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Clinic of Internal Diseases and Family Medicine

Kaafiyo Hassan, 2019, Group II

INTEGRATED STUDY MASTER'S THESIS

Clinical Manifestation, Diagnosis And Management of Functional Gonadotroph Adenoma: Literature Review.

Supervisor: MD PhD, Agné Abraitienė

Head of department: Prof. Vytautas Kasiulevičius

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Kaafiyo.Hassan@mf.stud.vu.lt

Abstract

Functional gonadotroph adenomas (FGAs) are uncommon, benign tumors of the pituitary gland that produce active levels of the hormones FSH and/or LH. Because these tumors are rare and their symptoms are often vague or nonspecific, they are difficult to identify, and accurate data on how often they occur is limited. Many pituitary tumors that do not cause symptoms still show markers of hormone production, which can lead to confusion in diagnosis.

True FGAs are rarely diagnosed, partly because they often mimic other conditions. In women, symptoms may include menstrual issues, infertility, ovarian cysts, or signs of overstimulation of the ovaries. In men, signs might be enlarged testicles or problems with sexual function. Unlike other hormone-producing pituitary tumors, FGAs often go unnoticed until they become large enough to press on nearby structures, leading to headaches, vision problems, low hormone levels, or unexpected sexual hormone changes.

Medications like dopamine agonists or somatostatin analogs usually don’t work well for treating FGAs. As a result, surgery—typically through the nose using a transsphenoidal method—is the most common treatment. The goal is to reduce pressure on surrounding areas, normalize hormone levels, and confirm the diagnosis through tissue analysis. After surgery, regular follow-up is important to track hormone levels and catch any signs of the tumor coming back.

In summary, FGAs can show up in many different ways, including reproductive and hormonal symptoms or pressure-related effects if the tumor grows large. Diagnosis usually involves hormone testing, MRI scans, and examining tumor tissue. Surgery is the main treatment, with radiation used only when necessary.

Keywords: functional gonadotroph adenoma, gonadotropins, pituitary tumor, ovarian overstimulation, early puberty, testicular enlargement, pituitary surgery.

1.Introduction

Rare, benign pituitary tumors known as functional gonadotroph adenomas (FGA) release one or both gonadotropins in a physiologically active state, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (1-3). Because FGAs are uncommon and their symptoms are nonspecific, as well as because there is frequently a discrepancy between the pathological assessment of tumor specimens and their clinical presentation, there are few epidemiological researches on the condition (1, 2, 4, 5). Pathological analysis often misidentifies many non-functioning pituitary adenomas that originate from gonadotroph cells as generating FSH or LH. Actually, one or more of the glycoprotein hormone subunits (alpha, LH beta, FSH beta, and TSH beta) are expressed by the majority of clinically non-functioning pituitary adenomas (7,7).

Several studies have shown that, while non-functioning gonadotroph adenomas are relatively common, functional gonadotroph adenomas are much rarer (6, 8-10). Given the diagnostic and pathological challenges associated with this condition, there are few published case series of patients with clinically and pathologically confirmed FGAs (1, 11-22). According to a number of studies, functional gonadotroph adenomas are significantly less common than non-functioning ones (6, 8–10). Few published case series of patients with clinically and pathologically confirmed FGAs exist because of the diagnostic and pathological difficulties associated with this illness (1, 11-22).

Functional gonadotroph adenomas typically appear with diffuse clinical symptoms, in contrast to other functional pituitary adenomas that have identifiable presentations (1, 4, 6, 16, 23). Men may develop testicular enlargement and sexual dysfunction as a result of FGA, while women may experience disorders like ovarian hyperstimulation syndrome (OHSS), infertility, irregular menstruation, and polycystic ovarian syndrome (PCOS) (5, 22-28).

Gonadotropin-producing adenomas are frequently undetected until they become large enough to produce mass effects, including headaches, visual field deficits, and hypopituitarism, which ironically can include hypogonadism, because these symptoms can be mistaken for other

systemic conditions (1, 11, 13-17, 29-32). Medical treatments such as somatostatin analogs or dopamine agonists typically have no effect on FGAs (1, 12, 33). Tumor surgical removal is the usual treatment for FGAs (2, 24, 27, 29). In addition to improving endocrine dysfunction and decompressing the optic chiasm, surgery gives a conclusive pathological diagnosis (1, 24, 33, 34).

1.2. Aims and Objectives

The purpose of this review is to provide an overview of the current knowledge about functioning gonadotroph adenomas (FGAs), which are uncommon pituitary tumors that actively secrete gonadotropins. Due to the rarity of these tumors, most of the available data derive from individual case reports or small case series.

2.Literature review research and Methodology

I carried out a narrative review by reading and summarizing relevant English-language articles. These articles were found through PubMed by using specific search terms, such as "functioning gonadotroph adenoma," "ovarian hyperstimulation syndrome," "testicular enlargement," "precocious puberty," as well as terms related to diagnosis and treatment like "FSH/LH-secreting pituitary adenoma," "endoscopy," "microsurgery," and "transsphenoidal surgery." This review compiles existing information and discusses potential approaches to the management and follow-up of patients with FGAs. In total, approximately 124 articles were reviewed and analyzed for this paper.

Additionally, parts of this review were refined with the assistance of OpenAI's ChatGPT tool. The model supported the writing process by enhancing the academic tone and identifying spelling and grammatical errors [125]. However, all content selection, analysis, and interpretation were carried out independently by the author.

3. Results

3.1 Pathology

It's still unknown why certain gonadotroph adenomas exhibit hormone activity. According to a popular concept, which is these tumors may release FSH gradually but steadily, which could stimulate several ovarian follicles and raise the synthesis of estrogen, much like the action of FSH-based fertility treatments (Pigny et al., 2000 [5]). The biological activity of the FSH produced by these tumors may potentially be enhanced by modifications to its chemical makeup or structure. FSH from functional gonadotroph adenomas, for instance, may differ

from normal FSH in terms of acidity and glycosylation patterns, which increases its body activity (Pigny et al., 2000 [5]; [5–7]). According to studies, male patients with tumors that produce FSH frequently exhibit higher levels of FSH activity than either healthy people or those with tumors that do not function. Rarely, tumors that seem to be non-functioning may yet generate FSH that is biologically active [8] [125]. Even when the hormone levels itself are not very high, women with ovarian hyperstimulation syndrome (OHSS) and FSH-secreting tumors have been observed to have increased FSH bioactivity [9]. Other observations, however, indicate that some patients with same symptoms might exhibit normal FSH activity, indicating that there may be additional unidentified factors at play [10]. Patients with FSH-secreting pituitary tumors have not been discovered to have mutations in the FSH receptor, despite the fact that these mutations have been connected to OHSS in other circumstances [11,12] [125].

Even though no detrimental gene mutations have been found, there is evidence that functioning tumors express higher levels of the gonadotropin-releasing hormone receptor (GnRHR), which may contribute to abnormal hormone production (Kottler et al., 2001 [13]. Rarely, gonadotroph adenomas that are not functional may eventually develop hormone activity and exhibit symptoms of elevated estrogen production [14]. The SF-1 transcription factor is typically positive in functioning gonadotroph adenomas, and they may exhibit variable staining for α-subunit, β-FSH, and β-LH (9,15–17]. Isolated LH-producing adenomas are exceptionally uncommon [18,19]. Lastly, a study discovered that the gene Kiss1, which has an impact in hormone regulation, was more active in patients with hormone-producing gonadotroph adenomas. Additionally, the level of expression appeared to be associated with increased estrogen levels prior to surgery, indicating that it might be involved in tumor function (Wang et al., [20]) [125].

3.1 Clinical Findings in Females

The main causes of the wide range of clinical symptoms that women frequently display are hormone imbalance and tumor-related mass effects. Menstrual irregularities are the most prevalent presenting complaint, and the reproductive system is most frequently impacted. These include irregular cycles, amenorrhea, oligomenorrhea, heavy menstrual bleeding, intermenstrual spotting, or prolonged and irregular uterine bleeding [22,23,24].

Another important characteristic of many patients is infertility, which frequently leads to an initial medical evaluation [24]. Spontaneous ovarian hyperstimulation syndrome (OHSS), an

uncommon but dangerous illness marked by pelvic pain, abdominal distension, and, in rare cases, consequences such ovarian torsion and ascites, may occur in some patients [18,25,26,27]. Spontaneous ovarian hyperstimulation syndrome (OHSS) usually manifests as multifollicular ovarian enlargement on ultrasonography when it happens spontaneously rather than as a result of reproductive therapies [22]. These enlarged ovaries can have a diameter of well over 15 cm [13,15], and in certain situations, up to 20 cm [16].

Ovarian enlargement can cause discomfort, increased girth, and noticeable abdominal distension. Some women have also reported experiencing gastrointestinal problems like nausea and vomiting [14,18]. Although modest ascitic fluid buildup has been reported on occasion, particularly in situations where human chorionic gonadotropin (hCG) or LH activity is increased, the majority of individuals do not show with ascites [18,19]. One characteristic that sets iatrogenic OHSS apart is the prevalence of ascites [13,16,17].

Endometrial hyperplasia is one of the additional complications that might occasionally arise from the tumor's hormonal alterations, which can result in chronically elevated estradiol levels [17,21,23]. Due to increased bioactivity or a malfunctioning feedback system, FSH may still cause OHSS even though its levels may stay within the normal range in certain patients [24,25,26]. In some instances, the idea of poor negative feedback is further supported by the evidently higher FSH levels [24].

LH levels are frequently decreased, although the generation of estradiol persists. This implies that either other mechanisms, like hCG cross-reactivity or increased FSH action, are at work or that little LH stimulation may still be adequate for estrogen production [19,21,22,25]. Both LH and FSH are necessary to maintain healthy ovarian function, according to the standard two-cell, two-gonadotropin model of estrogen production. LH induces the generation of androgens by theca cells, which are then transformed into estrogens by granulosa cells under the influence of FSH [17,25]. Many individuals continue to produce substantial estradiol output in spite of reduced LH levels, suggesting adequate hormonal interaction for the synthesis of estrogen [19].

Multiple ovarian follicles and irregular menstruation can cause the clinical picture to occasionally resemble polycystic ovarian syndrome (PCOS). But there are some significant distinctions. Follicles are typically smaller (2–9 mm) and the FSH/LH ratio is frequently lower in PCOS. Gonadotroph adenomas, on the other hand, usually show up with bigger cysts and a greater FSH/LH ratio [20]. Less frequently, women may develop galactorrhea, a

disorder marked by improper lactation, which can be brought on by excessive estrogen levels or higher prolactin levels from tumor-induced pituitary stalk compression [12,21,26]. This hyperprolactinemia is occasionally the first hormonal anomaly to be identified and may also be a contributing factor to reproductive failure [13,25].

When the tumor gets big enough to put strain on nearby structures, neurological symptoms could appear. In addition to headaches and, in rare cases, reduced visual acuity, few patients have experienced visual abnormalities, especially bitemporal hemianopsia (loss of peripheral vision) [17,21].

Affected women's ages range greatly, from early adolescence to the mid-40s, while younger individuals may also exhibit early-onset OHSS or premature puberty [14,18,25]. Menstrual irregularities continue to be the most frequent cause of seeking medical attention among all documented instances, with infertility and pelvic discomfort coming in second and third [1,17,21] .

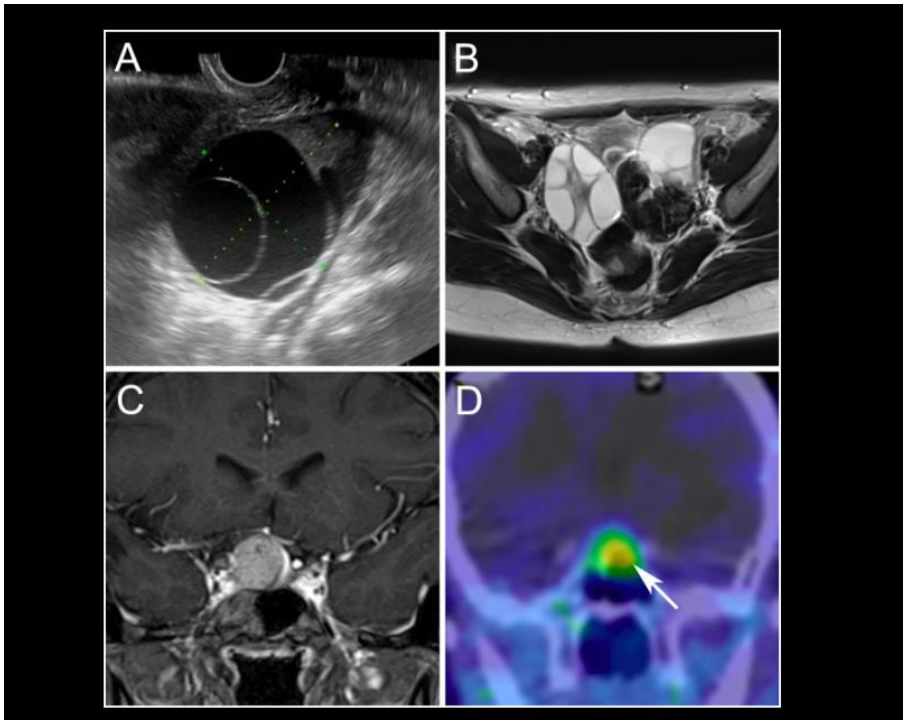

Figure 1: Pituitary and ovarian lesions seen on preoperative imaging. A: transvaginal ultrasound revealed a big cystic ovary with septation. B: Bilateral multi-cystic ovaries were visible on the axial T2-weighted pelvic MRI. C: A mass lesion with suprasellar extension was discovered by preoperative pituitary MRI (coronal postcontraste T1-weighted picture). D: The

pituitary lesion had higher tracer uptake, according to preoperative 111In-pentetreotide scintigraphy (arrow) [85].

3.3 Clinical Findings in Males

Males rarely have functioning pituitary adenomas (FGAs) that produce gonadotropins, particularly FSH [41,42,43]. Most of these tumors are large in size (macroadenomas) and tend to grow upward or laterally, often affecting surrounding brain structures [41,42,43]. There is only one reported case of a possible FSH-producing microadenoma in an adolescent male, but it lacked histological confirmation through tissue analysis [44]. Typically, FSH levels are elevated, while LH and testosterone levels are either within the normal range or decreased [45,46]. Because FSH stimulates the seminiferous tubules, some men exhibit enlargement of both testicles [42, 45]. The testicles' growth rate varies, though; in certain instances, they have been reported to be greater than 30 mL [42,43,47]. The slow action of FSH, differences in FSH activity, or the length of time the tumor was active prior to diagnosis could all be contributing factors to this variation [3,47].

Additionally, it is possible that the FSH produced in some of these situations has little to no biological activity. For example, a 55-year-old male with a large pituitary mass presented with reduced testicular volume, no rise in sperm count, and extremely high FSH levels. Testicle size was normal in another patient with extremely high FSH, but there were no indications of improved function [48]. The lack of testosterone's boosting effects may also restrict the response to FSH in males with hypogonadism. Men with elevated FSH may have enlarged testicles, which could aid in differentiating between intrinsic testicular failure and gonadotropin-producing malignancies. Due to their tendency to rise in malignant tumors, inhibin B levels may aid in diagnosis [45]. However, it's important to take into account possible reasons of testicular enlargement [3].

Not everybody has sexual dysfunction. While less than half of the six men in one study experienced sexual problems [41], all six men in another study had sexual problems (even if their testosterone levels were not low) [46]. Some men may not exhibit any outward signs of low testosterone [45,49]. Pressure-related symptoms can nevertheless be caused by large tumors that only produce a minor quantity of FSH [50].

In extremely rare instances, tumors generate active LH rather than FSH. Only men have been reported to have these LH-producing tumors, and they typically don't present with a distinct clinical symptom [15,17,51,52]. Nevertheless, polycythemia was formed in two men with

elevated testosterone from LH-secreting tumors, but it resolved upon treatment [48,53]. The conversion of excess testosterone to estrogen resulted in gynecomastia in another case [53].

These tumors frequently have extremely high FSH levels [48,49], although occasionally they are only marginally elevated [46,54]. Low, normal, or slightly raised LH are all possible [8,46]. Alpha-subunit hormone levels can also occasionally rise [55]. The resulting FSH or LH may not always be physiologically active [56]. Nonetheless, the FSH generated in two of the six patients under investigation was much more physiologically active than usual (2.5 and 4.1 vs. a normal range of 0.3–1.5) [8]. It is not always possible to differentiate FGAs from nonfunctioning adenomas (NFAs) using inhibin B levels [8]. Inhibin B may be low even when FSH levels are high, suggesting that the FSH may not be functioning correctly [48]. However, some FGAs do raise inhibin B, which may indicate FSH activity [44]. Usually, only FSH or both FSH and LH are produced by these malignancies. Other pituitary hormones, such as TSH [57], prolactin [58], or ACTH [59], have been reported to be produced by them as well. Gonadotropin levels in FGAs frequently remain unchanged following stimulation with sex hormones or GnRH, indicating that the tumor cells act on their own [49,60,61].

Although TRH normally has no effect on gonadotropins, FSH and LH levels in patients with FGAs frequently rise initially and then further after receiving TRH. Compared to healthy individuals or those with nonfunctioning adenomas, these increases are typically greater [6,63]. According to earlier research, a rise in LH-β following TRH may be a more effective way to distinguish FGAs from other cancers than only examining FSH or alpha-subunit levels [64]. Although some cancers don't create alpha-subunit at all, which makes interpretation challenging [67,68], measuring alpha-subunit levels following TRH stimulation may aid in diagnosis prior to surgery [66,67].

Semen analysis may be normal even when FSH is extremely high, indicating that FSH may not always have a significant biological impact [49,69,70]. In contrast, one patient with a tumor secreting both FSH and LH showed increased sperm count and elevated testosterone levels [71]. In another case involving a man with high FSH levels, testicular biopsy showed normal seminiferous tubules and Sertoli cells, along with sparse and inactive Leydig cells and mild abnormalities in sperm production [62].

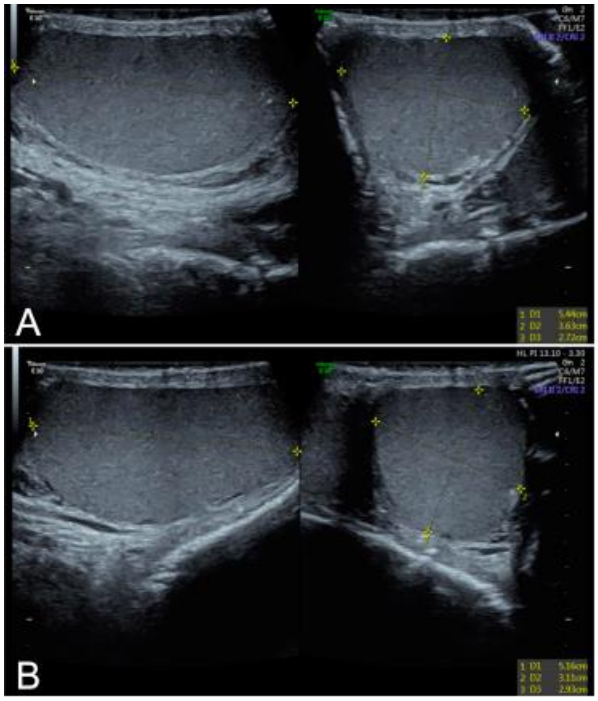

Figure 2: Scrotal ultrasound used to measure testicular size reveals bilaterally enlarged testicles. A: The right testis, which measures 5.44 x 3.63 x 2.72 cm with a volume of 38.14 cm, has a normal echotexture and form, several calcific foci, and no hydrocele. B. Left testis, 5.16 x 3.11 x 2.93 cm, volume 33.38 cm, echotexture normal, numerous calcific, no hydrocele [65].

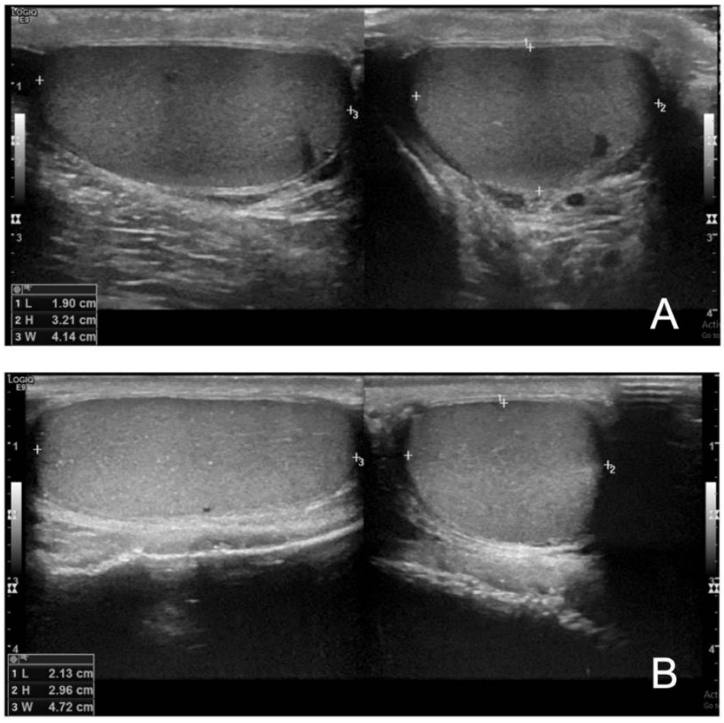

Figure 3: Scrotal ultrasound used to measure testicular size reveals testicles of normal size. A: Right testis measuring 4.14 x 3.21 x 1.9 cm – 17.93 cm: normal shape and echotexture, multiple calcific foci, no hydrocele. B: left testis measuring 4.72 x 2.96 [65].

3.4 Clinical Findings in Children

Functioning gonadotroph adenomas (FGAs) are extremely uncommon in the pediatric population [76,77,78]. Among the reported cases, most involve macroadenomas, with only two suspected to be microadenomas [72]. Depending on the child's age and sex, these tumors may exhibit different endocrine-related symptoms. Clinical presentation differs with age in girls. Cases of FGAs in children as young as 3 to 7 years old have been linked to central precocious puberty [58,72,73,74,75]. Menstrual irregularities such amenorrhea has been reported in postmenarcheal girls [76,77,78]. Abdominal distension, nausea, and pain have been documented in several instances where bilateral, numerous ovarian cysts are present [77]. Large ovarian cysts can occasionally develop and show up as palpable abdominal lumps on clinical examination [76]. In contrast to teenagers or women of reproductive age, this dramatic presenting approach seems to be far less common in pediatric cases [80].

Many affected girls, especially those with FSH-secreting tumors, have noticeable ovarian enlargement [79]. Unnecessary surgical procedures, including bilateral oophorectomy, have been carried out in rare and unfortunate cases due to severe ovarian alterations before the underlying reason was identified [78]. These incidents demonstrate how crucial it is to do a thorough clinical evaluation on any youngster exhibiting symptoms of early puberty or aberrant ovarian development [73,77].

Testicular enlargement is a crucial clinical indicator in boys and might manifest without other obvious symptoms [44, 3]. Unusual development patterns or early puberty symptoms might be caused by hormonal imbalances. Some boys may appear with raised LH and testosterone, or with simultaneous increases both in gonadotropins and testosterone [58,74], whilst others may have elevated FSH and inhibin B levels in combination with low LH [44].

Transient elevations in gonadotropins at that time (referred to as "mini-puberty") can lead to confusion during clinical evaluation, even though no FGAs have been observed in infants under the age of two [81]. However, genuine instances of precocious puberty brought on by gonadotroph adenoma, including LH-secreting varieties, have been documented starting at age 3 [75]. Depending on the tumor size and hormone secretion profile, such tumors among kids can cause a wide variety of symptoms. Before considering any irreversible treatments, a

detailed and comprehensive evaluation is necessary due to the clinical symptoms that coincide with more prevalent disorders such as CNS lesions or idiopathic precocious puberty [81].

3.5 Neurological and Ophthalmological Symptoms Due to Mass Effect

As with other pituitary macroadenomas, FGAs can exert pressure on surrounding structures, leading to mass effect symptoms [50]. These symptoms become more prominent as the tumor enlarges beyond the sella turcica and compresses adjacent neural and vascular structures. Patients with pituitary macroadenomas commonly experience headaches, a symptom that is often associated with coexisting follicular growth disturbances such as FGAs [50]. While the exact mechanism is not fully understood, it is likely related to increased intrasellar pressure, distortion of the dura mater and cavernous sinus, and direct compression of pain-sensitive structures surrounding the pituitary [50]. The nature of headaches can vary from mild to severe and may be mistaken for tension headaches or migraines [50,68].

The pituitary gland's proximity to the optic chiasm makes visual disturbances a hallmark feature of large adenomas [68]. Symptoms often include bitemporal hemianopsia, a loss of peripheral vision caused by compression of the optic chiasm, decreased visual acuity if the optic nerves themselves are affected, and diplopia (double vision) in cases where the tumor extends into the cavernous sinus and impacts cranial nerves III, IV, or VI. Visual deficits tend to be progressive and irreversible if left untreated [68]. Therefore, early detection and intervention are critical in preventing long-term vision loss. Large FGAs can compress the normal pituitary gland, leading to hypopituitarism [68].

4. Diagnosis

Diagnosing functional gonadotropin-secreting adenomas (FGAs) begins with a thorough clinical assessment, which includes a detailed patient history and physical examination [59]. Symptoms can vary based on the patient's sex, age, and the specific hormones secreted by the tumor [25,36]. In females, common symptoms include menstrual irregularities such as oligomenorrhea, secondary amenorrhea, menorrhagia, and abnormal vaginal bleeding. Some women may also experience infertility, ovarian hyperstimulation syndrome (OHSS), or persistent abdominal pain due to excessive hormonal stimulation of the ovaries [25,36].
In males, symptoms may include testicular enlargement, sexual dysfunction, gynecomastia, or erythrocytosis, depending on the hormonal activity [41,42,45,46,]. Increased secretion of LH and FSH can disrupt normal testosterone regulation, often resulting in infertility.

In children, FGAs may cause isosexual precocious puberty, characterized by the early development of secondary sexual characteristics due to elevated gonadotropins [73,74,76].. As the tumor enlarges, it may exert pressure on nearby structures, leading to headaches, visual disturbances such as bitemporal hemianopsia, and cranial nerve palsies. In some cases, patients may remain asymptomatic, with the adenoma being discovered incidentally during imaging. A careful clinical assessment is essential to differentiate FGAs from other pituitary disorders and reproductive endocrine conditions [59].

Patient	Pre-Operative FSH	Pre-Operative LH	Pre-Operative Prolactin	Pre-Operative Estradiol	Pre-Operative Testosterone	Post-Operative FSH	Post-Operative LH	Post-Operative Prolactin	Post-Operative Estradiol	Post-Operative Testosterone
1	27.8*	4.5	10.8		253.9	1.8	0.3	3.3		442.4
2	17.3*	<0.1*	122.9*	130		8.3	1.3	13.3	21	
3	159.1*	4.2	6.5		830.0	139.6*	2.6	7.2		502
4	9.4	0.04*	45.9*	458*		13.2*	11.7	8.7	153	
5	125.3*	2.5	8.7		48.0*	7.1	2.9	5.6		358.3
6	25.0*	2.2	21.8*		233	4.7	3.1	6.0		310.0
7	39.4*	4.5	9.5		457	8.7	4.7	8.3		396.0

*abnormal result

Figure 5: Endocrine test results for patients with functional gonadotroph adenomas. *Abnormal test [41].

4.1 Imaging Studies

MRI plays a key role in diagnosing and evaluating pituitary neuroendocrine tumors (PitNETs), with imaging approaches tailored to the tumor's size and functional status [66]. For microadenomas (less than 1 cm), the main objective is to detect and accurately localize the tumor within the pituitary gland. Dynamic contrast-enhanced MRI is particularly effective in this regard, as microadenomas typically show delayed contrast uptake compared to the normal gland, with the greatest contrast occurring around 1–2 minutes post-injection. Tracking changes in signal intensity over time helps reduce false positives caused by magnetic susceptibility artifacts or partial volume effects from bone or air [66,67]. Standard contrast-enhanced images taken too early can lead to misinterpretation, especially around the limbus of the anterior pituitary lobe. Because microadenomas can be very small,

indistinct, or multifocal, high spatial resolution is essential. Using thin-slice (1–1.2 mm) 3D T1-weighted post-contrast sequences such as VIBE, especially when enhanced with deep learning-based reconstruction, significantly improves the detection of small lesions [66,67]. On the other hand, macroadenomas (larger than 1 cm) are usually more conspicuous and require a comprehensive assessment of their internal structure (e.g., cystic areas, hemorrhage), shape, and extent. Imaging must also evaluate the position of the compressed normal pituitary gland, optic chiasm and nerves, cavernous sinus invasion, bony erosion, and proximity to major blood vessels—information that is crucial for surgical planning [66,67]. Dynamic MRI can help distinguish the normal gland, which enhances earlier than the tumor, especially when compressed. When macroadenomas extend upward into the suprasellar space, they are often constricted at the level of the diaphragma sellae, producing a characteristic "snowman" appearance [66,67]. Compression of the optic chiasm typically occurs in a superior-to-posterior direction; however, if the chiasm lies anterior to the tumor (a prefixed chiasm), surgical access becomes more complex, making preoperative identification essential. The CE-FIESTA sequence, a heavily T2-weighted contrast-enhanced technique, is particularly useful for assessing compression of the optic nerves and chiasm[66,67]. T2 hyperintensity of the optic nerve has been linked to visual impairment. Many macroadenomas are cystic, and about half show a fluid–fluid level within the cyst, which is usually a sign of intratumoral hemorrhage. This feature is rare in other sellar masses such as Rathke’s cleft cysts or adamantinomatous craniopharyngiomas, so its presence strongly suggests a cystic PitNET [66,67]. Computed tomography (CT) scanning serves as an alternative, though MRI offers superior resolution for detecting pituitary adenomas and assessing tumor size and invasiveness. Additionally, in cases of ovarian hyperstimulation, pelvic ultrasound or MRI may reveal enlarged ovaries with multiple cysts, which can mimic the appearance of polycystic ovarian syndrome (PCOS) [66,67].

4.2 Differential Diagnosis

Because functioning gonadotroph adenomas (FGAs) can present with a wide range of symptoms, it's important to carefully distinguish them from other endocrine disorders. One key differential diagnosis is prolactinoma, which is typically indicated by significantly elevated prolactin levels (over 200 ng/mL), a finding not seen in FGAs. Polycystic ovarian syndrome (PCOS) is another condition that can cause menstrual irregularities and enlarged ovaries; however, PCOS is marked by features such as high androgen levels, insulin resistance, and a higher LH-to-FSH ratio, rather than excess gonadotropins [21,22,30,33]. Hypogonadotropic hypogonadism, on the other hand, is characterized by low levels of LH and

FSH, in contrast to the elevated or inappropriately normal gonadotropin levels seen in FGAs. Non-functioning gonadotroph adenomas (NFGAs) do not cause hormonal symptoms and are often identified only when they grow large enough to cause mass effect symptoms, such as vision changes or headaches [50,68] [125]..

5.Management

5.1 Transsphenoidal surgery

Transsphenoidal adenomectomy (TSA) is the main treatment approach for functioning gonadotroph adenomas, aiming to normalize hormone secretion and relieve symptoms—whether caused by tumor pressure or hormonal excess [32,1,46,83]. In women of reproductive age, successful surgical removal often resolves ovarian hyperstimulation syndrome [28,83], reduces the size and number of ovarian cysts [32,79,84], restores regular menstruation, and can even lead to spontaneous pregnancies [19,30,32,34,85]. Surgical removal of the ovarian cysts themselves, such as through bilateral ovarian cystectomy, is typically not beneficial, as the cysts tend to recur [36,86].

For male patients, TSA generally lowers elevated gonadotropin levels [46,49], may lead to reduced testicular volume [42], and often results in noticeable symptom improvement [46]. While some men may develop hypogonadotropic hypogonadism after surgery and require hormone replacement therapy [51], others regain normal testosterone levels without further treatment [87].

Children who undergo successful TSA also show good outcomes, including the resolution of early puberty symptoms and normalization of hormone levels [58,73,74,76].

However, there is a risk of tumor regrowth or worsening of any remaining tumor after surgery [88]. One study showed that six out of seven patients stayed in remission after surgery during a median follow-up of 10 months [1]. At this time, there are no clear markers to predict recurrence. The Ki-67 index is not a reliable indicator of tumor progression or recurrence, although one study suggested that larger tumors and younger age at diagnosis may be associated with a higher risk of recurrence [88].

5.2 Microsurgical Technique

The microsurgical approach to transsphenoidal surgery utilizes an operating microscope equipped with a sophisticated optical system that offers adjustable magnification through two sets of lenses. This system includes its own powerful lighting source aligned with the visual axis, which reduces shadowing and improves clarity during surgery [120]. The visualization provided by this technique, however, is inherently constrained by the narrow surgical corridor created by the nasal speculum—resulting in what is often referred to as "tubular vision."

[figure 8]. Despite this limitation, the binocular setup of the microscope grants the surgeon true three-dimensional depth perception, which is a major advantage during delicate dissection. Additionally, the design of the system allows the surgeon to remain seated close to the operative field, enhancing control and precision [120].

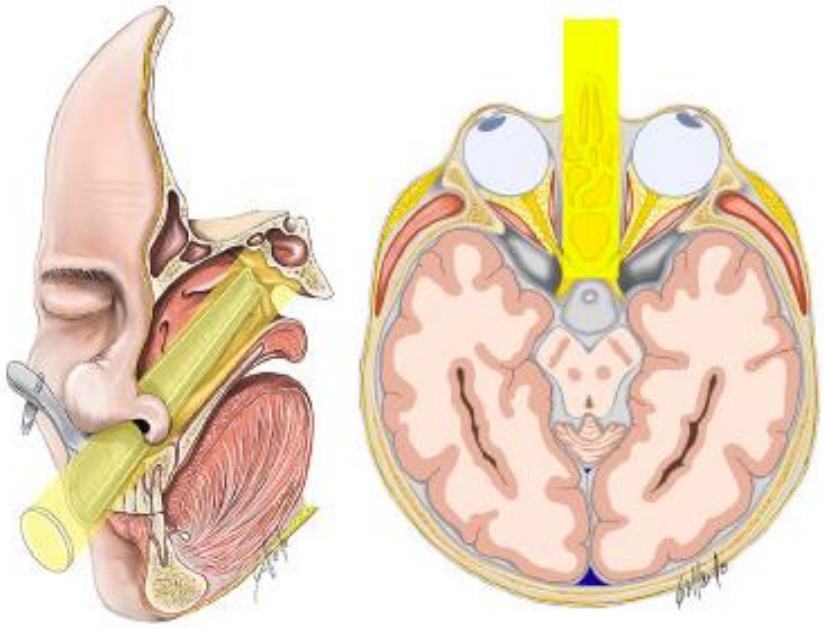

Figure 8. The diagram shows the surgical field accessible through the microsurgical transsphenoidal technique using the sublabial approach. On the left side, a 3D view illustrates how the surgeon's line of sight is centrally aligned with the sella turcica—the main focus of the operation. On the right, an axial slice reveals the narrow, tunnel-like view typical of this method, often referred to as "tubular vision," which restricts side visibility but allows direct access to the midline sellar area [120].

Microsurgical transsphenoidal surgery (mTSS) can be performed through several approaches, including the endonasal (direct or submucosal) and sublabial routes. The direct endonasal method involves inserting the nasal speculum straight through one nostril until the sphenoid rostrum is reached and removed, giving access to the sella and tumor. This technique is generally quicker and less invasive, as it avoids disrupting the anterior nasal mucosa and eliminates the need for postoperative nasal packing. However, operating through a single nostril restricts the angle and width of access, which can limit exposure—especially on the same side as the nostril used [120].

The submucosal endonasal technique follows a similar trajectory but requires dissection beneath the nasal mucosa. While this still allows access to the sphenoid sinus and sella, it

involves additional tissue disruption, necessitating the use of nasal packing post-surgery. As a result, patients typically remain hospitalized longer, with packing removal usually scheduled between the fourth and fifth day after the operation [120].

The sublabial approach involves making a horizontal incision along the upper gum line (gingivolabial sulcus), followed by submucosal dissection through the cartilaginous nasal septum. The septum is then detached from the bony structures of the nose to expose the sphenoid rostrum. This technique involves a more extensive dissection compared to endonasal methods but offers a broader view of the sellar area. Because the speculum is introduced through the wider opening of the pyriform aperture rather than a single nostril, surgeons gain better access to key anatomical landmarks, including the entire sella, both carotid prominences, parts of the anterior skull base, and a segment of the clivus. The downside of this approach lies in the increased trauma to nasal tissues, which necessitates postoperative nasal packing and may prolong recovery [120].

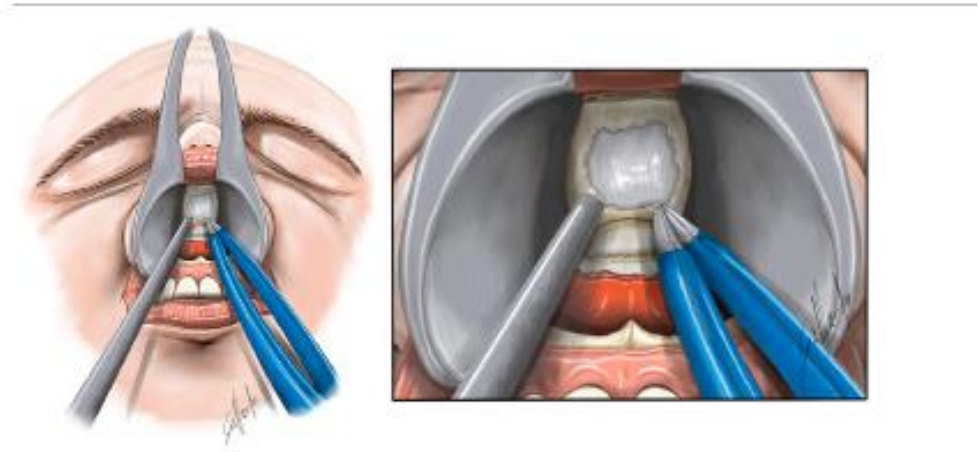

Figure 9: This figure presents the operative view obtained during microsurgical transsphenoidal surgery performed via the sublabial approach. The left panel shows the macroscopic, unaided view of the surgical field, while the right panel displays the enhanced visualization through the operating microscope. The image demonstrates how this technique allows for broad exposure of the sellar region, enabling precise instrument control and ample working space for bimanual microsurgical manipulation [120].

Although the microsurgical approach offers a narrow visual field, this "tubular" view provides ample space for maneuvering surgical instruments with both hands, mimicking the ergonomics of other open microsurgical procedures. This setup allows the surgeon to maintain precise instrument handling throughout the operation. Nevertheless, due to the limited visual

landmarks within the nasal cavity, particularly when approaching deep-seated lesions, intraoperative imaging such as fluoroscopy can be crucial. It helps confirm anatomical orientation and ensures the surgical path is accurate and safe, especially in cases where the usual landmarks are obscured or unreliable [120].

5.3 Endoscopic

The endoscope used in endoscopic transsphenoidal surgery (eTSS) features a rigid rod lens connected to a monitor, which displays an image from a short distance from the tip of the instrument. The light source is integrated into the system, shining through optical fibers that emit light from the tip of the endoscope along the viewing axis. One of its main advantages is the ability to be inserted through narrow passages, allowing access to deep areas and enabling the exploration of large regions within the surgical field. Additionally, angled lenses improve the surgeon's vision, allowing for better maneuverability, such as "looking around corners." The images from the endoscope provide superior illumination and a wider, clearer view of the surgical area compared to a microscope, though they are typically two-dimensional [120].

However, the lens may often come into contact with blood or nasal secretions, which can blur the image and require frequent cleaning or irrigation, thus increasing the surgical time. Furthermore, as the surgeon must focus on the monitor while manipulating instruments away from their line of sight, repeated insertion and removal of the endoscope and tools can potentially cause damage to the nasal tissues, especially in less experienced hands [120,122,124].

eTSS allows for expanded access to areas beyond the sella, both in the sagittal and coronal planes, and even into the subarachnoid space, providing a more extensive view of the suprasellar region. Since the nostrils are narrow, the surgeon must become skilled at maneuvering instruments around the sphenoid sinus. To ensure smooth operation with both hands, the endoscope is typically placed on a holder or, ideally, managed by an experienced assistant who can dynamically adjust the camera to follow the surgeon's movements [120,122,124].

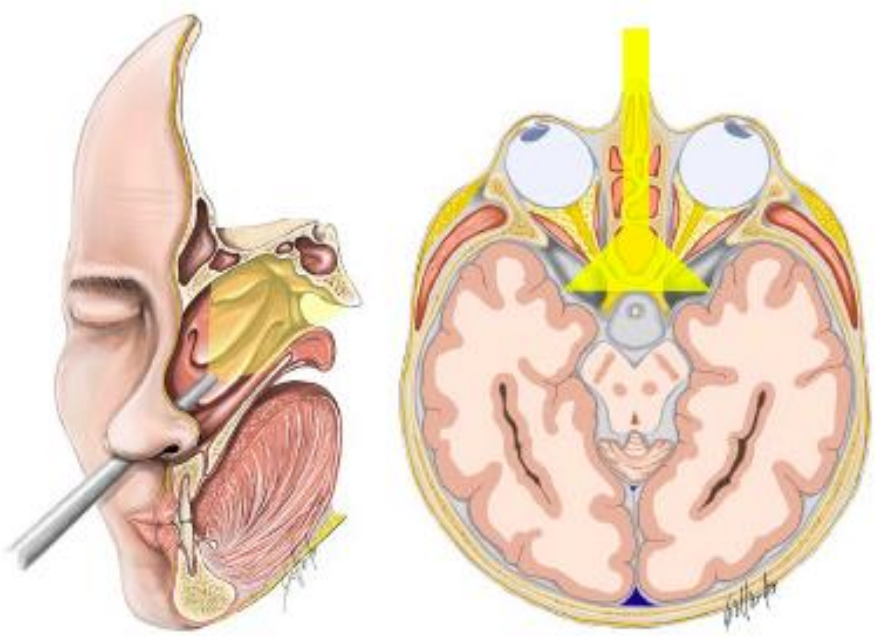

Figure 10: Diagram showing the exposure achieved through eTSS. On the left, a three-dimensional perspective illustrates how the visual field is broader compared to mTSS. On the right, an axial view is shown, highlighting that while the nasal passage is narrow, the visibility within the surgical area is significantly improved [120].

Although there are different variations of eTSS, the bi-nostril approach is the most commonly used and provides the greatest freedom and visibility during surgery. In this method, the endoscope and surgical instruments are inserted through both nostrils to remove the posterior nasal septum and mucosa, exposing the sphenoid rostrum. Once the sphenoid rostrum is removed, the endoscope is positioned within the sphenoid sinus, allowing for clear identification of key anatomical landmarks to guide the procedure. In some cases, the middle turbinates may be shifted or, less frequently, removed to create a wider surgical path. The nostril used for inserting the endoscope and instruments can be alternated to improve maneuverability and visibility in specific areas. Since the mucosa of the anterior nasal septum is typically left intact (unless a nasoseptal flap is being harvested), nasal packing is generally not required [120,124].

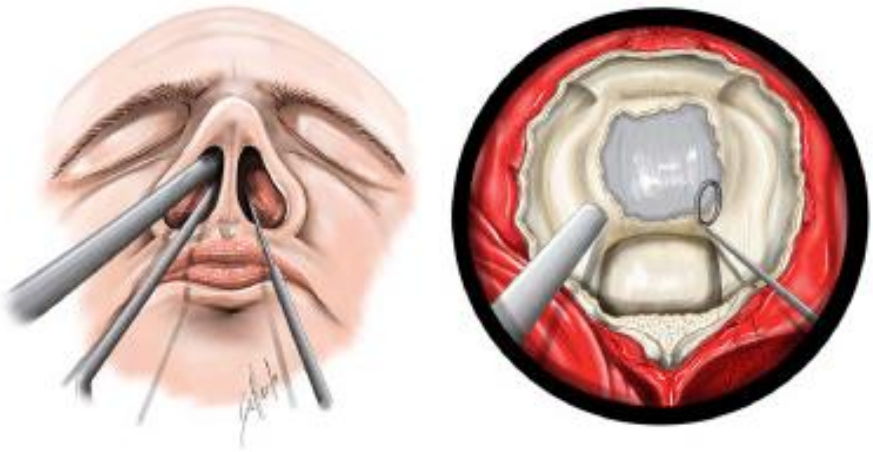

Figure 11: Surgical view of eTSS with the bi-nostril technique. On the left, a macroscopic view is shown, while on the right, an endoscopic view is displayed. The surgical exposure is wider compared to microsurgery. Utilizing both nostrils with a pivoting motion enhances the maneuverability of the instruments [120].

Medical Treatment

If surgery isn't successful or cannot be done, medical treatment can be tried to see if the FGA responds positively.

6.1 Oral Contraceptives

In two reported cases, FGAs were diagnosed after patients stopped taking oral contraceptives [9,16]. Reintroduction of contraceptive therapy failed to suppress FSH levels or prevent ovarian hyperstimulation in one patient [9]. In two additional cases, administration of low-dose estrogen–progestin combinations temporarily suppressed pituitary activity and led to a reduction in ovarian volume; however, the ovarian enlargement recurred shortly thereafter [22].

6.2 Dopamine Agonists

Some isolated case reports indicate that a few FGAs may respond to dopamine agonists. In one case, levels of LH and alpha-subunit hormones dropped Following a four-hour administration of dopamine infusion [89]. Other reports found a similar hormone-lowering effect after longer treatment with dopamine agonists like bromocriptine [69,90,91].
In some patients, low doses of bromocriptine (2.5–5 mg) were effective in reducing hormone levels; however, this didn't happen in every case [54,92]. In older studies, some patients

showed quick improvement in vision, suggesting the tumor might have shrunk within a few days or weeks [90,93]. Others showed a slow decrease in tumor size over time with prolonged use of bromocriptine [93,94]. Nevertheless, in the majority of cases—even with a reduction in hormone levels—the tumor did not reduce in size [54,69]. In one instance, cabergoline (another dopamine agonist) was administered for 13 weeks, successfully lowering both FSH and prolactin levels, which resulted in a pregnancy [95]. However, in other cases, cabergoline either proved ineffective [44] or had only partial success [96]. Some reports indicate that both bromocriptine [40] and cabergoline [95,97] were beneficial in managing ovarian hyperstimulation, restoring ovulation and improving fertility [40].
In some cases, this even led to pregnancy [37,40,95]. However, there were also cases where dopamine agonists made the condition worse [98]. A high number of dopamine D2 receptors and estrogen receptor alpha (ERα) might explain why some tumors respond better to dopamine agonists, but studies have shown mixed results [17]. A systematic review showed that dopamine agonists slightly lowered hormone production or reduced ovarian size in 8 out of 18 cases [30]. Overall, dopamine agonists are not generally considered effective for controlling symptoms or shrinking the tumor. But since we can't predict which cases might respond, trying this treatment may be reasonable in select patients.

6.3 Somatostatin Analogs (SSA)

Gonadotroph tumors can have somatostatin receptors type 2 and 3 [99], but this doesn't always mean the drugs will work. For example, in one case, the tumor absorbed labeled octreotide (SSA) on a scan, but the drug didn't reduce hormone levels or tumor size [100].

Still, there are rare cases where SSAs were helpful. In one woman, an SSA helped stop ovarian hyperstimulation [101], and in another case, it improved vision and slowly reduced tumor size [102]. A tumor that made both TSH and LH also shrank with SSA treatment [103]. But in many other cases, SSAs didn't significantly reduce hormone levels or tumor size [43,100], and their hormone-suppressing effect was inconsistent.

A test using octreotide to check for short-term response has been suggested. However, in one woman, octreotide quickly lowered LH and alpha-subunit levels, but long-term treatment with lanreotide didn't maintain that effect [104]. In one report, a combination of SSA and dopamine agonist provided brief symptom relief, slight hormone improvement, and mild tumor shrinkage [48], while another case showed continued hormone reduction for six months

[53]. To date, there have been no reported cases of treatment with pasireotide, a newer somatostatin analogue (SSA) that targets multiple receptors.

6.4 Gonadotropin releasing hormone (GnRH) Agonists/Antagonists

Research has shown that GnRH antagonists may help reduce hormone levels in patients with functioning gonadotroph adenomas (FGAs), although the outcomes have not been consistent across all studies [98,105,106,35]. One study found that treatment with Nal-Glu GnRH led to a reduction in FSH levels in two out of four patients with FSH-secreting tumors, with one patient achieving full normalization [106]. In a separate study involving seven patients who had previously undergone unsuccessful surgery, a single dose of the antagonist caused a modest yet statistically significant decline in FSH levels within 12 hours, though there was substantial variation in individual responses [105]. In contrast, another case showed no decrease in FSH or alpha-subunit levels following treatment [35]. While some reports suggest that GnRH antagonists can be beneficial in controlling ovarian hyperstimulation syndrome in the context of FGAs, this effect has not been universally observed [98,38].

Tests done on functional gonadotroph adenoma cells in the lab showed mixed results when exposed to GnRH. In one study, only one out of three tumors showed reduced hormone production after treatment with a GnRH agonist [107]. In one patient, treatment failed to produce the expected response [43]. In fact, GnRH agonists can sometimes increase FSH levels and make the condition worse [34], including increasing tumor size or triggering pituitary bleeding (apoplexy) [108,109].

Also, a strong initial response to leuprolide (a GnRH agonist) did not mean the patient would respond well to longer treatment [106]. Longer use (3–12 months) typically lowered hormone levels but didn’t shrink the tumor [110,111], though a few cases did show some reduction in size [71].

A recent review showed that GnRH agonists or antagonists were used in 11 patients. Some had mild symptom or hormone improvement, but in 4 cases the treatment made things worse, including tumor growth [30].

In conclusion, medical therapy often does not work well to reduce tumor size, although it may help symptoms or hormone levels in some cases. Because of this, medication should not be the first treatment choice, but it can be considered if surgery isn’t possible or as a trial in selected situations [30].

7. Radiotherapy

Radiation therapy has been used both to manage tumor regrowth [30,41,69] and to limit the progression of residual tumor tissue after partial surgical removal [60,71,96]. However, due to limited long-term follow-up, its sustained effectiveness over time remains uncertain. Whether or not to offer radiotherapy after surgery should be decided on a case-by-case basis, ideally with input from a team of different medical specialists. In one case, a very small remaining tumor (less than a centimeter) stayed inactive for many years without treatment [86]. This suggests that it might be better to wait and only use radiotherapy if the tumor clearly starts growing again. In another case, after multiple surgeries, the remaining tumor did not grow for six years [1].

Older forms of radiotherapy didn't always succeed in controlling hormone levels, even after long-term follow-up (up to 12 years) [60,69]. Based on results from treating more common types of pituitary tumors, it's likely that modern radiotherapy techniques, such as standard fractionated RT and especially radiosurgery, could give better results. Radiosurgery is often considered the best radiotherapy option when it's available [112,113].

Some case reports have shown that tumors can be kept under control for at least 8 years after using stereotactic radiotherapy following surgery for tumor regrowth [1].

8. Long-Term Outcomes and Management of Functional Gonadotroph Adenomas (FGAs)

The long-term prognosis of functional gonadotroph is still unclear, mainly because most published cases lack extended follow-up. Sometimes, the disease course may include spontaneous changes in hormone levels and symptoms. One such example is a 40-year-old woman experienced significant changes in estradiol concentrations and ovarian size over a one-year period
[114].

Gonadotropin-secreting tumors have a high chance of coming back or getting worse over time, so regular monitoring is essential. The size of the tumor, particularly the antero-posterior (AP) diameter, is the most reliable predictor of recurrence or progression. In fact, for every 5 mm increase in AP diameter, the risk of recurrence or progression doubles [88].

Previous research also shows that larger non-functioning tumors are more likely to relapse [115].

In a study examining 50 cases of functional gonadotroph adenomas in women of reproductive age, 12 out of the 25 patients who underwent surgery had their tumors completely removed. However, 5 of these 12 patients experienced a recurrence during an average follow-up of 25 months [85]. When recurrences occur, treatment options include further surgical intervention [30,36], radiation therapy [30,101], or pharmacological treatments, sometimes combined with radiotherapy [53,101].

A more recent systematic review analyzed 65 cases of FGAs in premenopausal women. Out of these, 63 (96.9%) underwent surgery, and 77.8% had full tumor removal and resolution of symptoms. However, the follow-up period was too short to accurately assess the long-term risk of recurrence. Some patients needed radiotherapy or another surgery, while others were managed with observation or even ovarian surgery, without further pituitary treatment [21].

Although there are cases where the tumor has not returned even after 12 years [24], it is crucial to continue long-term follow-up through clinical check-ups, blood tests, and imaging.

The outlook for fertility is generally positive if treatment is successful. In one retrospective review, 12 out of 14 women who had available pregnancy data were able to conceive [30]. If natural conception doesn't occur after treatment, assisted reproductive techniques like in vitro fertilization (IVF) with embryo transfer can still lead to pregnancy—even when hormone levels from the tumor remain elevated [116,24].

In extremely rare cases, FGAs may eventually transform into pituitary carcinoma. This has been seen in patients with multiple endocrine neoplasia type 1 (MEN1). In one case, the tumor kept recurring despite multiple surgeries and radiotherapy. Years later, a brain metastasis was found, showing changes in tumor behavior, including loss of typical hormone markers and only staining for steroidogenesis factor-1 [117].

Recently, Principe et al. discovered that gonadotroph Pituitary Neuroendocrine Tumors (PitNETs) have a higher number of CD68+ immune cells (macrophages) compared to other types like somatotroph, lactotroph, and corticotroph PitNETs. There is also a strong connection between the presence of CD68+ and CD163+ macrophages and how aggressive the tumor is [118]. This suggests that targeting macrophages could become a new treatment

option to slow the tumor's progression. For aggressive pituitary tumors, treatment with temozolomide (TMZ), either alone or combined with 5-fluorouracil (5-FU) or radiotherapy, has shown promise [119].

Conclusion

A functioning gonadotroph adenoma (FGA) can be difficult to diagnose and manage. It is frequently misidentified as a non-functioning macroadenoma due to its vague symptoms and is often linked to notable health complications. Clinicians should include FGA in the differential diagnosis when evaluating patients with pituitary tumors and reproductive issues. The preferred first-line treatment is transsphenoidal surgery, which may help restore hormonal balance, relieve headaches, enhance vision, and allow for thorough pathological examination of the tumor tissue.

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