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ScienceDirect
Theriogenology 69 (2008) 72–80
Theriogenology
www.theriojournal.com

Progress in understanding ovarian follicular dynamics in cattle

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Abstract

The study of follicular dynamics began in the mid-20th century, but progress has been particularly rapid in the last two decades through the use of tools that have enabled serial, non-invasive examination. A brief overview of early oogenesis and folliculogenesis is provided as a backdrop to the evolution of our understanding of follicular dynamics during the bovine estrous cycle. Studies to date support the concept that the pair of ovaries acts as a single unit and influences follicular development primarily via systemic endocrine routes involving ovarian and uterine products, the gonadotropins, and their receptors. Dominant and subordinate follicles pass through growing, static and regressing phases that have distinct morphologic and biochemical characteristics; these changes are the basis of efforts focused on diagnosing and manipulating follicular status. An update of research progress highlights recent findings on the repeatability (predictability) within individuals of follicle recruitment and wave pattern (two- versus three-wave cycles), the relationship between oocyte competence and follicular status, and the dynamics of small follicles. Recent studies documented that wave emergence and follicular dominance are apparent earlier than previously reported, and on the basis of periodic endogenous FSH surges and the presence of FSH receptors, the hypothesis that follicles become progressively entrained to waves from the earliest stages of development is introduced. Lastly, recent studies comparing old cows and their young daughters provide a new understanding of the effects of aging on gonadotropins and ovarian steroids, follicular dynamics, ovarian response to synchronization, superstimulation, and oocyte competence.

Keywords: Follicle dynamics; Estrous cycle; Bovine; Oocyte competence; Reproductive aging

1. Introduction—a history of ovarian research

Controversy has been a hallmark of the study of ovarian form and function from the earliest descriptions of the female gonad [1]. In the 5th century B.C., Hippocrates did not ascribe any generative role of the ovary, but rather suggested that generation of a new life was the result of the action of two kinds of semen—one from the male (ejaculate) and one from the female (menstrual blood). A century later, Aristotle characterized the ovary as an imperfect vestige of the male testis with no apparent function. It was not until the mid-1600s that the ovary was recognized for what it was—the producer of eggs. The Dutch physician, Regnier de Graaf, is often cited as the first to recognize the rightful role of the ovary in his ‘‘New treatise concerning the generative organs of women’’ published in 1672. The 31-year-old de Graaf, however, was embroiled in bitter arguments with his anatomy professor, Johannes van Horne, and classmate, Jan Swammerdam, who claimed that they had revealed the form (and by extension, the function) of the ovary in a short communication in 1668.

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doi:10.1016/j.theriogenology.2007.09.026

Their early scientific ''abstract'', however, was preceded by one of de Graaf's a few weeks earlier, in March 1668. Ironically, the conclusion of a committee tasked to settle the dispute was that neither de Graaf nor Van Horne was the first to have seen eggs in viviparous organisms, but rather another classmate, Niels Steno, who reported in his 1667 treatise that ''the testicles of women are analogous to the ovary.'' All of these early modern scientists, however, held the mistaken belief that the follicle itself was the egg—like a small bird's egg without a shell. It was not until 1827 when an Estonian physician, Karl Ernst von Baer, provided the first description of a mammalian egg from his microscopic study of ovarian vesicles (follicles) in the ovary of a dog. The first studies of the dynamics of follicle development, however, were not for another 100 years.

The purpose of this report is to provide a brief overview and historical background of our understanding of follicle dynamics in cattle, and to highlight some recent advances, primarily from the author's laboratory. It is not intended to be a comprehensive review. For brevity, reference is made to reviews of specific topics rather than original studies. Unless otherwise stated, the information presented is from results of studies on *Bos taurus*.

2. Early oogenesis and folliculogenesis

Oocytes originate as primordial germ cells from the endoderm of the embryonic yolk sac, and migrate by amoeboid movement via the dorsal mesentery of the hindgut to the gonadal ridge [2] by Day 35 of gestation in cattle [3]. Primordial germ cells undergo a limited number of mitotic divisions during migration and upon arrival at the gonadal ridge [2,4]. Primordial germ cells are internalized into the gonadal ridge through its surface epithelium—initially thought to be the source of primordial germ cells and mistakenly named the ''germinal'' epithelium. During the process of internalization, the primordial germ cells cease mitotic division, become enclosed in germ cell cords (ovigerous cords) composed of epithelial cells which are delineated from the surrounding mesenchymal cells by a basal lamina, and they become referred to as oogonia [4]. Meiosis of oogonia (transition to primary oocytes) begins by Days 75–80 of gestation in cattle and the first meiotic division does not proceed beyond the pachytene stage of prophase-I [3], at which time the chromosomes are decondensed and contained within the nuclear membrane—the germinal vesicle [2].

A single layer of flattened epithelial cells from the germ cell cords condense around the vast majority of surviving oocytes and enclose them to form primordial follicles [3,4]. Oocytes that fail to be surrounded by epithelial cells degenerate [2]. Initiation of follicular growth (activation) begins with the transformation of the flattened pre-granulosa cells of the primordial follicle into a single layer of cuboidal granulosa (follicular) cells—a primary follicle [5]. Proliferation of granulosa cells results in an increase from two to six layers around the oocyte (secondary follicle), to >6 layers of granulosa cells and a fluid-filled antrum (tertiary or antral follicle) [5,6].

3. Follicular dynamics during the bovine estrous cycle

3.1. Follicular waves

The estrous cycle and its phases in cattle were first described by Hammond [7], followed by McNutt [8], and Cole [9]. In 1946, Bullough [10] used a mouse model and described the relationship between ovarian follicular development and hormones. Studies of the dynamics of follicular development were first reported in rats by Mandle and Zukerman [11] and in monkeys in 1951 by Green and Zukerman [12]. Both studies involved a histological approach and both concluded that there was no cyclic variation in follicle numbers. Rajakoski [13] has been credited with the initial proposition of the two-wave theory of follicular growth during the bovine estrous cycle. For three decades after Rajakoski's report, many experiments were done on various aspects of follicular dynamics during the bovine estrous cycle, resulting in contradicting accounts of the nature of follicle development, ranging from the absence of waves to as many as three or four distinct waves per estrous cycle. In later reviews, the two-wave theory of Rajakoski was refuted on the basis that ''conclusions were based on qualitative assessment of data without current knowledge of the profile of gonadotropins and of ovarian steroids...'' (reviewed in [14]). Evidence was presented to support the concept that follicles are recruited continuously throughout the cycle and the follicle destined to ovulate is selected by coincidence of its stage of maturity (readiness) and the occurrence of the preovulatory gonadotropin surge. However, with the introduction of ultrasonography in the late 1980s, the barrier to our understanding of follicular dynamics was suddenly broken (reviewed in [15]).

Studies using ultrasonic imaging to monitor follicle populations in different size categories or to monitor