicular factors.

The systemic and intraovarian components of equine follicle selection have been the subject of an extensive review [12]. The present report recapitulates the salient aspects of the review for equine theriogenologists. All of the cited studies were done in mares unless otherwise indicated. Contemplation of follicle selection by theriogenologists may instill further awe and appreciation for the mechanisms of equine ovarian biology. On the practical side, the selection of the DF or selection of follicles that will become subordinates is a consideration in the development of protocols for transvaginal collection of oocytes or for superovulation in embryo transfer programs.

2. The Mare as a Research Model

The mare is a comparative model for research into the mechanisms of follicle selection owing to the large size and accessibility of follicles for monitoring diameters and for study of echotextural and blood flow indicators in the follicle walls by transrectal ultrasonic imaging. Transvaginal ultrasound guiding for targeting individual follicles during transrectal manipulation of an ovary is another useful approach (review [13]). Transvaginal injection of an intrafollicular factor into a specific follicle with subsequent sampling of intrafollicular fluid has been used to determine the effect of a factor on other factors or on follicle diameter [14,15]. In one study, follicular fluid was sampled (e.g., 90 μL), and the follicle was treated at the expected beginning of deviation and then sampled twice during the next 24 hours without altering follicle destiny [14].

The ultrasound-guided transvaginal approach is also used for ablation of follicles by aspiration of follicle contents [3] to eliminate a specific follicle for studying the follicle's endocrinologic aspects [16]. A useful procedure is the ablation of all follicles at a specified diameter (e.g., greater than 5 mm) on day 10 and thereby initiating a new wave uncomplicated by the intermingling of follicles from a previous wave [3,17–19]. The follicles of the new wave can be tracked beginning at a smaller diameter (e.g., 6 mm) than when a new wave is not induced (e.g., 15 mm). Ablation of the largest follicle at the beginning of expected deviation when it reaches 22.5 mm is being used to study the timing of events involved in the conversion of SF to a new DF (experimental or induced deviation) [20]. The transvaginal route can be also used for biopsy of the corpus luteum [21], a section of an antral follicle, or a section of ovarian tissue that may include, for example, preantral follicles [22].

The mare could potentially become a premier nonprimate model for comparative studies of follicle selection in women owing to the suitability of mares for research procedures that are impractical in women. Similarities between the two species in the characteristics of follicle selection include (1) 25% incidence of a major secondary anovulatory wave during early diestrus preceding the primary wave; (2) emergence of the future DF of the primary wave at a mean of 1 day before emergence of the SF; (3) percentage growth of follicles during the common-growth phase that precedes deviation; (4) maintenance of a mare:woman ratio in DF diameter (about two times larger in mares) during emergence, deviation, and preovulation; and (5) a wave-associated follicle stimulating hormone (FSH) surge that reaches a peak 3 days before deviation [17,23].

3. The Common-Growth Phase and Deviation

The first specific study of the common-growth phase and follicle deviation during the primary wave in mares was done in 1997 [3]. The operator was overwhelmed by the large number of follicles greater than 5 mm including intermingling of follicles from a previous major or minor (no DF) wave. Therefore, a two-follicle model was developed, wherein all follicles that were 5 mm or greater were ablated on day 10. When the largest follicle of the post-ablation or primary wave reached 15 mm, all follicles except the two largest were ablated. Results indicated that (1) the future DF emerged at 6 mm an average of 1 day earlier than the future SF, (2) the two follicles grew approximately in parallel during the common-growth phase when normalized to deviation and examined retrospectively, (3) deviation occurred 6 days after emergence of a 6 mm future DF, and (4) mean diameters of the future DF and SF on the day of deviation were 23 and 20 mm, respectively, equivalent to a 1 day difference in diameter (Fig. 1).

The finding of mean parallel growth rates of the two largest follicles when all follicles of the primary wave were retained and normalized to deviation was substantiated in subsequent studies of mares of various types and breeds [17,24,25]. The specific diameter interrelationships among follicles during the common-growth phase and the capacity of individual follicles for dominance have been described [26]. The follicles grow in parallel on average until the end of the common-growth phase. However, despite the averages, inspection of individual waves indicated that the two largest follicles switched in diameter ranking during the common-growth phase in about one-thirds of the waves. First emergence did not establish that a follicle was destined to become the DF. When one, two, or three of the largest follicles were ablated at the expected beginning of deviation (DF, 22.5 mm), the largest retained follicle became the DF in 76% of the primary waves. These results supported the hypothesis that the capacity for dominance at the expected beginning of deviation is shared by many follicles of the wave, and the potential is greatest for the largest (highest ranking) follicle and decreases progressively according to decreasing