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Clinical characteristics of functioning gonadotroph adenoma in women presenting with ovarian hyperstimulation: Audit of UK pituitary centres

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Abstract

Objective: Functioning gonadotroph adenomas (FGAs) are rare pituitary tumours stimulating ovarian function with potential life-threatening consequences in women. However, a lack of aggregated clinical experience of FGAs impairs management in affected women. The aim of this study is to present the clinical course of FGA-induced ovarian hyperstimulation syndrome (OHSS) cases as identified by some of the largest UK pituitary endocrine tertiary centres with a view to increasing awareness and improving diagnosis and management of women with FGA.

Design: A retrospective observational study; audit of eight UK regional pituitary centres for cases of FGAs.

Setting: Specialist neuroendocrine centres in the United Kingdom.

Patients and Measurements: Women diagnosed with FGA-induced OHSS. Description of their clinical course.

Results: Seven cases of FGA were identified in women, all causing OHSS. Mean age was 33.4 years at diagnosis. Abdominal pain, irregular periods, headache, and visual disturbances were reported at presentation by 100%, 71%, 57% and 43% of women, respectively. Three of seven women underwent ovarian surgery before FGA diagnosis. Six women underwent transsphenoidal surgery (TSS) with incomplete tumour resection in five of those, but all showed improvement or resolution in symptoms and biochemistry postoperatively.

Conclusion: FGA is a rare cause of spontaneous OHSS. TSS improves clinical and biochemical features of ovarian hyperstimulation in FGAs. Improved awareness of FGA will prevent inappropriate emergency ovarian surgery.

KEYWORDS

functioning gonadotroph adenoma, FGA, ovarian hyperstimulation syndrome, OHSS

1 | INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to excess gonadotrophin hormones resulting in morbidity and mortality. OHSS is a recognised complication of assisted reproductive technologies (ART). Additional risk factors include age < 35years, low body mass index (BMI), polycystic ovary syndrome (PCOS) and high serum oestradiol (E2).[1] OHSS is categorised into mild, moderate and severe with a prevalence of 15%–33%, 8%–23% and 0.008%–10% in ART cycles, respectively.[2]

The majority of OHSS cases are associated with ART. However, OHSS may occur with functioning gonadotroph adenomas (FGAs), neuroendocrine tumours with ectopic follicle-stimulating hormone (FSH) secretion, pregnancy or FSH-receptor (FSHR) gain-of-function mutation.[3-6] Gonadotroph adenomas represent the most common pituitary adenoma histologically but are usually clinically nonfunctioning, that is, secrete isoforms of gonadotrophins without the clinical syndrome of gonadal hyperstimulation. Rarely, FGAs secrete active gonadotrophins which stimulate the ovaries causing menstrual irregularities and/or subfertility in premenopausal women.[7]

FGAs are rare; hence data are limited. In this study, we retrospectively reviewed the clinical course of seven women presenting with OHSS with subsequent FGA. This was a UK-wide audit of pituitary centres. We analyse their clinical, biochemical and radiological features with treatment strategies.

2 | METHODOLOGY

Eight high-volume pituitary/endocrine tertiary units within the United Kingdom were contacted to audit records for cases of FGA-induced OHSS; seven patients were identified to date. In all cases, there was no recent exposure to ART or drugs known to induce OHSS. Given the large number of hormonal values, reference ranges of FSH, luteinising hormone (LH) and E2 for each case are provided in Supplementary Table 1.

3 | CASES

3.1 | Case 1

A 37-year-old woman presented to her local emergency department (ED) with severe, intermittent lower abdominal pain, nausea and vomiting. Examination revealed a distended abdomen without palpable masses. Initial investigations showed normal full blood count, biochemistry and C reactive protein, a negative pregnancy test and bilateral adnexa masses on computed tomography (CT) scan. Her past medical history included PCOS, with recent combined oral contraceptive pill (COCP) use. Following COCP discontinuation, she had amenorrhoea for several months followed by oligomenorrhoea. She was referred for a transvaginal ultrasound (TVUS) which showed hyperstimulated ovaries (Figure 1). Hormonal profile revealed FSH: 10.8 U/L, LH: 2.4 U/L and E2: 6992 pmol/L. The case was urgently discussed with the endocrine team requesting a full pituitary profile (Table 1) and subsequently magnetic resonance imaging (MRI) considering elevated E2, unsuppressed FSH, raised prolactin (PRL) and partial hypopituitarism. In the interim, she restarted the COCP for symptom relief without clinical benefit despite E2 reducing to 700 pmol/L, FSH: 6.3 U/L and LH: 1.2 U/L. She self-presented to ED with dyspnoea 1 week later; she was respiratory and haemodynamically stable. A CT-thorax/abdomen revealed a probable haemorrhage on a right adnexal cyst. She was discharged home following analgesia optimisation. The MRI-pituitary revealed a macroadenoma with suprasellar extension and bilateral cavernous sinus involvement (Figure 2). Visual fields assessment showed a left inferior nasal defect. Lanreotide 60 and 90 mg were prescribed on two occasions off-label. Repeat hormonal profile after 6 weeks showed no change. Following a discussion with the pituitary multidisciplinary team (MDT), she underwent transsphenoidal surgery (TSS). Histology confirmed a gonadotroph adenoma with approximately 20% and 30% of cells expressing LH and FSH, respectively. Postoperative MRI showed residual tissue within the left cavernous sinus, whilst serum FSH, LH and E2 had reduced to 0.5 IU/L, <0.1 IU/L and 180 pmol/L, respectively. On follow-up, she was amenorrhoeic with occasional

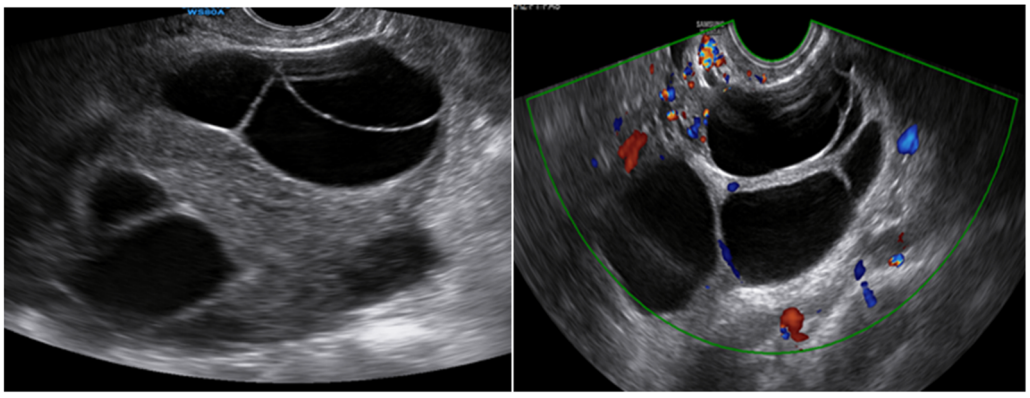

FIGURE 1 Ultrasound pelvis showing 'hyperstimulated' ovaries; right ovary measures 442 mL; left ovary measures 128 mL. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of women presenting with ovarian hyperstimulation syndrome due to a functioning gonadotroph adenoma.

Baseline characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age at diagnosis (years)	37	32	32	16	47	43	27
Ovarian surgery before diagnosis	No	Yes (10 years ago)	Yes (5 years ago)	No	No	No	Yes
Presenting complaint	Abdominal pain	Thyrotoxicosis	Abdominal pain	Abdominal pain	Visual disturbances	Irregular periods/ galactorrhoea	Abdominal pain
Menstrual irregularities	Yes	No	Yes	Yes	On depot progesterone	Yes	Yes
Abdominal pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Headaches	No	Yes	Yes	Yes	Yes	No	No
Visual disturbances	No	Yes	Yes	No	Yes	No	No
Galactorrhoea	No	No	No	Yes	No	Yes	No
Ultrasound findings	Complex multicystic, hyperstimulated ovaries, RO: 442 mL, LO: 128 mL, no ascites	Irregular mass of multiple simple cysts (168 × 146 × 94 mm)	Large semisolid/ cystic mass 14 cm	Bilateral large multiseptated cystic ovarian lesions. Moderate ascites	RO: 27 mL, LO: 33 mL, no ascites	Hypertrophied ovaries; RO: 43 mL, LO: 60 mL, no ascites	NA
Visual field assessment	Left inferior nasal defect	Left inferior homonymous quadrantanopia	Bitemporal hemianopia	Left lower temporal quadrantanopia	Bitemporal hemianopia	Normal	Left superior temporal defect
FSH pre/post-surgery (IU/L)[a]	10.8/3.3	26.7/14	32/6.8	33/11.9	8.3/3.1	26.1/NA	10.4/5.5
LH pre/post-surgery (IU/L)[a]	2.4/1.7	<0.5/0.5	<0.2/4.5	<0.5/0.2	0.8/3.1	<0.5/NA	<0.5/2
E2 pre/post-surgery (pmol/L)[a]	6992/<100–300	5738/800	3551/1535	>18,000/500–2500	2989/<80[b]	1451/NA	962/N/A
TSH (mIU/L) [Ref range]	1.68 [0.3–4.2]	6.18 [0.3–4.2]	4.4 [0.35–5.50]	1.1 [0.35–5]	2.26 [0.4–4.9]	1.89 [0.3–4.5]	0.3 [0.4–5.5]
FT4 (pmol/L) [Ref range]	8.8 [9–23]	44.7 [9–23]	8.2 [7–17]	15.3 [9–21]	8.2 [9–19]	13.5 [10–22]	8 [9–20]
PRL pre/post (mIU/L) [Ref range]	1808/200 [100–500]	387/NA [100–500]	1070/WNL [71–566]	3868/60 [0–630]	3300/370 [109–557]	1353 [100–500]	700/172 [60–620]

(Continues)

TABLE 1 (Continued)

Baseline characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Cortisol (nmol/L) [Ref range]	384 [160–550]	163 [160–550]	479 (WNL)	545 [121–536]	198 [172– 497]	510 [172–497]	143 [180–550]
IGF-1 (nmol/L) [Ref range]	9.9 [10–38]	3.6 [13–50]	7 [9–35]	WNL	14.8 [7.4–25.4]	12.5 [8.1–26.9]	9.4 [14–48]
Medical treatment	Lanreotide (6/52)	Lanreotide (12/52); POP	No	No	No	No	No
Pituitary adenoma size (mm)	41 × 41 × 24	Not available	48 × 27 × 21	36 × 18	27 × 24 × 25	13 × 16	38 × 30
IHC	FSH/LH staining	TSH, FSH	FSH/occasional TSH staining	FSH staining	Mild focal LH expression	Not available	Patchy staining LH/FSH
Ki67%	3%–4%	3%	<3%	Not given	<2%	Not given	3%–5%
Surgical cure	No	No	No	No	Indeterminate	No surgery yet	No
Other therapy	Due for radiotherapy	Radiotherapy	Surveillance	Plans for completion surgery	Surveillance	N/A	TSS × 5, radiotherapy × 2
Restoration of menses	One period	On POP (spotting)	Oligome-norrhoea	Yes	Oligome-norrhoea	N/A	Yes
Pregnancy	No	No	No	No	No	No	Yes (post first TSS)
Follow-up since diagnosis	1 year	5 years	7 years	2 years	<1 year	3 years	23 years

Abbreviations: E2, oestrogen; FSH, follicle-stimulating hormone; FT4, free thyroxine; IGF-1, insulin-like growth factor; IHC, immunohistochemistry; LH, luteinising hormone; LO, left ovary; NA, not available/applicable; POP, progesterone-only pill; PRL, prolactin; RO, right ovary; TSH, thyroid-stimulating hormone; TSS, transsphenoidal surgery; WNL, within normal limits.

[a]Supplementary Table 1 contains reference ranges of FSH, LH and E2.

[b]On depot progesterone.

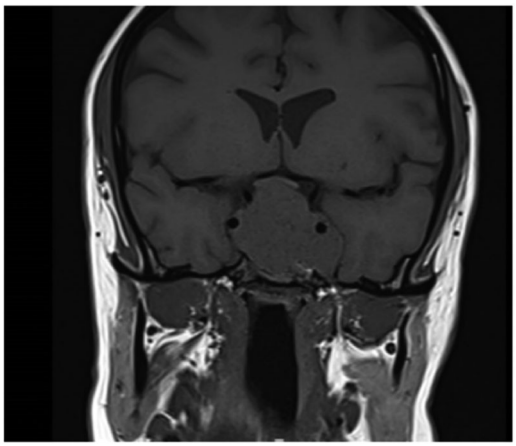

FIGURE 2 Magnetic resonance imaging pituitary, coronal view, pre-contrast. A 41 × 41 × 24 mm macroadenoma with suprasellar extension, bilateral cavernous sinus involvement and compression of the optic chiasm.

light spotting. Repeat TVUS showed smaller ovaries with normal morphology (right ovary: 56.8 mL, left ovary: 12.3 mL). FSH increased to 6.4 IU/L, PRL normalised and E2 ranged from <100 to 600 pmol/L over 9 months. She is under clinical follow-up with radiotherapy discussion and consideration of in vitro fertilisation. A 9-month postoperative MRI-pituitary showed stable appearances.

3.2 | Case 2

A 32-year-old nulliparous woman presented with thyrotoxicosis (TSH: 6.18 mIU/L, FT4: 44.7 pmol/L) and intermittent abdominal cramps with no menstrual cycle changes (FSH: 26.7 IU/L, LH < 0.5 IU/L, E2: 5738 pmol/L). (Remaining pituitary profile in Table 1.) She had a suboptimal response to short synacthen test (SST) and initiated hydrocortisone therapy. TVUS reported an irregular mass of multiple cysts (168 × 146 × 94 mm) superiorly to the uterus. She had undergone bilateral ovarian surgery for ovarian cysts 10 years prior; we cannot exclude ovarian hyperstimulation as a cause. MRI-pituitary revealed a large pituitary macroadenoma with suprasellar extension infiltrating the right cavernous sinus and foramen ovale. Visual field examination revealed left inferior homonymous quadrantanopia. The clinical features were suggestive for a TSH- and FSH-secreting pituitary adenoma. Debulking TSS followed by radiotherapy was proposed by the MDT with carbimazole, monthly lanreotide and progestogen contraceptive pill in the interim. However, surgery was delayed due to challenges including difficulty controlling her thyrotoxicosis, long waiting lists, and the patient being abroad. During the 6-month preoperative period, she developed nausea, worsening visual disturbances and headaches. Three months after lanreotide 90 mg treatment, repeat MRI-pituitary showed no adenoma size change, but evidence of new small foci of haemorrhage within the lesion. FT4 had normalised with TSH remaining elevated. TVUS showed stable appearances. TSS was performed but with incomplete tumour resection. Histology confirmed the high clinical suspicion of a cosecreting adenoma. Postoperatively, she continued the same agents; serum FSH ranged 10–20 IU/L, E2: 700–1100 pmol/L and TSH/FT4 normalised. Her headaches and vision improved. She received 28 fractions of intensity-modulated-radiotherapy (50.4 Gy). Overall, there was a reduction in serum FSH and E2 (mid 40 s to 8 IU/mL and 5000–404 pmol/L, respectively). On the progesterone-only pill, she reported spotting. Ovarian size mildly reduced compared to initial TVUS, yet the 'hyperstimulated' appearance persisted. She developed hypothyroidism requiring carbimazole cessation and levothyroxine replacement therapy, but subsequently developed thyrotoxicosis. The latter coincided with lanreotide treatment cessation for almost a year due to the SARS-CoV-2 pandemic's impact on clinics. FSH and E2 increased (FSH: 15–22 IU/L, E2: 1200–1800 pmol/L). She has recommenced lanreotide 90 mg monthly with regular thyroid and gonadal axis monitoring. It has proven difficult to normalise her thyroid function tests (TFTs) ranging from hyper- to hypothyroidism, and either treated with carbimazole or levothyroxine, respectively, along with monthly lanreotide. She is due to start a 'block and replace' regimen. Her vision remains stable.

3.3 | Case 3

A 27-year-old woman presented with acute abdominal pain, nausea, vomiting and fevers. She had a distended abdomen with a palpable mass. She had a history of PCOS and menorrhagia for which the COCP was offered but declined. The pregnancy test was negative. Blood results showed neutrophilia, mild anaemia (11.1 g/L) and hypoalbuminaemia (34 g/L). US-abdomen showed a large semisolid/cystic mass extending from the uterine fundus to the xiphisternum measuring 14 cm transversely. She underwent a right oophorectomy for a twisted gangrenous ovarian cyst (18 × 12 cm) and left ovarian cystectomy for a cyst (10 × 9 cm). Histology showed multiple simple cysts without a residual cyst lining and extensive haemorrhagic infarction on the right ovary. The specimen from the left ovary contained multiple, benign, follicular cysts with oedematous intervening stroma. A year later, she was re-referred to gynaecology services with menorrhagia. TVUS showed a multicystic left ovary. She was prescribed the COCP and tranexamic acid and discharged from the clinic following symptomatic control. Four years later, she presented with acute abdominal pain and was found to have a multicystic left ovary on US (largest cyst measuring 4 cm). Endocrine investigations undertaken for the first time demonstrated FSH: 32 IU/L, LH < 0.2 IU/L, E2: 3551 pmol/L, PRL: 1070 mIU/L, normal TFTs/9am-cortisol, and low insulin-like growth factor (IGF)-1. MRI-pituitary revealed a macroadenoma (Figure 3). On further questioning, she reported headaches and restricted vision; visual fields assessment showed bitemporal hemianopia. She underwent TSS. An immediate improvement in her headaches, vision and endocrine profile (FSH: 6.8 IU/L, LH: 4.5 IU/L, E2: 48 pmol/L, normal PRL, TFTs, IGF-1) occurred postoperatively but she developed oligomenorrhoea. Postoperative MRI-pituitary showed residual tumour measuring

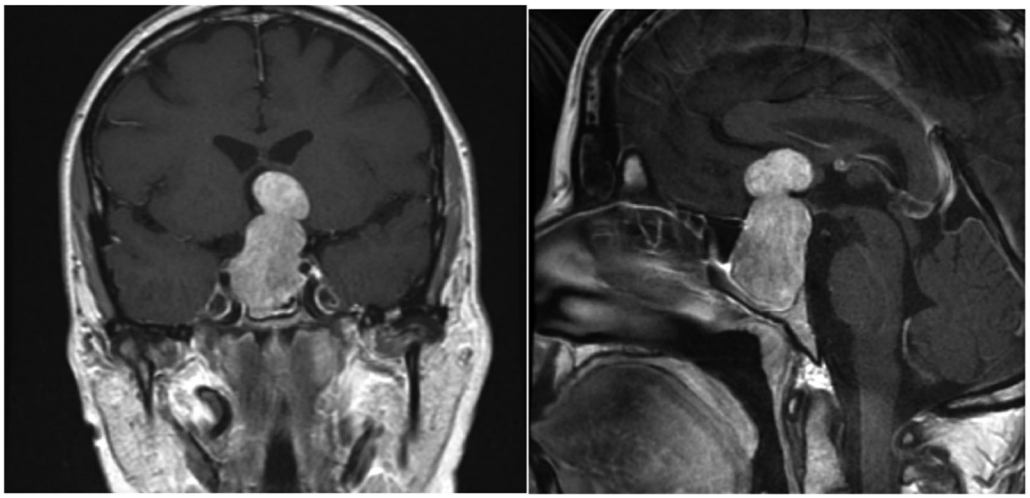

FIGURE 3 Magnetic resonance imaging pituitary coronal and sagittal planes: a 48 mm × 27 mm × 21 mm lobulated, well-circumscribed, heterogeneously enhancing extra-axial mass centred on the pituitary fossa with significant extension into the suprasellar cistern and interhemispheric fissure closely applied to the adjacent Circle of Willis vessels and bowing the chiasm significantly.

14 × 18 mm. Histology confirmed a pituitary adenoma staining positive for FSH, and occasional LH and TSH cells with Ki67 < 3%. She continued radiological surveillance with consideration of transcranial surgery or stereotactic radiosurgery in the event of regrowth. The residual tumour did not change over the following 6 years. Her last endocrine assessment showed FSH: 8.3 IU/L, LH < 0.5 IU/L, E2: 1535 pmol/L with remaining pituitary hormones within range. No data on menstrual history or endometrial thickness were available. She moved out of area and no further follow-up data are available.

3.4 | Case 4

A 15-year-old girl presented to primary care with abdominal pain and bloating. She denied nausea, vomiting or change in bowel habits, but reported new worsening headaches without visual disturbances. She had a low BMI (17–18 kg/m^2), with restrictive eating behaviours exacerbated by school exams. She was diagnosed with irritable bowel syndrome. Nine months later, she sought medical advice for menstrual irregularities (menorrhagia lasting 5 weeks followed by amenorrhoea) and galactorrhoea. Investigations revealed raised FSH, E2, PRL and suppressed LH (Table 1) prompting gynaecology and endocrinology referrals. Her menarche was at the age of 14, but menstrual cycles were irregular. Repeat hormonal profile was similar. TFTs and 9am-cortisol was normal. Clinical examination revealed a distended abdomen with two palpable masses. The pregnancy test was negative. Visual field assessment showed left lower temporal quadrantanopia. MRI-pelvis demonstrated bilateral large multi-septated cystic ovarian lesions and moderate pelvic ascites (Figure 4A,B). MRI-pituitary showed a 36 × 18 mm macroadenoma (Figure 4C). She underwent TSS. Histology demonstrated an FSH-immunopositive adenoma. Postoperatively, FSH and E2 fell to 5.8 U/L and 1000 pmol/L, respectively, over 1 week. PRL normalised. Repeat MRI-pituitary showed residual tissue, and she had unchanged visual fields. Restoration of her menstrual cycles occurred, but with persistent abdominal distention. US-pelvis showed enlarged ovaries containing multiple follicles of varying sizes (right ovary: 64 mL, left ovary: 71 mL). Her sex-hormonal profile was as follows: FSH: 9.9–16.4 U/L, LH: 0.2 U/L, E2: 700–2500 pmol/L. MRI-pituitary showed increased tumour size with visual field deterioration; repeat TSS has been scheduled.

3.5 | Case 5

A 47-year-old woman presented with a 3-month history of visual disturbances. Ophthalmological assessment showed bitemporal hemianopia. MRI-pituitary revealed a macroadenoma measuring 27.5 × 24.6 × 25.6 mm compressing the optic chiasm. Hormonal profile is summarised in Table 1. She also reported headaches and lower abdominal pain. Due to depot progestogen injection, her menstrual cycles could not be assessed. A TVUS revealed hyperstimulated ovaries (right ovary: 27 mL, left ovary: 33 mL) without ascites. She underwent TSS and histology confirmed a gonadotroph adenoma. Three-month postoperative MRI-pituitary was suggestive of a probable small residual tumour, however, the pituitary MDT concluded this may be postoperative changes. She continues clinical follow-up and is no longer on depot progestogen; she had two menstrual periods over the past 5 months. Repeat TVUS showed normal ovaries.

3.6 | Case 6

A 43-year-old woman presented to primary care with galactorrhoea and irregular periods. Investigations showed raised PRL (1353 mU/L) prompting an endocrinology referral. Her remaining pituitary profile

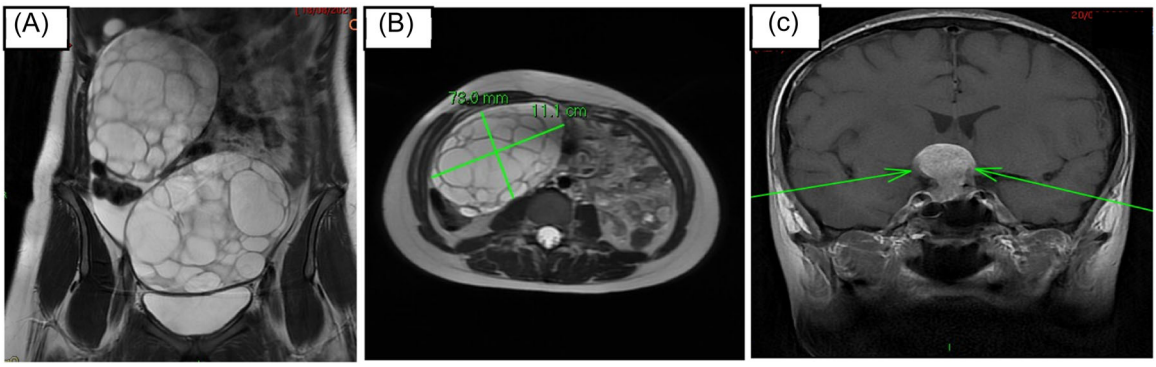

FIGURE 4 (A, B) Magnetic resonance imaging (MRI) pelvis, coronal and axial view: Bilateral circumscribed thin walled multiseptated cystic masses arising from the pelvis and extending into the abdomen. The right measures 13 × 11 × 7.3 cm, the left 13 × 12 × 8 cm. (C) Coronal view MRI pituitary: a 36 × 18 mm mass arising from the pituitary, with significant suprasellar extension. [Color figure can be viewed at wileyonlinelibrary.com]

demonstrated FSH: 26 IU/L, LH < 0.5 IU/L and slightly raised E2: 1451 pmol/L, normal TFTs, IGF-1 and optimal SST response (Table 1). Pituitary-MRI revealed a sellar mass lesion without optic chiasm compression. Ophthalmological assessment was normal. TVUS showed enlarged ovaries (right: 43 mL, left: 60 mL) with multiple large follicles and no ascites. A clinical diagnosis of FGA was made. TSS was discussed but she declined, opting for monitoring. A 10-week follow-up TVUS showed a normal-sized right ovary and reduction of left ovarian size, although still enlarged. During her follow-up, her menstrual cycle changed from frequent periods to oligomenorrhoea, and eventually amenorrhoea. She reported hot flushes and intermittent abdominal pain. Repeat TVUS demonstrated a markedly enlarged left ovary (110 mL), a smaller right ovary (25 mL) both containing multiple follicles. The pituitary macroadenoma was stable on repeat imaging. Surgery was offered again in view of her symptoms, and she accepted.

3.7 | Case 7

This case highlights the course of a 50-year-old woman who first presented to ED aged 25 with acute abdominal pain. She underwent emergency laparotomy; an enlarged (10 × 7cm) right ovary with numerous thick wall cysts and 360° torsion and a 5 cm multicystic left ovary were identified. A right oophorectomy and left cystectomy were performed. A one-week postoperative US showed a normal-sized left ovary. Over subsequent years, she experienced irregular periods and the ovary continued to enlarge on imaging. Her hormonal profile showed FSH: 16.3, LH: 6.8 and E2: 962 (units and reference range not provided). She was prescribed clomiphene for fertility, although there is no information on its effectiveness. Twenty months later she developed visual disturbances and headaches prompting an ophthalmological referral; the assessment found bitemporal hemianopia. MRI-pituitary revealed a large pituitary tumour and thus she was referred to endocrinology. On further questioning, she reported postural hypotension and intermittent abdominal pain. Her hormonal profile is shown in Table 1. She was diagnosed with FGA. She underwent TSS and despite a large postoperative residual mass, there was an improvement in her menstrual cycle, vision and hormones (FSH: 5.5 IU/L, LH: 2 IU/L, PRL: 172 mU/L, E2 not available). While awaiting radiotherapy, she conceived naturally. During her pregnancy, she reported worsening headaches. A small increase of the residual tumour without compromising the optic chiasm was seen on MRI. She continued the pregnancy to term. She underwent a second TSS 4 months postdelivery followed by radiotherapy. Sixteen years after her original surgery, she required a third TSS for FGA enlargement extending into the maxillary sinuses followed by a repeat TSS for significant nasal sinus residuum and plausible trigeminal neuralgia 3 years later. MRI-pituitary demonstrated further tumour growth 2 years later, thus requiring a fifth TSS and radiotherapy. Histopathological samples stained positive for FSH and LH, with a Ki67 of 3%–5%.

In summary, this patient required five TSSs and two radiotherapy courses over a 25-year period. She remains under clinical follow-up. The recent MRI-pituitary describes stable residual disease in the cavernous sinuses with extension through the foramen ovale.

Table 1 summarises the clinical characteristics of the seven women included in this study.

4 | DISCUSSION

Gonadotroph adenomas comprise 40%–60% of all clinically non-functioning pituitary adenomas (NFPA) on immunohistochemistry.[8] FGAs are rare but their incidence remains unknown.[7] Their clinical picture is sex- and age-specific due to the effect of biologically active gonadotrophins on the gonads as well as mass effect symptoms of the local tumour. Menstrual dysregulation, infertility and OHSS are recognised in premenopausal women. FGAs in the paediatric population mainly manifest as isosexual precocious puberty and OHSS, although limited cases have been published in this cohort.[9–11] Compressive symptoms including visual field defects and headaches are seen across all patient groups, presumably due to late

presentation and/or diagnostic delay. The pathophysiology of FGAs is not fully understood. FSH drives folliculogenesis and oestrogen production, which suppresses LH and stimulates PRL. Kisspeptin is a hypothalamic neuropeptide required for endogenous pulsatile secretion of gonadotrophin-releasing hormone (GnRH) necessary for gonadotrophin secretion.[12,13] There is limited research on the direct pituitary effects of kisspeptin, but it has recently been speculated that kisspeptin produced by pituitary adenomas may stimulate secretion of FSH and LH as evidenced by its messenger RNA (mRNA) expression on FGA tissue.[14] However, there are no data on protein expression, therefore this should be interpreted cautiously. Additionally, the presumed increase in Kiss1-mRNA may be the result of the increased E2 levels rather than the driver of gonadotrophin secretion by the FGA as seen in an animal model where KiSS-1 gene expression in gonadotrophs was upregulated in the presence of oestradiol treatment.[15] The GnRH-receptor gene has been reported to be preferentially expressed in women with FGAs over non-FGAs.[16] Activating mutations in the FSHR have also been associated with OHSS, evidenced in cases with spontaneous OHSS (gestational and nongestational),[5,17–19] but not FGAs. Mutant receptors can have broadened specificity with increased sensitivity to hCG inducing massive luteinisation of the ovaries and over secretion of vasoactive mediators responsible for spontaneous OHSS associated with pregnancy.[20] In vitro studies confirmed that FGA cells oversecrete FSH in the presence of oestradiol and inhibin-A, despite maintaining oestrogen receptor-a and activin receptors.[21]

In this study, women had a mean age of 33.4 years (range: 16–47 years) at diagnosis, similar to previous reports.[14,22] The reproductive hormonal profile of FGAs may vary; however, serum FSH is mostly higher than LH. A proposed categorisation for FGAs is according to the dominant secreted gonadotrophin, which correlates with the clinical presentation.[14] For example, OHSS is not seen in LH-predominant FGAs, although only five cases have been described. Despite this, immunohistochemistry of FGAs does not correlate with serum gonadotrophin levels. A literature review of 12 FGA cases observed staining for both LH and FSH, LH only, and FSH only, in seven, four and one women, respectively[14]; however, this had no significant correlation with serum FSH or E2. In our series, a biochemical signature of elevated FSH, E2 and PRL, but suppressed LH, was observed in most cases. Specifically, preoperative LH was below the detection limit of the assay in five of seven women, and low to normal of the reference range in the remaining two women. Serum FSH ranged from 8 to 33 IU/L and was higher than LH in all cases. E2 and PRL were above the reference range in all, but one woman studied. Furthermore, most women had other pituitary hormone deficiencies. Rarely, FGAs cosecrete other pituitary hormones such as TSH and PRL.[22] Case 2 from our series presented with overt thyrotoxicosis, and subsequent immunohistochemistry was positive for TSH staining. Case 3 had evidence of scattered TSH staining without clinical sequelae. Serum PRL can be elevated but this is likely due to stalk compression and/or hyperestrogenemia.

Thirty-seven percent of 171 NFPA-diagnosed tumours stained for gonadotrophins, but few presented with OHSS.[23] Similarly, a recent case series of 12 women with FGAs reported that four cases had been initially misdiagnosed as NFPA.[14] Furthermore, in a systematic review by Hasewaga et al., approximately half of the women had undergone pelvic surgery before resection of the adenoma.[22] With the exception of adnexal torsion, ovarian surgery could have been avoided if FGA was promptly diagnosed. Unnecessary ovarian surgery in young women may not only affect fertility, but have widespread implications including adverse cardiovascular and neurodegenerative outcomes due to oestrogen deficiency.[24–26] In our series, two women required surgery for ovarian torsion and torted gangrenous ovarian cyst. Additionally, one woman had a history of bilateral cystectomies 10 years before diagnosis. Case 3 had evidence of multiple follicular cysts with oedematous stroma and superimposed infarction of the right ovary on histopathology. Other conditions such as PCOS (although smaller follicle size), OHSS of other aetiology and ovarian neoplasms might have a similar clinical picture to FGA-induced OHSS. Mucinous neoplasms that can manifest as large multiloculated cystic masses should be considered in premenopausal women.[27] Cases 3 and 7 were only reviewed in the endocrine clinic 5 years and 20 months, respectively, following initial presentation, highlighting the delays of women with FGA-induced OHSS in reaching diagnosis and specialist endocrinological review.

The women in our series had differing clinical pictures at diagnosis, with abdominal pain being a common symptom. Two women presented acutely, with the remaining five reported intermittent pain. Our study suggests that other common symptoms of FGA are related to pituitary mass effect (headaches, visual disturbances), menstrual disturbance, OHSS (bloating, nausea, vomiting) and hyperprolactinaemia (galactorrhoea). Wang et al reported similar rates of menstrual dysregulation (86.7%), bloating (46.7%) and galactorrhoea (32.3%) in their case series.[14] However, they found fewer women complained of compressive effects of FGAs, namely headaches (23.1%) and visual disturbances (26.2%) compared to our series.[14]

MRI-pituitary revealed macroadenomas in all our patients, which corresponds with published data indicating that 89% FGA are macroadenomas.[14] Total tumour resection has been reported as 25%–78% cases previously[14,22]; five of our six cases had partial tumour resection due to local infiltration, whilst one case remains indeterminate at this stage.

Surgical resection is the mainstay of treatment of FGAs, with normalisation of FSH levels and biochemical remission achieved.[22] There are limited published data regarding medical therapies, with disappointing efficacy rates.[22] Dopamine agonists, somatostatin analogues and GnRH agonists/antagonists have been trialled with conflicting results.[22] Additionally, GnRH agonists may exacerbate the symptoms of OHSS. Increasing levels of E2/FSH and further cyst enlargement has been documented in previous reports.[14,28,29] Tumour size increase has also been reported.[22,30] GnRH agonists are known to cause ovarian cysts.[31] In our study, two of the seven women were treated with the monthly somatostatin analogue

lanreotide for 6 and 12 weeks, however, no clinical or biochemical improvement was noted. The expression of somatostatin receptors (SSTRs) types 2 and 3 have been described in gonadotroph adenomas[32] but this does not translate into efficacy of treatment, probably because of the low levels of SSRT2 expression.

There is a paucity of follow-up data on FGA-induced OHSS, owing to the rarity of cases. A recent literature review reported a mean postoperative follow-up of 25 months which may not be sufficient to see data on pregnancy status.[22] Furthermore, our data show that FGA may recur many years after initial presentation. Previous reports suggest that only a minority of cases achieve normalisation of serum FSH and E2, but postoperative ovarian size normalised in almost all patients, and most women are able to conceive naturally.[22] Long-term follow-up is required to clarify the natural history and management of FGAs. The small number of cases prevents prediction for future pregnancy after FGA. Additionally, due to the retrospective analysis, data may be missing and the clinical picture may be incomplete. FGAs with mild symptoms may be classified as NFPAs.

5 | CONCLUSION

FGAs are a rare cause of spontaneous OHSS posing diagnostic and therapeutic challenges. Outside an ART setting, enlarged ovaries containing multiple large follicles should prompt urgently biochemical assessment of the pituitary gland. Elevated serum E2 and unsuppressed normal/high FSH should subsequently prompt pituitary imaging. Increased awareness of FGAs may allow timely diagnosis which is crucial in avoiding unnecessary ovarian surgery. Further research is needed to understand the pathophysiology of FGAs and explore further management options. Surgical excision remains the mainstay of treatment, and prolonged follow-up is recommended due to their potentially aggressive nature and risk of recurrence.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data available on request from the author.

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