SUMMARY

Excess androgen biosynthesis is a diagnostic feature of polycystic ovary syndrome. The excess circulating androstenedione and testosterone is produced primarily by the ovary. The ovarian theca cells, the site of de novo androgen biosynthesis, are increased in number in polycystic ovaries, and they have increased steroidogenic capacity. The increase in steroidogenic capacity is caused by overexpression of steroidogenic enzymes because of increased transcription and mRNA stability. Primary factors in the hyperstimulation of thecal androgen production appear to be increased luteinizing hormone (LH) concentrations in some women and elevated insulin concentrations secondary to insulin resistance. Additional contributions may be made by other intraovarian factors that can augment the stimulatory effects of LH on thecal androgen biosynthesis.

The granulosa cells in arrested follicles in polycystic ovaries fail to increase the expression of aromatase, causing markedly decreased estrogen secretion. They also express higher concentrations of 5α-reductase enzymes, leading to the production of 5α-androstane-3,17-dione, a competitive inhibitor of aromatase activity. The granulosa cells prematurely express the cholesterol side-chain cleavage enzyme and LH receptors, hence they are overresponsive to LH and produce increased amounts of progesterone compared to granulosa cells from follicles at a similar developmental stage in regularly cycling control women. Thus, polycystic ovaries produce increased concentrations of androgens and progesterone, decreased concentrations of estrogens, and abnormally high concentrations of 5α-reduced androgens, compared to normal ovaries.

Key Words: Ovary; theca cell; granulosa cell; steroidogenesis; androgens; estrogens; progesterone; polycystic ovary syndrome.

1. INTRODUCTION

The polycystic ovary syndrome (PCOS) is a heterogeneous disorder in which abnormalities of steroidogenesis are inherent to the etiology. Excess circulating androgen concentrations are a cardinal feature of PCOS that is central to the diagnosis. Evidence supporting a central role for hyperandrogenism as a cause of PCOS includes the development of polycystic ovaries in female-to-male transsexuals treated with high concentrations of testosterone and in girls with excess adrenal androgen secretion because of congenital adrenal hyperplasia, and the observation that PCOS can be reversed in some women by reducing circulating androgen concentrations using insulin-sensitizing therapy. Therefore, understanding ovarian steroidogenic abnormalities in PCOS is central to understanding the etiology of the disorder.

2. BACKGROUND

Ovarian steroidogenesis in PCOS affects androgen and estrogen—and possibly progesterone—production.
2.1. Abnormal Androgen Production

2.1.1. Contribution of the Ovary to Abnormal Androgen Production in PCOS

The serum concentrations of androstenedione and testosterone are elevated in women with PCOS. In up to 50% of hyperandrogenic women, dehydroepiandrosterone sulfate is also increased (2). Although it is clear that the ovary and the adrenal gland are the principal sources of circulating androgens in women, it is important to understand the relative contributions of each gland. Direct measurement of androgens in selectively catheterized ovarian and adrenal veins and the use of ovarian and adrenal stimulation and suppression have not unambiguously defined the relative contributions of each gland to elevated circulating androgens. However, selective suppression of ovarian androgen production with long-acting gonadotropin-releasing hormone agonists that do not affect adrenal androgen production indicate that the ovary is the principal source of the excessive androstenedione and testosterone in hyperandrogenic women (3). In hyperandrogenic women in whom congenital adrenal hyperplasia involving 3β-hydroxysteroid dehydrogenase (3β-HSD), 21-hydroxylase, or 11-hydroxylase deficiency have been ruled out, up to 50% have both ovarian and adrenal hyperandrogenism, and the remainder have exclusively ovarian hyperandrogenism. These data lead to the conclusions that the ovary is the principal source of excessive androstenedione and testosterone in hyperandrogenic women and that the ovary plays a major, although not exclusive, role in female hyperandrogenism.

2.1.2. Excessive Androgen Production by Theca Cells From Polycystic Ovaries

In the ovarian follicle steroidogenesis is accomplished through the cooperation of the theca and granulosa cells (Fig. 1). The theca cells are the exclusive source of androstenedione in women. The 17β-hydroxysteroid dehydrogenase enzyme is predominantly expressed in the granulosa cells; hence much of the testosterone is produced in the granulosa cells. Regardless of the site of metabolism of androstenedione to testosterone, the \textit{de novo} production of androgens in the ovaries is exclusive to the theca cells.

Clinically, women with PCOS respond to human chorionic gonadotropin (hCG) challenge with increased testosterone production compared with control women. The increased responsiveness of the polycystic ovary to gonadotropin stimulation implies an increased steroidogenic capacity of the theca interna. In vitro studies confirm that theca cells from polycystic ovaries produce more androgen both in the unstimulated and in the gonadotropin-stimulated state (4). Thus, it is clear that the polycystic ovary has enhanced capacity to secrete androgens. Two principal factors influence the total amount of androgen secreted by the ovary: the total number of theca cells in the ovary and the steroidogenic capacity of each of the theca cells.

2.1.3. Excessive Theca-Cell Proliferation in Polycystic Ovaries

In the polycystic, unlike the normal, ovary there is an accumulation of small antral follicles 3–7 mm in diameter forming the classic “string-of-pearls” morphology. Thus, the ovaries in women with PCOS contain more antral follicles than normal. Many of the follicles in polycystic ovaries demonstrate a hypertrophied theca interna containing many more layers of differentiated steroidogenic cells than the three to five layers in the normal theca interna (Fig. 2). Because of these factors, the polycystic ovary contains more steroidogenic cells in the theca interna than normal, which is consistent with the excessive androgen secretion in PCOS. In contrast, the granulosa cell layers are underdeveloped, and the polycystic ovary contains fewer potential estrogen-producing cells than would be expected for the stage of follicle development.

Little is known about the factors regulating human theca-cell proliferation. Most of the data originate from studies in animals. Chronic exposure of theca cells to luteinizing hormone (LH) (or hCG) leads to a marked increase in the number of cells in the theca interna. There is also evidence that intraovarian growth factors can support theca-cell proliferation. Among these are activin, epidermal growth factor or transforming growth factor (TGF)-α, insulin and insulin-like growth factor (IGF)-1,