Accounting for the Follicle Population in the Polycystic Ovary

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Summary

Recruitment of primordial follicles through selection of the dominant follicle and its eventual ovulation requires complex interactions between reproductive and metabolic functions, as well as intraovarian paracrine signals to coordinate granulosa cell proliferation, theca cell differentiation, and oocyte maturation. Early follicle development to an initial antral stage is relatively independent of gonadotropins and relies mostly on mesenchymal–epithelial cell interactions, intraovarian paracrine signals, and oocyte-secreted factors. Beyond this stage, cyclic follicle development depends upon circulating gonadotropins in combination with these locally derived regulators. Recruitment, growth, and subsequent selection of the dominant follicle are perturbed in women with polycystic ovaries (PCO). Ovarian hyperandrogenism, hyperinsulinemia from insulin resistance, and altered intrafollicular paracrine signaling contribute to the accumulation of small antral follicles within the periphery of the ovary, giving it a polycystic morphology. Prenatal androgen excess also entrains multiple organ systems in utero and demonstrates that the hormonal environment of intrauterine life may program the morphology of the ovary in adulthood.

Key Words: Polycystic ovaries; androgens; insulin; kit ligand; inhibin; anti-Mullerian hormone; growth differentiation factor-9.

1. INTRODUCTION

Initiation of primordial follicle recruitment, selection of the dominant follicle, and ovulation of a single mature oocyte require a constellation of reproductive, metabolic, and intraovarian events that coordinate granulosa cell proliferation and
differentiation, theca cell function, and oocyte maturation. Relatively independent of gonadotropins, preantral and early antral follicle development depends mostly on mesenchymal–epithelial cell interactions, intraovarian paracrine signals, and oocyte-secreted factors. Beyond these stages, cyclic follicle development depends upon circulating gonadotropins as well as intraovarian paracrine signals so that a dominant follicle is selected for eventual ovulation, while subordinate follicles undergo atresia.

Any of these mechanisms can be perturbed in women with polycystic ovaries (PCO), leading to the accumulation of small antral follicles within the periphery of the ovary, giving it a polycystic morphology. Ovarian hyperandrogenism, hyperinsulinemia from insulin resistance, and altered intraovarian paracrine signaling can disrupt normal folliculogenesis by enhancing follicle recruitment, impairing follicle growth, or both. In animal models, prenatal androgen excess also entrains multiple organ systems in utero, demonstrating that the hormonal environment of intrauterine life can theoretically program the morphology of the ovary in adulthood. This chapter addresses crucial metabolic, endocrine, and intraovarian mechanisms governing normal follicular development and discusses how abnormalities in the regulation of these processes initiate a cascade of events predisposing to PCO by increased follicle recruitment and/or by impairing follicle growth.

2. NORMAL FOLLICULAR GROWTH

As an essential element of female reproduction, human follicle development is an ordered process, in which primordial follicles are recruited into a cohort of growing follicles, from which one antral follicle is selected to ovulate, while the others undergo atresia. At the beginning of this process, the primordial follicle consists of an oocyte arrested at the diplotene stage of prophase one and surrounded by squamous granulosa cells. When the primordial follicle initiates growth, its oocyte begins to synthesize ribonucleic acid (RNA), and its squamous granulosa cells enlarge into a single layer of mixed squamous and cuboidal granulosa cells (i.e., intermediate follicle) or of cuboidal granulosa cells entirely (i.e., primary follicle) (1,2). With continued granulosa cell proliferation into two or more layers, the secondary follicle is formed. Theca cells are recruited from surrounding stromal stem cells and are organized into distinct theca cell layers around the follicle, establishing mesenchymal–epithelial cell interactions that promote development of the follicle and its oocyte.

Initiation of primordial follicle growth is only minimally follicle-stimulating hormone (FSH) dependent (2). Instead, growth of primordial follicles is influenced primarily by paracrine/endocrine factors as FSH receptor messenger ribonucleic acid (mRNA) expression does not occur in human primordial follicles and is poorly coupled with the adenylate cyclase second messenger system in intermediate and primary follicles (3,4). Granulosa cell-derived paracrine factors can activate resting primordial follicles [e.g., kit ligand (KL), transforming growth factor alpha (TGF-α), and epidermal growth factor (EGF)] or can inhibit them and may originate locally or from neighboring growing follicles responsive to FSH (2,5). In mammals, expression of granulosa cell-derived KL and its receptor c-kit on oocytes and theca cells of growing follicles is particularly important for initiating early folliculogenesis, inducing mesenchymal–epithelial cell signaling, and developing the oocyte (1,2). In rodents, for example, KL initiates primordial follicle development and oocyte growth (6,7). It