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State of The Hypothalamic-Pituitary-Ovarian Axis in Patients with Polycystic Ovary Syndrome

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ABSTRACT

Objective: To evaluate the functional state of the hypothalamic-pituitary-ovarian (HPO) axis in women with polycystic ovary syndrome (PCOS).

Materials and Methods: An outpatient examination was conducted at the Department of Neuroendocrinology of the Republican Specialized Scientific and Practical Medical Center of Endocrinology (Tashkent, Uzbekistan) involving 120 women of reproductive age diagnosed with PCOS (mean age: 25.5 ± 4.3 years; disease duration: 7 months to 9 years). Twenty healthy age-matched women comprised the control group. All patients underwent comprehensive clinical, biochemical (fasting blood glucose, oral glucose tolerance test), and hormonal assessments on cycle day 14, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, estradiol, progesterone, free testosterone, dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone (17-OHP), anti-Müllerian hormone (AMH), and insulin. Additionally, pelvic ultrasonography (transabdominal and transvaginal) with dynamic folliculometry on cycle day 14, magnetic resonance imaging (MRI) of the sella turcica, and clinical questionnaires were performed.

Results: Patients were stratified into two groups: Group 1 included 94 women with primary infertility, and Group 2 included 26 women with secondary infertility. In Group 1, a statistically significant decrease in both pituitary (LH, FSH) and ovarian (estradiol, progesterone) hormones on cycle day 14 was observed against a background of hyperandrogenemia (elevated free testosterone and DHEA) and mild hyperprolactinemia compared to controls. In Group 2, a significant reduction in gonadotropins (LH, FSH) was likewise accompanied by hyperandrogenemia, mild hyperprolactinemia, and markedly elevated AMH levels, whereas basal ovarian steroid levels (estradiol and progesterone) remained within normal limits. Pituitary MRI revealed pituitary hyperplasia (adenomatosis) in 49 of 120 patients (40.8%), empty sella syndrome in 26 patients (21.6%), and pituitary microadenomas in 16 patients (13.3%).

Conclusion: Dysfunction of the hypothalamic-pituitary-ovarian axis in PCOS is characterized by blunted mid-cycle gonadotropin secretion (LH, FSH) alongside hyperandrogenemia, hyperprolactinemia, and structural pituitary abnormalities. The severity of hormonal imbalance depends on the phenotype of reproductive dysfunction: primary infertility is associated with combined pituitary-ovarian deficiency, whereas secondary infertility is characterized by isolated gonadotropin deficiency accompanied by a high ovarian reserve (elevated AMH).

Abbreviations: PCOS: Polycystic Ovary Syndrome; HPO: Hypothalamic-Pituitary-Ovarian; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; AMH: Anti-Müllerian Hormone; 17-OHP: 17-Hydroxyprogesterone; DHEA; Dehydroepiandrosterone; MRI: Magnetic Resonance Imaging; IGF-1: Insulin-Like Growth Factor-1; OHSS: Ovarian Hyperstimulation Syndrome; NK3R: Neurokinin-3 Receptor

Background

Polycystic ovary syndrome (PCOS) remains the most prevalent endocrinopathy among women of reproductive age, affecting 10% to 13% of the global female population and representing the leading cause of anovulatory infertility and hyperandrogenism [1,2]. According to the 2023 International Evidence-Based Guideline (ESHRE/ASRM) and recent global consensus statements, PCOS is recognized not merely as a reproductive disorder, but as a complex, multifactorial endocrine-metabolic condition carrying substantial risks for insulin resistance, type 2 diabetes mellitus, and cardiovascular morbidity [1-3]. Primary neuroendocrine dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis is established as a central mechanism in the pathogenesis of PCOS [4,5]. Contemporary evidence demonstrates that hyperactivity of hypothalamic KNDy neurons (co-expressing kisspeptin, neurokinin B, and dynorphin) coupled with impaired sex-steroid negative feedback drives accelerated pulsatile secretion of gonadotropin-releasing hormone (GnRH) [4,6]. Sustained high-frequency GnRH pulsatility preferentially stimulates luteinizing hormone (LH) hypersecretion over follicle-stimulating hormone (FSH), promoting excessive androgen synthesis in ovarian theca cells and arresting follicular maturation [2,5]. Furthermore, elevated anti-Müllerian hormone (AMH) levels in PCOS exert direct central and peripheral effects by stimulating GnRH neuronal excitability and inhibiting granulosa cell aromatase activity, thereby exacerbating hyperandrogenemia and anovulation [7,8].

Insulin resistance and compensatory hyperinsulinemia, present in 75–95% of women with PCOS, serve as critical metabolic modifiers of reproductive dysfunction [9,10]. Insulin acts synergistically with LH to amplify theca-cell steroidogenesis via insulin and insulin-like growth factor-1 (IGF-1) receptors while suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing bioavailable free testosterone fractions [9-12]. Concurrently, mild hyperprolactinemia and structural pituitary findings—such as pituitary hyperplasia, microadenomas, and empty sella syndrome—are frequently encountered in clinical practice, necessitating careful neuroimaging and differential diagnosis to exclude concomitant neuroendocrine pathology [13,14]. Despite the adoption of updated ovulation induction protocols in which letrozole is recommended as first-line pharmacological therapy [1,10], fertility management in PCOS remains challenged by treatment resistance and the risk of ovarian hyperstimulation syndrome (OHSS). Emerging targeted neuroendocrine therapies, including kisspeptin-54 agonists for physiological ovulation triggering and neurokinin-3 receptor (NK3R) antagonists to normalize LH pulsatility, offer promising avenues for restoring reproductive function [6,14]. Thus, a comprehensive evaluation of the HPO axis in relation to metabolic profiles and pituitary neuroimaging across distinct infertility phenotypes remains a highly relevant clinical objective.

Objective of the Study

To investigate the functional state of the hypothalamic-pituitary-ovarian axis in women with PCOS.

Materials and Methods

Between September 2015 and July 2016, 120 women of fertile age with PCOS were examined on an outpatient basis at the Department of Neuroendocrinology, Republican Specialized Scientific and Practical Medical Center of Endocrinology, Ministry of Health of the Republic of Uzbekistan. The mean age of patients was 25.5 ± 4.3 years, with disease duration ranging from 7 months to 9 years. Twenty healthy women of comparable age served as the control group. All participants underwent a standardized diagnostic workup comprising routine clinical tests (complete blood count and urinalysis), biochemical assays (fasting plasma glucose and oral glucose tolerance test), and basal serum hormone measurements on day 14 of the menstrual cycle (LH, FSH, prolactin, estradiol, progesterone, free testosterone, DHEA, 17-OHP, AMH, and insulin). Transabdominal and transvaginal pelvic ultrasonography with dynamic folliculometry was performed on cycle day 14. Pituitary morphology was evaluated using magnetic resonance imaging (MRI) of the sella turcica (DiarmedikCenter Clinic, Tashkent), complemented by structured patient questionnaires. Statistical analysis was performed using Microsoft Excel and STATISTICA 6.0. The significance of differences between quantitative variables in larger samples ($n > 12$) was assessed using the Mann-Whitney U / Wilcoxon rank-sum test for independent samples, while Fisher's randomization test and Fisher-Irwin exact test were applied for small samples ($n < 12$) and categorical variables, respectively. Data are presented as mean ± standard error of the mean (M ± m). Differences were considered statistically significant at $p < 0.05$.

Results

Based on reproductive history, patients were divided into two groups: Group 1 comprised 94 women (78.3%) with primary infertility, and Group 2 comprised 26 women (21.7%) with secondary infertility. (Table 1) summarizes the prevalence of clinical and neuroendocrine manifestations across both cohorts (with mathematically verified percentages). (Figure 1) To further characterize endocrine function,

basal serum hormone concentrations were analyzed on cycle day 14 in both study groups relative to healthy controls (Table 2 & 3). As shown in (Table 2). Group 1 patients exhibited a statistically significant reduction in both pituitary (LH, FSH) and ovarian (estradiol, progesterone) hormones on cycle day 14, accompanied by pronounced hyperandrogenemia (elevated free testosterone and DHEA) and higher prolactin levels compared to controls. In Group 2, pituitary gonadotropins (LH and FSH) were also significantly lower than in controls against a background of hyperandrogenemia and elevated prolactin; however, ovarian steroidogenic output remained preserved, and serum AMH levels were markedly elevated ($p < 0.05$). (Figure 2) Pituitary neuroimaging findings obtained via MRI of the sella turcica are presented in (Table 4). Overall, pituitary neuroimaging identified pituitary hyperplasia (adenomatosis) in 49 of 120 patients (40.8%), likely reflecting chronic compensatory pituitary stimulation secondary to ovarian dysfunction. (Figure 3) Empty sella syndrome was the second most frequent finding (26 cases, 21.6%), followed by pituitary microadenomas (16 cases, 13.3%).

Table 1: Prevalence of Clinical and Neuroendocrine Disorders by Study Group.

Clinical / Neuroendocrine Manifestation	Group 1 (n = 94)	Group 2 (n = 26)
Secondary amenorrhea	34 (36.1%)	6 (23.1%)
Primary amenorrhea	9 (9.6%)	—
Hyperpolymenorrhea	25 (26.6%)	11 (42.3%)
Opsomenorrhea	16 (17.0%)	7 (26.9%)
Oligomenorrhea	18 (19.1%)	2 (7.7%)
Obesity (Grades 1–3)	76 (80.8%)	12 (46.2%)
Pseudo-Cushing syndrome	5 (5.3%)	—
Hirsutism	90 (95.7%)	22 (84.6%)*
Acanthosis nigricans	56 (59.6%)*	17 (65.4%)
Acne	74 (78.7%)	15 (57.7%)*
Hyperandrogenemia	92 (97.9%)	22 (84.6%)*
Anovulation	94 (100.0%)	15 (57.7%)
Hypoovulatory syndrome	—	9 (34.6%)

*Note: Percentages have been mathematically verified against group sample sizes (n=94 and n=26). Overlapping menstrual cycle irregularities were observed in several patients.

Table 2: Basal Serum Hormone Levels on Cycle Day 14 in Group 1 (Primary Infertility, n = 94).

Hormone	Group 1 (M ± m)	p-value	Control (n = 20)	Reference Range (Ovulation / Age)
LH (IU/L)	4.8 ± 0.4	<0.05*	29.3 ± 2.1	15.0–90.0 IU/L (ovulatory peak)
FSH (mIU/mL)	2.1 ± 0.3	<0.05*	15.2 ± 4.3	5.0–16.0 mIU/mL (ovulatory peak)
Prolactin (mIU/L)	223.5 ± [verify]	<0.05*	154.3 ± 9.5	120–900 mIU/L
Free testosterone (ng/mL)	3.3 ± 0.3	<0.05*	0.2 ± 0.05	0.2–1.0 ng/mL
Progesterone (nmol/L)	22.5 ± 3.5	<0.05*	44.3 ± 9.3	11.0–80.0 nmol/L
Estradiol (nmol/L)	0.28 ± 0.04	<0.01*	1.7 ± 0.01	0.34–1.80 nmol/L
DHEA (mcg/mL)	6.7 ± 0.2	<0.05*	3.1 ± 0.4	0.29–7.81 mcg/mL (ages 18–30)
17-OHP (mg/day)	2.6 ± 0.1	>0.05	2.9 ± 0.6	1.54–6.10 mg/day
AMH (ng/mL)	5.3 ± 0.3	>0.05	3.9 ± 0.6	1.0–10.6 ng/mL

*Note: Statistically significant difference compared to the control group ($p < 0.05$). DHEA — dehydroepiandrosterone; 17-OHP - 17-hydroxyprogesterone; AMH - anti-Müllerian hormone.

Table 3: Basal Serum Hormone Levels on Cycle Day 14 in Group 2 (Secondary Infertility, n = 26)

Hormone	Group 2 (M ± m)	p-value	Control (n = 20)	Reference Range (Ovulation / Age)
LH (IU/L)	6.7 ± 0.3	<0.05*	29.3 ± 2.1	15.0–90.0 IU/L (ovulatory peak)
FSH (mIU/mL)	4.2 ± 0.2	<0.05*	15.2 ± 4.3	5.0–16.0 mIU/mL (ovulatory peak)
Prolactin (mIU/L)	227.8 ± 17.6	<0.05*	154.3 ± 9.5	120–900 mIU/L
Free testosterone (ng/mL)	2.5 ± 0.2	<0.05*	0.2 ± 0.05	0.2–1.0 ng/mL
Progesterone (nmol/L)	42.5 ± 3.5	>0.05	44.3 ± 9.3	11.0–80.0 nmol/L
Estradiol (nmol/L)	3.6 ± 0.4	<0.01*	1.7 ± 0.01	0.34–1.80 nmol/L
DHEA (mcg/mL)	6.8 ± 0.2	<0.05*	3.1 ± 0.4	0.29–7.81 mcg/mL (ages 18–30)
17-OHP (mg/day)	4.6 ± [10.1 — verify]	<0.05*	2.9 ± 0.6	1.54–6.10 mg/day
AMH (ng/mL)	16.3 ± 2.6	<0.05*	3.9 ± 0.6	1.0–10.6 ng/mL

*Note: Statistically significant difference compared to the control group ($p < 0.05$).

Table 4: Pituitary MRI Findings in Patients with PCOS.

Pituitary MRI Finding	Group 1 (n = 94)	Group 2 (n = 26)
Pituitary hyperplasia (adenomatosis)	35 (37.2%)	14 (53.8%)
Pituitary microadenoma	14 (15.0%)	2 (7.7%)*
Empty sella syndrome	23 (24.5%)*	3 (11.5%)
Normal variant	22 (23.4%)	7 (26.9%)

*Note: Percentages have been mathematically verified against group sample sizes (n=94 and n=26).

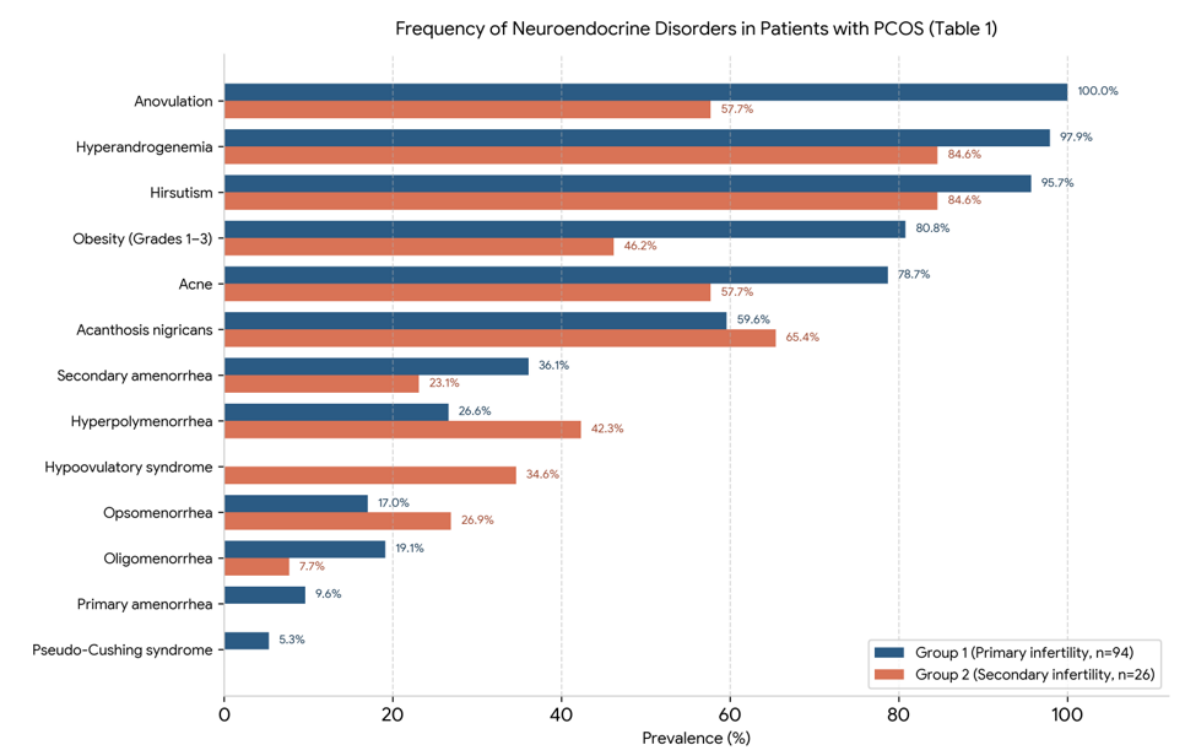

Figure 1: Frequency of clinical and neuroendocrine disorders in patients with PCOS (Table 1).

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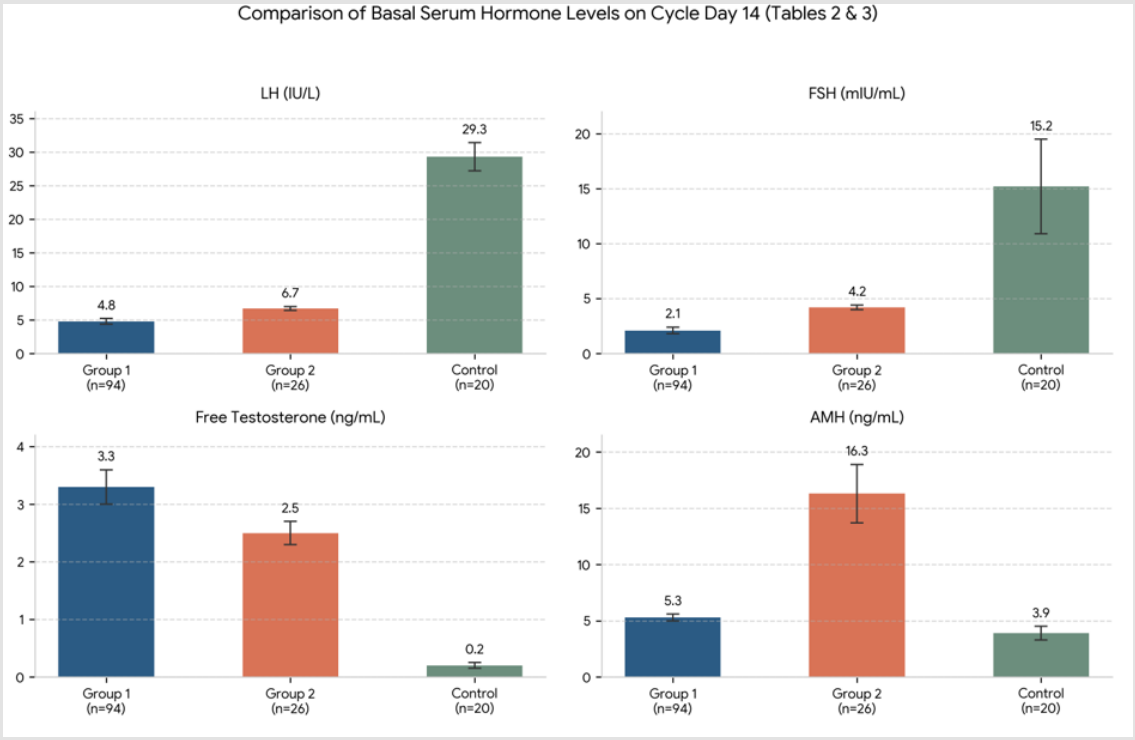

Figure 2: Comparison of mean basal serum hormone levels on cycle day 14 across study groups (Tables 2,3).

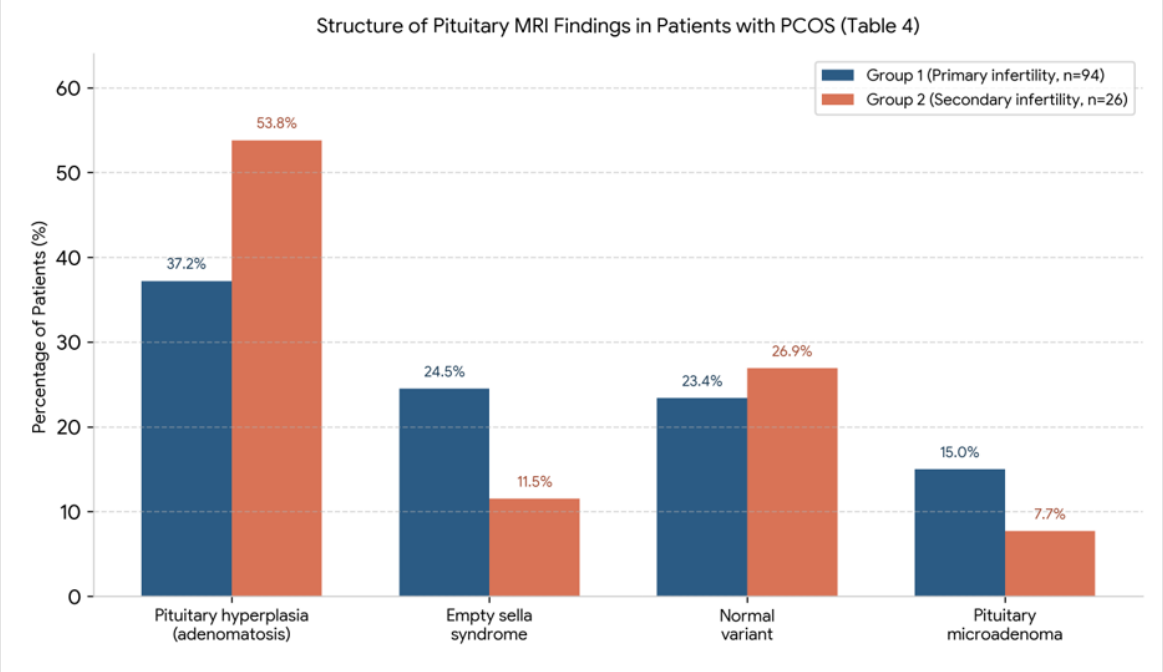

Figure 3: Structure of pituitary MRI findings in patients with PCOS (Table 4).

Discussion

In women with PCOS presenting with varying degrees of obesity and reproductive disturbances ranging from menstrual irregularities to infertility, marked impairment of pituitary gonadotropic function was identified as blunted mid-cycle LH and FSH secretion on day 14. According to modern neuroendocrine models of reproductive regulation, normal menstrual cyclicity and ovulation depend on tightly coordinated pulsatile gonadotropin release, whose pulse frequency and amplitude vary dynamically across cycle phases under the influence of hypothalamic KNDy neurons and gonadal steroid feedback [4, 5, 6]. The role of prolactin and mild hyperprolactinemia in modulating fertility and pituitary morphology in PCOS remains an active subject of clinical investigation [14,15]. In our cohort of obese women with PCOS and reproductive dysfunction, serum prolactin concentrations were significantly higher than in healthy controls across both groups, correlating with a substantial prevalence of pituitary hyperplasia (40.8%), empty sella syndrome (21.6%), and microadenomas (13.3%) on MRI [14,15]. Collectively, the most severe disruption of the hypothalamic-pituitary-ovarian axis was observed in Group 1 patients with primary infertility, who demonstrated concurrent suppression of both pituitary gonadotropins (LH, FSH) and ovarian sex steroids (estradiol, progesterone) on cycle day 14 against a backdrop of hyperandrogenemia and mild hyperprolactinemia, corroborated by ultrasonographic evidence of follicular arrest and anovulation.

Conclusions

1. In Group 1 patients with primary infertility, a statistically significant decline in both pituitary (LH, FSH) and ovarian (estradiol, progesterone) hormones was observed on cycle day 14 against a background of hyperandrogenemia (elevated free testosterone and DHEA) and mild hyperprolactinemia.
2. In Group 2 patients with secondary infertility, significant reductions in gonadotropins (LH, FSH) were accompanied by hyperandrogenemia, mild hyperprolactinemia, and markedly elevated AMH levels, while basal estradiol and progesterone levels remained preserved.
3. Across both PCOS cohorts, mid-cycle hypogonadotropism coexisted with mild hyperprolactinemia, hyperandrogenemia, and a high prevalence of structural pituitary abnormalities on MRI (pituitary hyperplasia, empty sella syndrome, and microadenomas).

Summary Conclusion

Dysfunction of the hypohalamic-pituitary-ovarian axis in PCOS is characterized by blunted mid-cycle gonadotropin secretion (LH, FSH) alongside hyperandrogenemia, hyperprolactinemia, and morphological pituitary changes. The depth of endocrine imbalance reflects the clinical phenotype of reproductive dysfunction: primary infertility is associated with combined pituitary-ovarian deficiency, whereas secondary infertility is marked by isolated gonadotropin deficiency accompanied by a high ovarian reserve (elevated AMH).

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