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Case Report

Safe Continuation of Pegvisomant During Pregnancy in a Patient With Fibrous Dysplasia/McCune-Albright Syndrome

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Abstract

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare genetic disorder resulting from a postzygotic activating mutation of the *GNAS* gene, leading to mosaic activation of the G_s protein. FD/MAS encompasses skeletal and extraskeletal manifestations, including GH excess. Medical management of GH excess in FD/MAS can be complex, especially during pregnancy, due to limited safety data on pharmacotherapy. We describe a 31-year-old female with FD/MAS who continued pegvisomant for a GH and prolactin cosecreting pituitary adenoma during her pregnancy to minimize the risk of GH-induced craniofacial fibrous dysplasia progression and consequent visual loss. She had an uncomplicated pregnancy with delivery of a healthy baby girl at term. This case demonstrates safe and efficacious use of pegvisomant in managing GH excess during pregnancy and is the first report in an individual with FD/MAS, underscoring its potential role in similar cases.

Key Words: McCune-Albright syndrome, acromegaly, pegvisomant, pregnancy

Introduction

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare genetic disorder due to a postzygotic gain-of-function mutation of the *GNAS* gene, leading to mosaic activation of the α subunit of the G_s protein [1, 2]. FD/MAS encompasses a wide spectrum of manifestations, often categorized as either skeletal or extraskeletal. According to the 2019 consensus statement by the FD/MAS international consortium, McCune-Albright syndrome (MAS) is defined as either (1) fibrous dysplasia (FD) of the bone with one or more extraskeletal features or (2) 2 or more extraskeletal features including café-au-lait skin macules, hyperfunctioning endocrinopathies (gonadotrophin-independent precocious puberty, nonautoimmune hyperthyroidism, GH excess, or neonatal adrenal hypercortisolism) and intramuscular myxomas [1]. Another notable feature is fibroblast growth factor-23 mediated hypophosphatemia, which is regarded as a marker of FD severity.

Case reports and small series highlight that fertility is impaired in FD/MAS predominantly in patients with anovulatory cycles due to autonomous ovarian activity. However, successful pregnancy is often achievable with no negative effect on skeletal disease [2-4]. However, challenges arise from the complexities of managing endocrinopathies during pregnancy. In particular, decisions around pharmacotherapy for GH excess are challenging. There are limited safety data for the use of medications to control GH excess during pregnancy [5, 6]. However, if therapy is stopped, elevated GH levels can exacerbate FD, particularly in the craniofacial region, potentially leading to serious complications [2, 3, 7-9].

We report the case of a pregnant female with FD/MAS in whom pegvisomant was safely continued, resulting in an uncomplicated pregnancy and no adverse maternofetal outcomes.

Case Presentation

A 31-year-old female presented to the obstetrics-endocrine clinic at 14 weeks' gestation of her first pregnancy. She had a history of MAS requiring ongoing treatment with pegvisomant. The pregnancy followed planned intrauterine insemination, necessitated by her husband's low sperm count.

She first presented at age 26 years with an 8-month history of oligomenorrhea but no galactorrhea. There was no history of precocious puberty with regular menstrual cycles following menarche at age 14 years and thelarche at age 12 years. However, on examination there was evidence of expansion of the mandible. She had no bony pain, skin lesions, or clinical features of acromegaly. She had right eye proptosis with 4 mm inferior dystopia. There was evidence of a relative afferent pupillary defect but no diplopia. Investigations revealed hypogonadotropic hypogonadism [mid-cycle estradiol 27.5 pg/mL (International System of Unit [SI]: 101 pmol/L) [reference range, 40.0-408.6 pg/mL (SI: 150.0-1500.0 pmol/L)], LH 4.7 mIU/mL (SI: 4.7 IU/L) [reference range, 15.0-100.0 mIU/mL (SI: 15.0-100.0 IU/L)], FSH 9.2 mIU/mL (SI: 9.2 IU/L)

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[reference range, 4.0-22.5 mIU/mL (SI: 4.0-22.5 IU/L)], hyperprolactinemia [5167.0 mIU/L (SI: 242.7 µg/L)] [reference range, 8.0-500.0 mIU/L (SI: 4.0-23.5 µg/L)], and an elevated IGF-1 [749.6 ng/mL (SI: 98.0 nmol/L)] [reference range 197.0-351.8 ng/mL (SI: 14.0-46.0 nmol/L)]. She had a normal morning cortisol [12.5 µg/dL (SI: 346.0 nmol/L)] [reference range, 6.2-18.1 µg/dL (SI: 170.0-500.0 nmol/L)] and thyroid function tests [TSH 2.5 mIU/L (reference range, 0.5-4.0 mIU/L); free T4 1.0 ng/dL (SI: 13.4 pmol/L)] [reference range, 0.7-1.5 ng/dL (SI 9.0-19.0 pmol/L)]. Cortisol level after 1 mg dexamethasone suppression test was 0.4 µg/dL (SI: 11.0 nmol/L) [normal response if <1.81 µg/dL (SI: < 50.0 nmol/L)]. A 75 g oral glucose tolerance test demonstrated a lack of GH suppression with a nadir GH of 4.3 ng/mL (SI: 4.3 µg/L). She had isolated elevation of alkaline phosphatase (ALP) level of 149 IU/L (reference range, 20-105 IU/L) while phosphate concentration was normal.

Magnetic resonance imaging (MRI) demonstrated a 10.6 × 5.4 × 8.6 mm T1-hypoenhancing lesion in the left anterior pituitary consistent with an adenoma and a 4 mm Rathke cleft cyst; there was no suprasellar extension (Fig. 1A and 1B). The pituitary gland was otherwise prominent, measuring 8 × 10 × 18 mm, but midline with an intact posterior pituitary bright spot. There was extensive craniofacial fibrous dysplasia involving the right frontal, sphenoid, and mandibular bones, causing obliteration of the right sphenoid sinus, narrowing of the superior orbital fissure, and optic nerve compression within the right optic canal. A subsequent bone scan identified polyostotic fibrous dysplasia with expansion and hyperemia involving the right medial orbit (thought to be the sphenoid bone) and skull base, right mandible, and left superior rib (Fig. 2A and 2B). Formal ophthalmology assessment showed a right temporal scotoma and axial proptosis due to optic nerve compression. Optical coherence tomography showed global thinning of the retinal nerve fiber layer (75 µm) in the right eye. There was pallor of the right optic disc, but the macula was normal. Based on the clinical and investigation findings, a diagnosis of MAS was made.

Cabergoline was initiated and uptitrated to 1 mg twice weekly, leading to normalization of prolactin concentrations. However, there was no change in IGF-1 concentration. Lanreotide was started as local guidelines mandate somatostatin analogue therapy before pegvisomant can be accessed. IGF-1 initially reduced to 489.5 ng/mL (SI: 64.0 nmol/L) but subsequently increased to 696.0 ng/mL (SI: 91.0 nmol/L) despite dose escalation to 120 mg every 28 days. Lanreotide was ceased and pegvisomant was started, achieving IGF-1 normalization at a dose of 20 mg daily (Fig. 3). Treatment was associated with a gradual improvement in visual fields without requiring decompressive surgery. The degree of right eye proptosis, inferior dystopia, and pallor of optic disc remained unchanged. Aside from a stable isolated elevation of ALP (120-160 IU/L), liver function tests were within normal limits. Annual MRIs showed stable fibrous dysplasia and a slight reduction in pituitary adenoma size.

The patient ceased taking the combined oral contraceptive pill when pregnancy was desired, 2 years following cabergoline commencement with regular 28-day menstrual cycles established shortly thereafter. Investigations during the luteal phase of menstrual cycle showed estradiol 144.9 pg/mL (SI: 532 pmol/L), LH 4.2 mIU/mL (SI: 4.2 IU/L), FSH 2.7 mIU/mL (SI: 2.7 IU/L), and progesterone 11.2 ng/mL (SI: 35.7 nmol/L) [reference range, 1.6-23.6 ng/mL (SI: 5.0-75.0 nmol/L)], consistent with spontaneous ovulation. Cabergoline was discontinued when pregnancy was achieved, while pegvisomant was continued. Preconception IGF-1 concentration was 282.4 ng/mL (SI: 37 nmol/L), and prolactin was 317.0 mIU/L (SI: 14.9 µg/L).

Diagnostic Assessment

At 14 weeks' gestation, IGF-1 concentration was within the normal range (33.0 nmol/L; SI: 252.0 ng/mL). Visual fields and extraocular movements were normal, with no diplopia. There was longstanding right inferior dystopia without progression since diagnosis. Liver function tests showed an isolated elevated ALP (146 IU/L), consistent with prepregnancy levels. Phosphate levels were normal.

Treatment

To prevent fibrous dysplasia expansion, particularly affecting the right optic nerve, pegvisomant was continued. The patient was closely monitored for symptoms of expanding lesions (eg, headache, vision changes) and potential adverse effects of pegvisomant (eg, liver function derangement).

Outcome and Follow-up

During her pregnancy, the patient did not develop hypertension or gestational diabetes. Second-trimester morphology scans

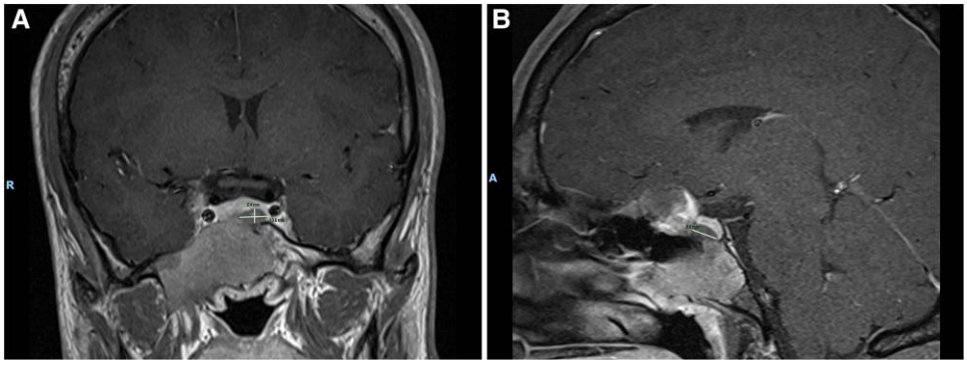

Figure 1. (A) and (B) The T1-weighted images (coronal and sagittal views) of pituitary magnetic resonance imaging on initial diagnosis. The white lines demonstrate the 10.6 × 5.4 × 8.6 mm T1-hypoenhancing lesion in the left anterior pituitary, consistent with an adenoma. There was no suprasellar extension. The pituitary gland was otherwise prominent, measuring 8 × 10 × 18 mm, but remained midline with maintained posterior pituitary bright spot. There is also a separate 4 mm Rathke cleft cyst, not shown in this figure.

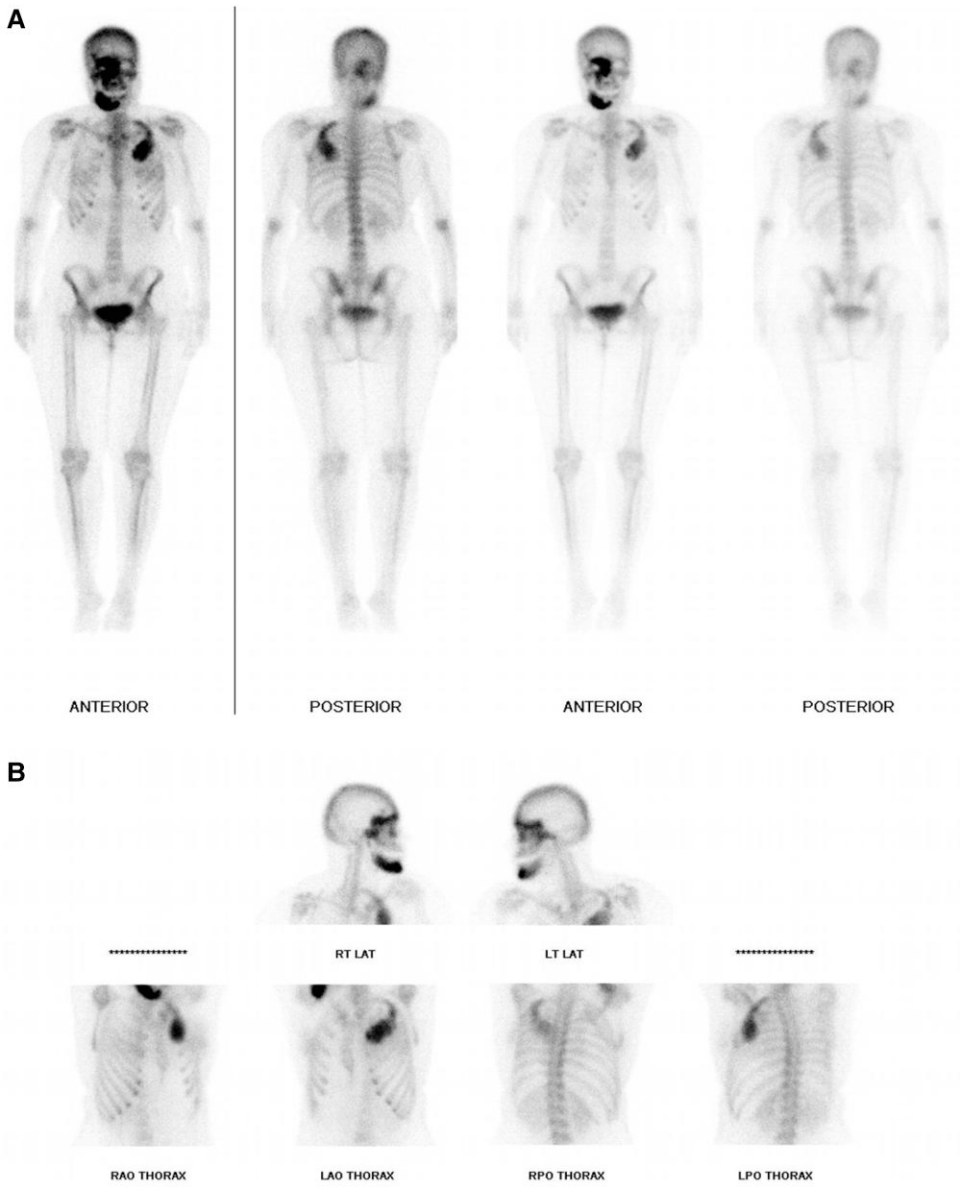

Figure 2. (A) and (B) The whole-body bone scan findings on initial diagnosis consistent with polyostotic fibrous dysplasia with expansion and hyperemia involving the right medial orbit (thought to be the sphenoid bone) and skull base, right mandible, and left superior rib.

and subsequent growth scans (4 weekly) showed normal fetal development within the 40th to 50th percentile. IGF-1 remained within the age-adjusted normal range throughout the pregnancy (Fig. 3). ALP levels rose to 281 IU/L prior to delivery (also seen in normal pregnancy), with all other liver enzymes remaining normal. At 34 weeks' gestation, MRI confirmed stable craniofacial fibrous dysplasia and pituitary adenoma, with no changes in ophthalmologic assessment and findings.

At 40 weeks' gestation, she had a spontaneous vaginal delivery of a healthy female infant weighing 3235 g and measuring 50.5 cm, with Apgar scores of 9 at 1, 5, and 10 minutes.

Cabergoline was not resumed postpartum to facilitate breastfeeding. The patient's clinical findings remained stable at follow-up reviews.

Discussion

This case demonstrates the safe use of pegvisomant during pregnancy in an individual with MAS and extensive craniofacial FD, which previously caused vision complications. While there are several reports of pegvisomant continuation in individuals with acromegaly from a GH-secreting adenoma during pregnancy, this is the first report in a patient with FD/MAS. Control of IGF-1 was maintained throughout pregnancy, with clinical and imaging evidence of stability in underlying FD and pituitary disease. No adverse maternal or fetal outcomes were observed, and fetal growth parameters were normal.

Individuals with FD/MAS may have GH excess, which not only impacts skeletal complications but is also associated with pregnancy-related complications such as hypertension and gestational diabetes [10-12]. Guidelines for managing GH excess during pregnancy generally recommend cessation of pharmacotherapy prior to or upon confirmation of a viable pregnancy [3, 5, 6]. For pegvisomant, this is due to limited data regarding its use during pregnancy or breastfeeding, rather than established teratogenic effects [5, 6, 10, 12]. Current recommendations are based on outcomes for patients

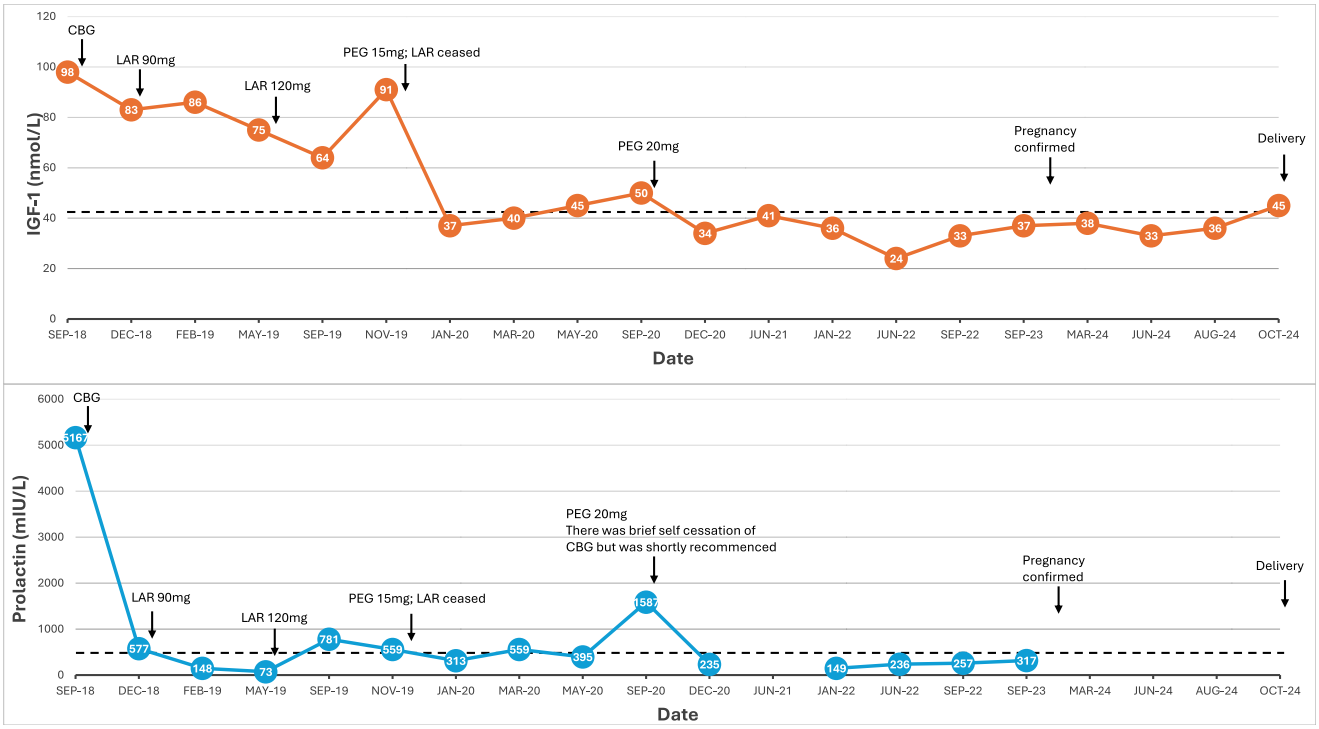

Figure 3. The measured levels of IGF-1 and prolactin from the initial diagnosis of McCune-Albright syndrome to the present day (just after delivery). The dotted line represents the upper limit of the normal range for each test (42 nmol/L for IGF-1 and 500 mIU/L for prolactin, respectively). Significant changes in management, confirmation of pregnancy, and delivery are depicted within the graph with arrows pointing to the corresponding date.

Abbreviations: CBG, cabergoline; LAR, lanreotide; PEG, pegvisomant.

with a GH-secreting pituitary adenoma, in whom the risk of disease progression during a pregnancy is low and adverse maternal and fetal complications are rare [6, 13]. However, the management of GH excess in MAS poses additional challenges due to the potential for FD expansion, which can lead to complications, particularly when craniofacial structures are involved [2, 3, 7-9].

While surgery is the preferred initial treatment for acromegaly, it is rarely recommended in FD/MAS [1-3, 7, 14]. This is because the mutated mammosomatotrophs are diffusely distributed throughout the pituitary gland, often necessitating total hypophysectomy and resulting in panhypopituitarism, which complicates fertility and pregnancy management [2, 3, 9]. Additionally, craniofacial FD involving the skull base can make surgical approaches technically challenging, further supporting pharmacotherapy as the preferred option [1, 7, 9, 14].

In this case, the decision to continue pegvisomant during pregnancy was based on prior vision-threatening craniofacial FD and the inefficacy of somatostatin analogues. Pegvisomant, a GH receptor antagonist, inhibits GH action at the receptor level, effectively normalizes IGF-1 in most individuals with acromegaly [5, 7, 15]. While it does not suppress GH secretion, making tumor growth possible, blocking GH action was crucial to prevent FD-related complications [2, 3, 8, 12, 16].

Biochemical monitoring of acromegaly through IGF-1 levels during pregnancy is generally not recommended as physiological changes affect GH/IGF-1 concentrations. Early pregnancy is marked by hepatic GH resistance due to elevated estrogen concentration, which initially reduces IGF-1 [6, 13]. Placental GH secretion begins around week 5 and becomes the predominant GH source by the second trimester, stimulating IGF-1 production while suppressing pituitary GH secretion in nonacromegalic individuals [5, 11, 12]. In individuals with autonomous pituitary GH secretion, its combination with a rise in placental GH can increase IGF-1 in the third trimester, hence an increase in IGF-1 does not necessarily reflect a change in the pituitary [17, 18]. However, we monitored IGF-1 in our patient to ensure adequate GH-receptor blockade to minimize risk of FD progression.

The safety profile of pegvisomant during pregnancy and breastfeeding is not well established, with limited available data. However, published reports (summarized in Table 1) suggest reassuring outcomes with uncomplicated pregnancies observed with pegvisomant exposure, including a report of negligible pegvisomant levels in fetal blood and breast milk [16, 17, 19-21]. These findings are encouraging, but further research is needed to establish a definitive safety profile for pegvisomant during pregnancy and lactation.

In conclusion, this case highlights the importance of individualized management in patients with FD/MAS during pregnancy. In this patient, pegvisomant was safely continued, likely preventing complications related to GH excess and FD expansion, while achieving favorable maternal and fetal outcomes.

Table 1. Fetal outcomes from published case studies of pregnancies in individuals with acromegaly (all with GH-secreting macroadenoma) where there was either PEG exposure at conception or continuation of PEG throughout pregnancy

Author, year	Cases	PEG details	Fetal outcomes
Guarda et al, 2020 [19]	4 pregnancies in 3 individuals with GH-secreting macroadenoma	Ceased on conception • 1 case at 10 mg/day dose for first pregnancy, then 40 mg/day for second; 1 case at 10 mg/day, another unspecified	• Normal birthweight, no fetal complications • Normal growth and development in cases up to 5 years
Qureshi et al, 2006 [20]	1 pregnancy in 1 individual with GH-secreting macroadenoma	Ceased on conception—dose 20 mg/day	• Normal birthweight, no fetal complications • Normal growth and development after 1 year
Van der Lely et al, 2015 [21]	35 pregnancies in 33 individuals, reported from Pfizer global safety database including ACROSTUDY and Pfizer postmarketing programs	27 pregnancies with maternal PEG exposure • 3 continued PEG throughout—average dose 12.1 mg/day 8 pregnancies with paternal PEG exposure	• 3 that continued PEG had "normal newborns"—2 at term, 1 preterm • Overall, 18 documented live births out of 35 pregnancies—14 with normal fetal outcomes, 4 unspecified • For remaining 17 pregnancies ○ 5 elective termination of pregnancy ○ 2 non-PEG related spontaneous abortion ○ 1 ectopic pregnancy ○ 9 outcome unspecified
Cheng et al, 2012 [17]	1 pregnancy in individual with GH-secreting macroadenoma	Continued in first trimester of pregnancy, ceased before 20 weeks—dose 10 mg/day	• Normal birthweight, no fetal complications • Growth and development not reported
Brian et al, 2007 [16]	1 pregnancy in individual with GH-secreting macroadenoma	Continued throughout pregnancy—dose 25 mg/day	• Normal birthweight, no fetal complications • Normal growth and development after 6 months

Abbreviation: PEG, pegvisomant.

Learning Points

- Pegvisomant treatment for GH excess in MAS can prevent FD-associated complications.
- Although data on pegvisomant use in pregnancy and breastfeeding are limited, existing reports indicate it may be safe in selected cases.
- Management of GH excess in FD/MAS requires a nuanced approach, particularly when FD expansion poses a significant risk.

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Contributors

All authors made individual contributions to authorship. J.C. and M.B. were involved in the initial diagnosis and management of the underlying condition prior to pregnancy. J.T., J.C., H.N., and J.H. were involved in peripartum management of the patient. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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