Functioning Gonadotroph Adenomas

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Context: Functioning gonadotroph adenomas (FGAs) are pituitary tumors secreting biologically active gonadotropins. The published literature includes only small case series or individual case reports. This review summarizes the published data on this rare entity and, based on them, suggests guidance on the follow-up of these patients.

Evidence Acquisition: A review of articles in English retrieved from the PubMed up to December 2013 was conducted. The following terms were used for the search: "functioning gonadotroph adenomas," "FSH secreting adenomas," "LH secreting adenomas," "gonadotroph adenomas," "ovarian hyperstimulation," "macroorchidism," "testicular enlargement," and "precocious puberty."

Evidence Synthesis: All reported cases of FGA were assessed, and information on presenting manifestations, management approaches, and long-term outcome was reviewed.

Conclusions: FGAs cause distinct manifestations and, based on the limited published literature, they are mostly macroadenomas. Their pathogenesis remains enigmatic. Systematic series on their optimal management are lacking, but the primary therapy remains surgical excision of the adenoma. Given the risk of recurrence, long-term clinical and imaging follow-up is needed, and radiotherapy may be required. There is little evidence that medical therapies are particularly helpful, certainly in terms of tumor control. Central registration would enhance our insight regarding their pathology and optimal management. **(*J Clin Endocrinol Metab* 99: 4423–4433, 2014)**

Functioning gonadotroph adenomas (FGAs) are adenomas expressing and secreting biologically active gonadotropins and causing distinct clinical manifestations (mainly menstrual irregularity and the ovarian hyperstimulation syndrome in premenopausal females and adolescent girls, testicular enlargement in males, and isosexual precocious puberty in children). The vast majority of the immunohistochemically confirmed gonadotroph adenomas are hormonally silent (presenting only with mass effects), which in a surgical series accounted for 64% of all clinically nonfunctioning pituitary adenomas (1). However, clinically FGAs are very rare; whereas their exact prevalence is not known, in a community-based cross-sectional study in the United Kingdom including 81 449 inhabitants, no case of FGA was identified (2). Thus, the published literature includes only small case series or individual case reports. In this review, we will focus on the main presenting manifestations, the reported management options, and the long-term outcome of the FGA, and using these data, we will suggest guidance on the follow-up of the patients with this very rare entity.

Pathology and Pathogenesis

FGAs are morphologically identical to nonfunctioning gonadotroph tumors. Macroscopically, the adenoma is soft and well-vascularized, with occasional areas of hemorrhage or necrosis. On microscopic examination, chromophobic cells arranged in a trabecular, papillary, or sinusoidal pattern are seen. Prominent pseudorosette

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Abbreviations: DA, dopamine agonist; FGA, functioning gonadotroph adenoma; MRI, magnetic resonance imaging; PCOS, polycystic ovarian syndrome.

formations around the blood vessels and focal oncocytic changes are also common (3–6). There is strong nuclear staining with steroidogenic factor-1 and variable intensity of immunoreactivity for α-subunit, β-FSH, and β-LH (5, 7–9). On electron microscopy, well-differentiated tumor cells are elongated, with the nucleus occupying one pole and secretory granules accumulating at the opposite pole, whereas poorly differentiated cells are generally ovoid or polygonal and lack polarity. The rough endoplasmic reticulum is usually composed of short, dilated profiles with flocculent material; the Golgi bodies are perinuclear, large, and globular; whereas the secretory granules are generally small (250 nm), variable in number, and located close to the cell membrane (3, 6, 10–13).

The pathogenesis of FGAs remains unknown, and research in this area is hampered by their rarity. Kottler et al (14) have demonstrated that whereas the GnRH receptor gene is mainly expressed in functioning rather than in nonfunctioning gonadotroph adenomas, no mutations in its coding region have been identified, supporting the view that this mechanism is not implicated in their pathogenesis. Davis et al (15) have shown that these tumor cells in culture secrete mainly FSH, which is unaffected by coincubation with estradiol, inhibin A, or a combination of both hormones, reflecting the lack of normal negative feedback. Furthermore, they are strongly positive for estrogen receptor-α, Bβ-activin, activin receptor-II, activin receptor-IIB, secretogranin-II and chromogranin-A, suggesting that normal gonadotroph signaling and packing proteins are present in these cells (15).

In a number of reports, it has been confirmed that FGAs produce intact and biologically active FSH with an increased bioactivity to immunoreactivity ratio (16–19); this notion is also supported by cases of women with FGAs with "physiological" levels of FSH, which are nevertheless adequate to cause an ovarian hyperstimulation syndrome that resolved after tumor removal (4, 16, 20–24). Pigny et al (18) performed chromatofocusing analysis of FSH isoforms from a male with a FGA and found that the adenoma was characterized by more basic FSH isoforms; this was in contrast to normal pituitaries and nonclinically active gonadotroph adenomas, in which the major proportions of FSH isoforms were detected at a pH value less than 5.5. It has been proposed that basic isoforms are more active than the acidic ones, at least in vitro, providing a possible explanation for the enhanced serum FSH bioactivity. Finally, the degree of glycosylation of the gonadotropins affects their biological activity, and the secretion of glycosylated variants with increased biological activity cannot be excluded. Despite these observations, the mechanism driving the production and secretion of the gonadotropins responsible for the clinical syndrome seen in FGAs remains unclear.

Presenting Clinical Manifestations, Biochemical and Imaging Data

Premenopausal women

Most published reports involve premenopausal women aged 10–43 years at diagnosis. There are only two cases of adolescent girls (6, 25). The most common presenting clinical manifestations include menstrual irregularity (secondary amenorrhea [8, 9, 22, 25–30], oligomenorrhea [4, 21, 23, 31–38], spontaneous vaginal spotting [8], or severe menorrhagia [20]), infertility (26, 28, 33, 39), galactorrhea (15, 22, 27, 32, 40), and mass effects (mainly headaches and visual deterioration) (8, 32) (Table 1). The ovarian hyperstimulation syndrome may also be present; indeed, the first case related to a histologically confirmed FGA was reported in 1995 by Djerassi et al (27). The FGAs associated with the ovarian hyperstimulation syndrome varied in size from microadenomas to large invasive tumors. The syndrome is usually mild, with the enlarged ovaries increasing abdominal girth and causing pain and discomfort of varying severity due to irritation of the peritoneum (7–9, 16, 20, 22–24, 26–42). Acute abdomen attributed to multiple ovarian cysts causing bilateral adnexal torsion has also been reported (4). Furthermore, severe ovarian hyperstimulation syndrome with fluid shift to the third space and serious complications (ascites and thromboembolism) has been described in one woman with an FGA presenting during gestation (41, 43). Notably, the FGA was diagnosed in two women after exacerbation of ovarian hyperstimulation syndrome during treatment with a GnRH agonist for assisted reproduction (in vitro fertilization) (28, 36) and in two others during pregnancy (in one of these cases the pregnancy was ended at a very early stage due to ovarian hyperstimulation syndrome and in the second one termination of pregnancy was required due to massive thrombophlebitis and severe ovarian hyperstimulation syndrome) (23, 43). Finally, in a small number of cases, the adenoma was found after investigation for recurrence of ovarian cysts (4, 39, 40).

Hyperestrogenism is a predominant biochemical finding (20, 22, 23, 27, 28, 32, 33, 38, 40, 42), and estrogen levels may range from marginally elevated (8, 21, 24, 34, 35, 37) to markedly elevated (7, 9, 20, 29, 30, 31, 33, 39, 42). In a few cases, they have been found to be normal (4, 16, 41) or fluctuating (34, 41). Notably, the ovarian hyperstimulation syndrome has been reported even with marginally increased estrogen levels (7, 35). Serum FSH

Table 1. Summary of Main Presenting Manifestations and Biochemical and Imaging Data in Women, Men, and Children with FGA

Group of Patients	Presenting Manifestations	Biochemical Findings at Presentation	Imaging Findings at Presentation
Women			
Premenopausal	Menstrual irregularities (oligo-/amenorrhea, spotting-menorrhagia), infertility, galactorrhea, mass effects (headaches, visual deterioration), ovarian hyperstimulation syndrome.	Hyperestrogenism (occasionally normal or fluctuating estrogen levels); serum FSH within reference range or mildly elevated; serum LH suppressed or within reference range; serum α-subunit and inhibin normal or elevated.	Pelvic imaging: multiseptated cysts of variable size (often larger than 5 cm) in both ovaries (anechoic on ultrasound and with low T1- and high T2-weighed intensity on MRI). Pituitary MRI: mostly macroadenomas.
Postmenopausal[a]			
Men	Testicular enlargement, hypogonadism, mass effects (headaches, visual deterioration).	Serum FSH elevated; serum LH and T slightly below the reference range, normal, or elevated; serum α-subunit and inhibin normal or elevated; increased sperm count.	Ultrasound of scrotum in cases with testicular enlargement: increased testicular volumes. Pituitary MRI: all (except one) macroadenomas.
Children	Isosexual precocious puberty, mass effects (visual deterioration).	Serum FSH elevated, serum LH low or elevated, estradiol and T (males) elevated.	Pituitary MRI: micro- or macroadenoma.

[a] No clinical syndrome has been demonstrated because the ovaries are depleted of preantral follicles and are insensitive to FSH stimulation. Diagnosis of a FGA in this age group is difficult, particularly given the misinterpretation of gonadotropin increase secondary to the menopause.

levels have been described within the reference range (4, 7, 9, 16, 20–23, 28, 31, 34, 35, 39, 41, 42) or mildly elevated (8, 27, 29, 30, 32, 33, 37–40). Serum LH is usually suppressed, even in cases of FGA showing positive LH immunoreactivity (4, 7, 16, 23, 24, 27, 29, 30, 32–35, 38–41) and, less often, may be within the reference range (9, 20, 22, 42). It has been proposed that the existing pulses of LH allow adequate thecal androstenedione synthesis, thereby providing the substrate for the FSH-induced aromatase activity in the granulosa cells, which finally leads to estrogen secretion. The decreased LH levels may be attributed to the impairment of the function of the normal gonadotrophs by the FGA or by the negative feedback of the high estrogens on LH secretion. Normal (16, 23, 28, 32, 38) or elevated (27, 30, 33, 37, 40) levels of α-subunit and inhibin (9, 20, 22, 27, 32, 37, 39) have been reported. In a small number of cases, increased circulating progesterone (6, 7, 20, 34) and androgens (possibly due to stimulation of thecal cells by LH) have been found (20, 32), whereas hyperprolactinemia is frequent, most likely attributed to a stalk effect or to the hyperestrogenemia (5). TRH testing has shown inconsistent results, with a paradoxical rise in FSH, LH (21, 31–35, 37), and LH α-subunit (27, 30) or with no effect (7, 16, 22, 28, 29, 38).

Pelvic imaging reveals multiseptated cysts of variable size (often larger than 5 cm) in both ovaries (44), which are anechoic on ultrasound and with low T1- and high T2-weighed intensity on magnetic resonance imaging (MRI). The cysts demonstrate a characteristic "soap-bubble" or "wheel-spoke" appearance (6, 33, 39, 45, 46), describing the enlarged follicles arranged peripherally around the ovarian parenchyma with pseudosepta (from normal stroma compressed between the follicles) between the cysts (Figures 1, B and C, and 2, A and B). Interestingly, in two patients the morphology and the size of the ovaries fluctuated during follow-up (32, 34). Endometrial hyperplasia and a small amount of ascites are commonly detected. Histologically, the ovarian cysts are follicular with granulosa cells lining the cystic wall with/or without luteinization (23).

Most of the reported FGAs in premenopausal women are macroadenomas (Figures 1A and 2C), often showing a suprasellar extension, invasion into the cavernous sinus, and distortion of the optic chiasm; microadenomas have also been described (15, 21, 33, 34, 39).

The clinical picture is not usually pathognomonic, and needs to be differentiated from polycystic ovarian syndrome (PCOS), ovarian hyperstimulation syndrome at-

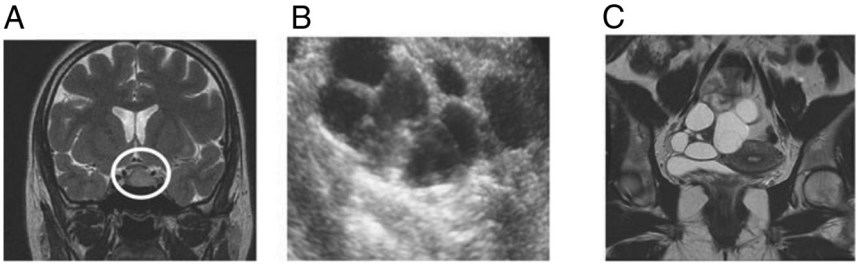

Figure 1. A, Pituitary MRI at diagnosis of a female with FGA and ovarian hyperstimulation syndrome. B, Transvaginal ultrasonography of the right ovary at diagnosis. The ovary is enlarged (130 mm) with multiple cysts (n = 15–20). C, Pelvic MRI confirmed multiple ovarian cysts the larger measuring 53 × 35 mm on the right ovary. [Reproduced from E. Jones et al: A functioning FSH-secreting pituitary macroadenoma causing an ovarian hyperstimulation syndrome with multiple cysts resected and relapsed after leuprolide in a reproductive-aged woman. *Gynecol Endocrinol*. 2012;28:56–59 (37), with permission. © Informa Healthcare.]

tributed to other causes, and ovarian neoplasms. In FGAs, the FSH is usually high or within the reference range, and the LH is usually low (with a consequent increased FSH/LH ratio); although not a consistent finding, in PCOS, LH tends to be high and FSH low (usually decreased FSH/LH ratio). In contrast to PCOS, hyperandrogenism is not a prominent feature of FGA, whereas hyperestrogenism dominates in FGA but not in PCOS. The ultrasonographic appearance of the ovaries in PCOS is that of mildly enlarged polycystic ovaries with cysts rarely exceeding 10 mm, usually subcapsular around an enlarged hyperechogenic central stroma. In females with FGAs, the ovaries are grossly enlarged, with cysts tending to measure at least 15 mm and adjacent to one another with little intervening stroma. Finally, patients with FGAs may show an increase of serum intact FSH, LH, and LH β-subunit in response to exogenous TRH, as well as a paradoxical increase of FSH in response to a GnRH agonist (28, 36). In contrast, in PCOS there is a decrease in gonadotropin secretion in response to a GnRH agonist (47). Ovarian hyperstimulation syndrome is usually an iatrogenic complication of ovulation induction therapies. However, spontaneous ovarian hyperstimulation syndrome has also been rarely seen in normal pregnancies (48, 49), in a case of fetal and placental triploidy (50), in molar pregnancies (51), and in association with PCOS (52). Severe primary hypothyroidism can cause mild ovarian hyperstimulation syndrome (45, 53–63) and may lead to pituitary hyperplasia mimicking a macroadenoma; achievement of euthyroidism leads to a resolution of these manifestations. Interestingly, an exceptional case of ovarian hyperstimulation syndrome due to ectopic secretion of FSH from a carcinoid tumor has been published (64). Granulosa cell tumors usually present during the perimenopausal or early postmenopausal period, may involve one or both ovaries, and show elevated estradiol and inhibin but suppressed gonadotropins. This is in contrast to FGAs, in which FSH is commonly not suppressed and indeed may be elevated. Moreover, on ultrasound, they appear as well-defined, unlobulated solid masses with scattered internal cystic portions or as septated cystic masses with a mean size of 10–15 cm. Hemorrhage is a common and characteristic finding on the MRI (65).

Postmenopausal women

No clinical syndrome has been demonstrated in postmenopausal women because the ovaries are depleted of preantral follicles and are insensitive to FSH stimulation (66). Therefore, the diagnosis of a FGA in this age group is difficult, particularly given the misinterpretation of gonadotropin increase secondary to the menopause (unless the LH levels are extremely low).

Males

FSH hypersecretion by a FGA in males can lead to testicular enlargement due to the trophic effect to the testicles, leading to increased length of the seminiferous tubules (67) (Figure 3 and Table 1). In 1976, Snyder and Sterling (68) reported a 51-year-old man with a FGA causing bitemporal hemianopia and hypopituitarism and a testicular size 7 × 3.5 cm bilaterally. Later, Snyder (69) reviewed 23 men with his-

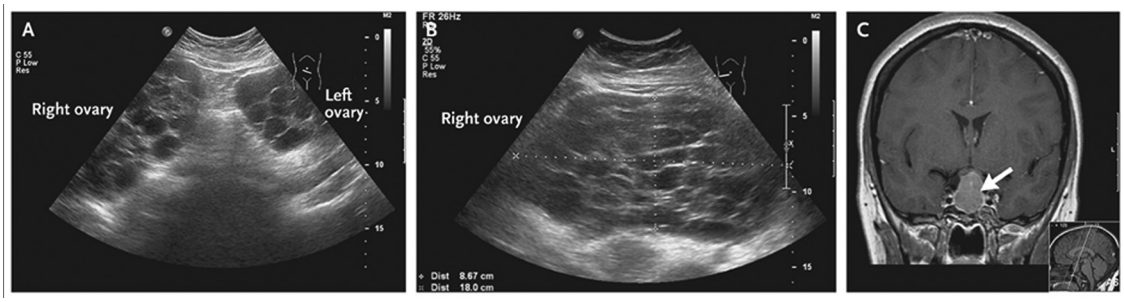

Figure 2. Pelvic ultrasonography in a 21-year-old woman with FGA (A and B) shown on pituitary MRI (C) and ovarian hyperstimulation syndrome. Bilateral enlarged polycystic ovaries are demonstrated. [Reprinted from J. P. van Wijk and E. W. ter Braak: Images in clinical medicine: amenorrhea, abdominal pain, and weight gain. *N Engl J Med*. 2011;365:e39 (44), with permission. © Massachusetts Medical Society.

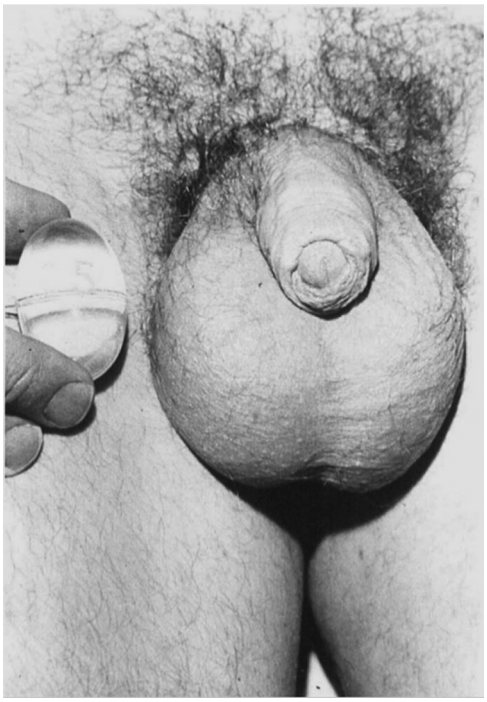

Figure 3. Testicular enlargement in a patient with FGA. Largest ellipsoid of Prader (25 mL) is shown for comparison; mean testicular volume is 108 mL. [Reproduced from D. Heseltine et al: Testicular enlargement and elevated serum inhibin concentrations occur in patients with pituitary macroadenomas secreting follicle stimulating hormone. *Clin Endocrinol (Oxf)*. 1989;31:411–423 (67), with permission. © John Wiley & Sons, Inc.]

tologically confirmed gonadotroph adenomas, in six of which the mean testicular length was 6–7 cm. Heseltine et al (67) reported macro-orchidism due to FGA in four men aged between 41 and 69 years; three of them presented with visual field defects and one with manifestations of hypogonadism. Their mean testicular volume exceeded the normal maximum of 25 mL (39, 37, 70, and 108 mL, respectively). Pigny et al (18) reported a 47-year-old man with testicular volume $>$ 30 mL who presented with visual disturbance, and Dahlqvist et al (70) reported a 56-year-old male with manifestations of hypogonadism and bilaterally enlarged testicles (7×5 cm and 6×4 cm [$>$25 mL]). Finally, Clemente et al (71) presumed that an apparent FSH-secreting microadenoma was stimulating testicular enlargement (30 and 40 mL, respectively) in a 12-year-old boy with pubertal stage G1–2 P2, but because the patient was not operated upon, there was no pathological confirmation. The variability in frequency of testicular enlargement may be attributed to the slow process of the development of this sign, which may escape the patient's attention. Thus, it has been proposed that mild to moderate testicular enlargement may be present, without obvious findings on physical assessment. Furthermore, the production by the FGA of multiple FSH species with variable biological activity on Sertoli cells cannot be excluded. An increased sperm count has been reported in two men with mean testicular lengths of 5.5 and 5 cm, respectively, by Snyder et al (69), and in a 45-year-old male with an invasive gonadotropinoma and testes measuring 3×4 cm by Zárate et al (72). There are also reports of excessive secretion of intact FSH and LH leading to elevated serum T, but distinct clinical manifestations of the high T were not noted (73–75).

FSH levels have been found elevated in all cases (18, 67, 69, 70). LH and T have been reported as slightly below the reference range, normal, or elevated (notably, in these last cases, LH levels have been measured below, within, or above the reference range) (67, 69, 71) and α-subunit and inhibin as normal or high (18, 67–70). The patient with increased spermatogenesis described by Zárate et al (72) had elevated FSH, LH, and T, whereas among the two men with increased spermatogenesis reported by Snyder (69), one had slightly elevated FSH and normal LH and T, and the second had normal levels of FSH, LH, and T and high levels of α-subunit. Finally, a paradoxical response of FSH and LH to the TRH stimulation test has been described (67, 69), although this was not confirmed in other cases (67, 69, 70).

Ultrasound of the scrotum in cases with testicular enlargement has demonstrated increased testicular volumes without cystic or solid masses (67, 70). Detailed data on testicular biopsies have been reported in two patients with elevated FSH levels, revealing increased length of seminiferous tubules, moderate hypospermatogenesis, and normal morphology of Sertoli and Leydig cells (67).

All published cases in adult males involve macroadenomas, some of which had significant suprasellar and parasellar extensions (18, 67, 69, 70, 72). A microadenoma has been described only in an adolescent male (71).

The testicular enlargement secondary to a FGA needs to be differentiated from other causes of increased testicular size including microlithiasis (76, 77), McCune-Albright syndrome (78), congenital testicular cysts (cystic testicular dysplasia), malignant testicular lesions, lymphomas, acute lymphoblastic leukemia (79), infections, aromatase deficiency (80, 81), macro-orchidism related to mental retardation due to fragile X syndrome (82, 83), or X-linked mental retardation (84). In young boys, primary hypothyroidism is associated with gonadal enlargement (85), but this has not been reported in adults. Finally, recently, an X-linked syndrome of central hypothyroidism and testicular enlargement due to novel loss-of-function mutations in the IGSF1 (Ig superfamily member 1) gene has been described (86).

Children

FGAs are extremely rare in childhood, and in the English literature we have identified only a few cases of iso-

sexual precocious puberty (6, 87–89) (Table 1). Di Rocco et al (87) described two girls aged 8.9 and 10.2 years with breast Tanner stage II and V, respectively, at presentation. Both had elevated FSH, LH, and estradiol levels, and imaging confirmed microadenomas. Faggiano et al (88) reported a 4-year-old boy with accelerated somatosexual growth and pubic hair and genitalia of an adult male. This patient also had galactorrhea, episodic ejaculation and visual deterioration, and elevated FSH, LH, T, estradiol, and prolactin levels. Imaging revealed a macroadenoma with suprasellar extension. Tashiro et al (5) described a girl 10 years and 11 months of age who presented with ovarian hyperstimulation syndrome (multicystic ovarian enlargement, abdominal distention, nausea, and menstrual disorders), breast Tanner stage III, and pubic/axillary hair Tanner I. She had elevated FSH and prolactin, low LH, and high estradiol and progesterone. Further investigations revealed a large tumor with suprasellar extension compromising her vision. Ambrosi et al (89) described a 7-year-old boy with Tanner P2, G3, testes measuring 4–5 mL, penis length of 9.5 cm, and visual field defects. His FSH, LH, and T were increased and showed a marked response of LH on GnRH and TRH testing. Pituitary imaging revealed a macroadenoma with suprasellar extension (89).

The differential diagnosis includes other causes of gonadotropin-dependent isosexual precocious puberty. These involve a wide range of pathologies as central nervous system lesions (arachnoid cysts, craniopharyngiomas, ependymomas, germinomas, low-grade gliomas), developmental anomalies (hypothalamic hamartomas, hydrocephalus), post-irradiation, genetic causes (gain-of-function mutations in the *kisspeptin-1* gene, and loss-of-function mutations in the *MKRN3* gene), and primary hypothyroidism (90–93).

Management

Systematic series on the optimal management of FGAs are lacking, and the relevant data rely on case reports or very small case series. Surgical removal of the adenoma remains the optimal approach and, if successful, leads to restoration of normal gonadotropin secretion, resolution of the ovarian hyperstimulation syndrome, reduction in ovarian size, and achievement of regular menstrual cycles in women (4–7, 15, 16, 22, 24, 28, 29, 31–33, 35–39, 41), and to reduction or normalization of FSH and inhibin and to reduction in testicular volume in males (67, 70). Interestingly, cases of premenopausal women presenting with multiple ovarian cysts managed by oophorocystectomy before the diagnosis of FGA was suspected have been described (31, 37), emphasizing the importance of considering this diagnosis before any surgical intervention in the ovaries is attempted. Furthermore, cases of spontaneous and noncomplicated pregnancies after successful surgical removal of the adenoma have been described (7, 4, 23, 28, 29). In children, after successful surgery, gonadotropin secretion returned to the appropriate level for pubertal status pattern, and the early pubertal signs were partially or fully reversed (87–89). Moreover, the paradoxical response of gonadotropins to TRH was lost (31, 35, 37, 89), and their normal responsiveness to GnRH was restored (15, 20, 88). Finally, hypogonadotropic hypogonadism has been described after surgical removal of a FGA (20, 67). The role of adjuvant radiotherapy after partial resection has not been clarified, and long-term follow-up data are not available (5, 6, 20, 72), but radiotherapy has been used in cases of tumor regrowth (8, 27).

Medical treatments with dopamine agonists (DAs), somatostatin analogs, and GnRH agonists and antagonists have been used in a few cases, but they have not been associated with tumor shrinkage, and their use as a primary therapeutic approach is generally not recommended (Table 2). Thus, whereas DAs have reduced FSH levels and improved ovarian hyperstimulation syndrome in a limited number of cases (25, 26, 33, 42), it is generally accepted that they are not beneficial in controlling the tumor itself or the clinical syndrome (9, 16, 20, 22). The combination of cabergoline (2 or 1 mg weekly) with depot medroxy-

Table 2. Available Treatments for FGAs

Mode of treatment	Comments
Surgery ± adjuvant radiotherapy	
Medical treatment	
Dopamine agonists	Females: limited cases with reduction of FSH levels and improvement of ovarian hyperstimulation syndrome but generally no benefit in controlling tumor or clinical syndrome. Males: no benefit.
Somatostatin analogs	Case of female with normalization of estradiol and ovarian volumes but no tumor shrinkage. Case of boy with precocious puberty with no benefit.
GnRH agonists	Females: no benefit and also risk of further stimulation of gonadotropin secretion and increase in tumor size. Males: possibly no clinical benefit.
GnRH antagonists	Cases with inconsistent results.

progesterone (50 mg monthly) in two patients normalized estradiol levels and decreased ovarian volumes within 6 months; FSH and LH ranged within normal limits, but the macroadenoma remained unchanged in one case and increased in the second (42). Treatment with bromocriptine (5 mg daily) for 1 month ameliorated ovarian hyperstimulation syndrome in a woman with a microadenoma who became pregnant, but later this treatment failed despite D2 receptor mRNA expression in the tumor cells (33). In the case of an adolescent girl with an invasive tumor, a short course of cabergoline (1 mg weekly) modestly reduced FSH and estradiol (25). Interestingly, Murata et al (33) reported the case of a woman with a micro-FGA who completed a successful pregnancy on DA offered before the surgical excision of the tumor; FSH and estradiol levels decreased, and during pregnancy the FSH remained within the normal follicular range despite increased estradiol levels, but both ovaries showed enlargement. The patient underwent transsphenoidal surgery 3 years after the delivery and the D2 receptor was found to be expressed in the adenoma cells (33). Cabergoline offered for 1 year in an adolescent boy with a presumed FGA did not prevent further testicular enlargement (71). Bromocriptine (2.5 mg daily) combined with cyproterone acetate (30 mg daily) did not decrease LH hypersecretion or tumor size in a 4-year-old boy with sexual precocity (88).

Long-acting octreotide (30 mg monthly for 2 mo) normalized estradiol levels and ovarian volumes in a woman with recurrent ovarian hyperstimulation syndrome related to a FGA (8). At that time, the tumor was also irradiated, and it had not changed in size 1 year later (8). Injection of sc octreotide (50 μg) did not modify hormone hypersecretion in a boy with precocious puberty attributed to a FGA (89).

Administration of a GnRH analog has either been unsuccessful in reducing estradiol and FSH levels and suppressing ovarian cyst growth (37, 39) or has even further stimulated gonadotropin secretion and exacerbated ovarian hyperstimulation syndrome in women (26, 28, 33, 36, 37, 41, 43). Interestingly, Knoepfelmacher et al (42) reported an increase in tumor size after the addition of GnRH analog for 3 months in a regimen of DA and medroxyprogesterone. The trial of a GnRH analog in an adolescent boy with macro-orchidism reduced only partially FSH and inhibin-B levels and had no effect on testicular size (71). Finally, Zárate et al reported the case of a male presenting with increased gonadotropins, T, and sperm count who had partial removal of a macro-FGA and 1 year after external irradiation was treated by a GnRH analog. Assessment 20 weeks later revealed significant reduction but not normalization of the gonadotropins and the sperm count; the serum T fell to the upper end of the normal limits and computed tomography scan suggested reduction of the suprasellar extension of the tumor. However, the impact of the previous radiotherapy in these changes cannot be excluded (72). Notably, pituitary apoplexy has been reported after the administration of GnRH agonist in a male with a FGA (94); this risk needs to be kept in mind when offering such treatment.

Administration of the GnRH antagonists Nal-Glu-GnRH (5 mg twice daily for 1 mo) and ganirelix (0.25 mg daily for 1 wk) did not suppress gonadotropins or estradiol in two women with FGAs (15, 27), although in another report, ganirelix (0.25 mg daily for 1 month) resulted in undetectable estradiol levels and reduction of ovarian volume (9).

Long-term Outcome

Long-term data on the outcome of patients after surgery combined or not with radiotherapy are very sparse because most published cases do not provide sufficient follow-up information. Based on the available literature, stable tumor appearances or no clinical recurrence have been described in females and males with FGA 2–5 years after surgery, whether or not combined with radiotherapy (4, 5, 29, 42, 67, 70). However, cases of tumor regrowth and of recurrence of the clinical manifestations have been reported in females, necessitating long-term clinical and imaging surveillance. Nevertheless, predictors of recurrence have not been identified. Recurrent tumors have been managed by repeat surgery, radiotherapy, or medical treatment (8, 27, 32). Thus, Djerassi et al (27) reported a case of FGA with multiple recurrences within 8 years that was treated by repeated transsphenoidal surgery and finally radiosurgery; the electron microscopy of the last specimen had shown a wide range of gonadotroph cell differentiation, from well-differentiated large cells to poorly differentiated ones with poorly developed organelles and sparse secretory granules. Karapanou et al (8) described a female diagnosed with regrowth of a FGA around 4 years after partial transsphenoidal removal; she had presented with irregular vaginal spotting and ovarian hyperstimulation syndrome and was offered a somatostatin analog (initially 500 μg octreotide three times daily, followed by long-acting octreotide); 2 months later, the estradiol levels returned to normal, and the ovaries regressed to normal size. At that time, she was also offered conventional radiotherapy for long-term tumor control, and subsequently she underwent hysterectomy and bilateral salpingoophorectomy due to suspicion of malignancy, which was not finally confirmed. The somatostatin analog was discontinued, and 1 year after the operation

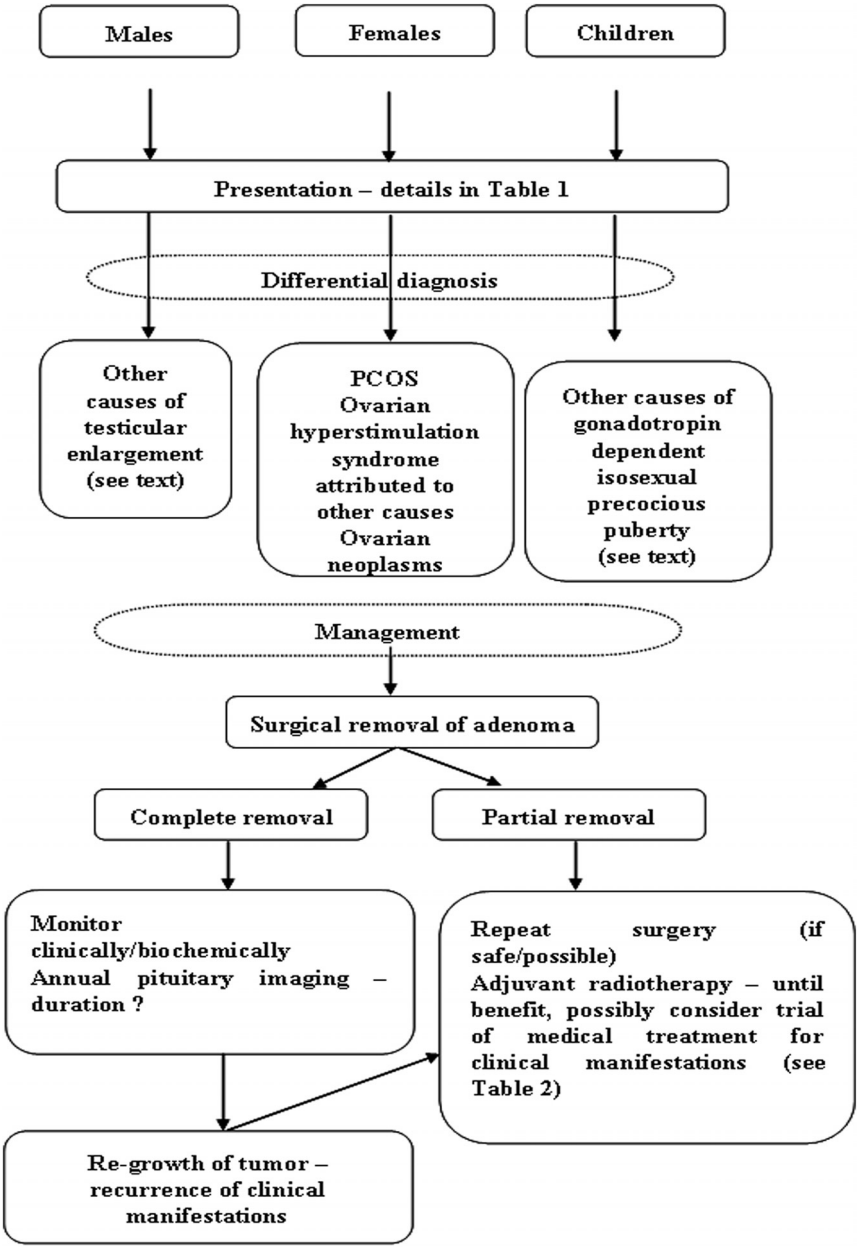

Figure 4. Flow chart with differential diagnosis and management of patients with FGA.

her gonadotropins remained elevated but with no evidence of further tumor growth. Pentz-Vidovíc et al (32) reported a case of a recurrent FGA detected on imaging 6 years after the first operation that, while waiting for a second surgery, developed apoplexy requiring urgent decompression. Finally, Benito et al (30) described a case of multiple endocrine neoplasia type 1 with the FGA being the first manifestation. The tumor showed multiple relapses within around 9 years treated by transsphenoidal surgery and later by radiosurgery. Seven years after the radiotherapy, the patient presented with a temporal lobe metastasis of the gonadotroph tumor, which was removed by craniotomy. The immunocytochemistry of the tumor cells revealed positive nuclear staining for synaptophysin and steroidogenic factor-1, but negative for gonadotropin subunits, indicating that the metastasis was less well differentiated compared with the primary pituitary lesion.

Conclusions

FGAs represent a rare clinical entity causing distinct manifestations (mainly menstrual irregularity and ovarian hyperstimulation syndrome in premenopausal females and adolescent girls, testicular enlargement in males, and isosexual precocious puberty in children). Their pathogenesis remains enigmatic and, based on the limited published literature, they are mostly macroadenomas. Increased awareness is necessary for early diagnosis aiming to avoid unnecessary surgical procedures for ovarian cysts, to ameliorate the sequelae of hormonal hypersecretion, to restore fertility, and to minimize the consequences of the mass effect. Systematic series on the optimal management of FGAs are lacking, but the primary therapy remains surgical excision of the adenoma. Given the risk of recurrence, long-term clinical and imaging follow-up is needed, and radiotherapy may be required. There is little evidence that medical therapies are particularly helpful, certainly in terms of tumor control, and in general their treatment follows that of nonfunctioning pituitary adenomas. Based on the published literature, a flow chart for their diagnosis and management is shown in Figure 4. It may be that central registration of these challenging tumors (including detailed phenotypic, biochemical/hormonal (with particular focus on the bioactivity of the secreted FSH molecules), imaging data, as well as long-term outcomes after various therapeutic interventions) would enhance our insight on their pathology and optimal management.

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