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Case Report

Successful Medical Management of Cushing Disease With Metyrapone Throughout Pregnancy: A Report of 2 Cases

Angeliki Theodorou[1,2] and Eliza B. Geer[3]

[1]Division of Endocrinology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA
[2]Department of Radiology, Columbia University Irving Medical Center, New York, NY 10032, USA
[3]Department of Medicine and Neurosurgery, Multidisciplinary Pituitary and Skull Base Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA

Correspondence: Eliza B. Geer, MD, Memorial Sloan Kettering Cancer Center, David H. Koch Center for Cancer Care, 530 East 74th Street, Box 76, New York, NY 10021, USA. Email: geere@mskcc.org.

Abstract

Cushing syndrome (CS) in pregnancy is a rare disorder with challenging diagnostic and therapeutic considerations. For patients with medically managed CS planning pregnancy, bilateral adrenalectomy is advised before conception. To our knowledge, no case of Cushing disease (CD) medically treated throughout pregnancy with cortisol synthesis inhibition has been described. We present 2 cases of CD in pregnancy managed with metyrapone, a non-Food and Drug Administration-approved drug for pregnancy. The first case involves a 31-year-old woman with recurrent CD who conceived twins via in vitro fertilization while on metyrapone. She had an uneventful pregnancy, delivering healthy twins at 37 weeks. Postpartum, she developed hypertension, which resolved spontaneously, and remained on metyrapone, with stable cortisol levels and normal development of her twins. The second case describes a 29-year-old woman with recurrent CD since adolescence, status post 2 transsphenoidal resections and gamma knife radiosurgery, who conceived naturally on metyrapone. After an uncomplicated pregnancy, she developed postpartum preeclampsia requiring temporary antihypertensive therapy. Both cases showed favorable maternal and fetal outcomes, highlighting metyrapone as a therapeutic option for managing CD during pregnancy.

Key Words: cushing disease, pregnancy, metyrapone

Introduction

Endogenous Cushing syndrome (CS) is a rare endocrine disorder characterized by chronic hypercortisolism due to an ACTH-secreting tumor (pituitary or ectopic) or an adrenal cortisol-secreting tumor. The incidence of CS in pregnancy is exceptionally low due to associated infertility, as excess corticosteroids suppress gonadotropin production and impair follicular development. However, recent advances in CS therapy may improve fertility, emphasizing the need for contraceptive counseling and pregnancy planning while on long-term medication and for an improved understanding of CS therapies during pregnancy [1].

Fewer than 300 cases of CS in pregnancy have been described, with adrenocortical adenoma being the predominant cause (44-50%) and Cushing disease (CD) representing 28% to 34% [2, 3]. According to the largest meta-analysis so far, among the 214 active CS cases involved, only 30 (14%) were diagnosed before pregnancy [2]. Hypercortisolism presents significant risks for the mother and the infant, including hypertension, gestational diabetes (GDM), preeclampsia, fetal growth restriction, and preterm delivery [2]. Guidelines advise bilateral adrenalectomy (BLA) for patients with medically managed CS planning pregnancy and transsphenoidal surgery (TSS) or adrenalectomy when diagnosed postconception for CD and adrenal CS, respectively, ideally in the second trimester [4].

When surgery is contraindicated or declined, pharmacologic management is an alternative. Among all cases described of CS in pregnancy, approximately 40 women received medical treatment, with fewer than 10 initiating therapy before conception [2, 3].

No Food and Drug Administration (FDA)-approved drugs exist for CS during pregnancy. While certain therapies have been used off-label, with metyrapone the most administered, their safety profiles during pregnancy remain uncertain [4]. Continuous metyrapone administration from preconception to delivery has not been previously reported.

We describe 2 cases of women with CD diagnosed before pregnancy who declined BLA and were managed with metyrapone from preconception through delivery. With close clinical and biochemical monitoring, both pregnancies proceeded without significant complications. These cases suggest the safety and efficacy of metyrapone in pregnancy while highlighting the importance of individualized treatment and close monitoring for women with CD during pregnancy.

Case Presentation

Case 1

A 31-year-old woman presented in 2011 with new-onset diabetes, progressive weight gain, easy bruising, and insomnia, suggestive of CS. Initial evaluation revealed elevated

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Table 1. Metyrapone dose changes and biochemical test results during pregnancy for case 1

Week	Metyrapone dose	Plasma ACTH	Serum cortisol	24-hour UFC	LNSC	Dose change
Week 10	500 mg TID	**76 pg/mL (16.7 pmol/L)**	**25.6 µg/dL (706 nmol/L)**	19 µg/24h (52 nmol/24 hours)	NL × 2	No
Week 13	500 mg TID	50.3 pg/mL (11.1 pmol/L)	**29.5 µg/dL (814 nmol/L)**	12 µg/24h (33 nmol/24 hours)	NA	Decreased to 250 mg/500 mg/500 mg
Week 16	250 mg/500 mg/500 mg	**71.5 pg/mL (15.7 pmol/L)**	**32.8 µg/dL (905 nmol/L)**	**80 µg/24h (221 nmol/24 hours)**	NL × 2	No
Week 20	250 mg/500 mg/500 mg	47 pg/mL (10.3 pmol/L)	**33.8 µg/dL (933 nmol/L)**	31 µg/24h (86 nmol/24 hours)	NA	Decreased to 250 mg/250 mg/500 mg
Week 23	250 mg/250 mg/500 mg	30.5 pg/mL (6.7 pmol/L)	**40.1 µg/dL (1106 nmol/L)**	18 µg/24h (50 nmol/24 hours)	NL × 2	Decreased to 250 mg TID
Week 27	250 mg TID	53.5 pg/mL (11.8 pmol/L)	**40.3 µg/dL (1112 nmol/L)**	27 µg/24h (74 nmol/24 hours)	NA	No
Week 31	250 mg TID	**66.5 pg/mL (14.6 pmol/L)**	**26.7 µg/dL (737 nmol/L)**	17 µg/24h (47 nmol/24 hours)	NL × 2	No
Normal range		<63 pg/mL (<13.9 pmol/L)	<25 µg/dL (<690 nmol/L)	<50 µg/24h (<138 nmol/24 hours)		

Abnormal values are shown in bold font. Values in parentheses are International System of Units.
Abbreviations: LNSC, late night salivary cortisol; NA, not available; NL, normal limit; TID, 3 times daily; UFC, urinary free cortisol.

24-hour urine free cortisol (UFC) of 154 µg/24 hours (423 nmol/24 hours) (normal reference range (NRR): < 50 µg/24 hours; < 138 nmol/24 hours) and serum cortisol of 4.1 µg/dL after 1 mg dexamethasone suppression (113 nmol/L) (NRR: < 1.8 µg/dL; < 49.7 nmol/L). Plasma ACTH was nonsupressed at 50 pg/mL (11 pmol/L) (NRR: < 63 pg/mL; < 13.9 pmol/L). Pituitary magnetic resonance imaging (MRI) revealed a sellar hypointensity consistent with an adenoma. She underwent TSS, and pathology confirmed a corticotroph tumor. Postoperatively, serum cortisol decreased to 3.4 µg/dL (94 nmol/L), and the patient required hydrocortisone replacement for 3 months. Follow-up testing confirmed remission, with UFC at 10 µg/24 hours (28 nmol/24 hours) and dexamethasone-suppressed cortisol at 0.7 µg/dL (19 nmol/L). The patient remained in remission until 2017, when testing identified a UFC value of 148 µg/24 hours (408 nmol/24 hours) and elevation of 1 of the 2 late-night salivary cortisol (LNSC) values. Repeat MRI imaging did not identify a visible tumor. She was started on ketoconazole, 200 mg daily, titrated to 200 mg twice daily (BID) with normalization of UFC levels. Due to severe hepatic toxicity, with alanine aminotransferase and aspartate aminotransferase levels of 1195 U/L (NRR: 8-48 U/L) and 699 U/L (NRR: 7-55 U/L), respectively, ketoconazole was discontinued and liver function normalized within 2 months. Metyrapone was then initiated at 250 mg daily and titrated to 500 mg 3 times daily. The patient expressed a desire to conceive but declined BLA.

Case 2

A 29-year-old woman with recurrent CD since the age of 12 presented to our center in 2016. She had undergone 2 TSSs in 1997 and 2000, followed by gamma knife radiosurgery for recurrence. She was managed with ketoconazole 400 mg BID for several years before tapering it off and remained asymptomatic without treatment for approximately 14 years. In 2016, recurrence was confirmed with elevated UFC and LNSC values at 127.5 µg/24 hours (351.9 nmol/24 hours) and 0.517 µg/dL (14.27 nmol/L) (NRR: < 0.09 µg/dL; < 2.5 nmol/L), respectively. MRI revealed postoperative changes without significant new findings. She was reinitiated on ketoconazole at 200 mg daily, which was increased to BID with normalization of her UFC values. The patient desired fertility but declined BLA.

Diagnostic Assessment

Case 1

After discussions regarding the lack of FDA-approved medical therapies for CS during pregnancy, the patient proceeded with in vitro fertilization while on metyrapone and metformin. Following a miscarriage, she conceived twins. Her pregnancy was closely monitored, with assessments for GDM, hypertension, and biochemical evaluation of plasma ACTH, serum cortisol, UFC, and LNSC values (Table 1, Fig. 1).

Case 2

Given available case report data on metyrapone use in CS during pregnancy, the patient was switched to metyrapone 250 mg 4 times daily and conceived naturally. Her plasma ACTH, serum cortisol, and UFC were monitored throughout pregnancy (Table 2, Fig. 2).

Treatment

Case 1

Metyrapone dose was adjusted based on biochemical results (Table 1, Fig. 1). Blood pressure (BP) and potassium levels were monitored every 3 to 4 weeks, without evidence of hypertension or hypokalemia. In 2022, at 37 weeks, she delivered via elective cesarean section 2 healthy infants, a male and a female, weighing approximately 3.2 kg each, without any signs of adrenal insufficiency postpartum. She continued metyrapone peri- and postpartum, receiving 100 mg hydrocortisone IV preoperatively and every 8 hours for 24 hours. Postpartum, due to systolic BP in the 140 to 150 mmHg range, she was started on nifedipine 30 mg daily, with a reduction of BP to 120 mmHg.

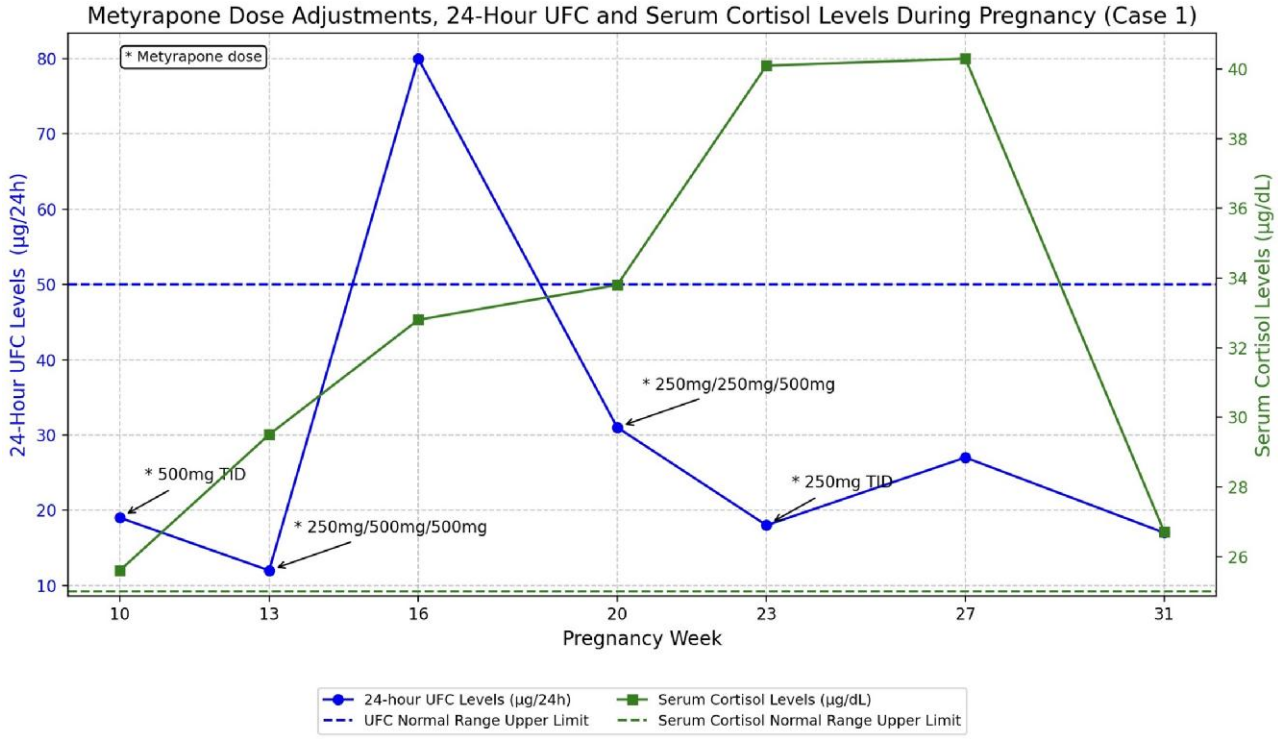

Figure 1. Shows metyrapone dose adjustments alongside the 24-hour UFC and serum cortisol levels throughout pregnancy for case 1. Dashed lines indicate the upper limit of normal for 24-hour UFC and serum cortisol in nonpregnant women. Metyrapone dose (asterisk) indicates if there was a change in the patient's prescription for each specific week of pregnancy.

Abbreviation: UFC, urinary free cortisol.

Table 2. Plasma ACTH, serum cortisol, and 24-hour UFC levels throughout pregnancy for case 2

Week	Plasma ACTH	Serum cortisol	24-hour UFC
Initial evaluation	NA	NA	46 µg/24h (127 nmol/24 hours)
Week 12	26.7 pg/mL (5.9 pmol/L)	17.2 µg/dL 474 nmol/L	**188 µg/24h (519 nmol/24 hours)**
Week 17	34.9 pg/mL (7.7 pmol/L)	**25.5 µg/dL 704 nmol/L**	**153 µg/24h (422 nmol/24 hours)**
Week 21	40.9 pg/mL (9.0 pmol/L)	**30.8 µg/dL 850 nmol/L**	**88 µg/24h (244 nmol/24 hours)**
Week 28	**72.7 pg/mL (16.0 pmol/L**	**33.1 µg/dL 912 nmol/L**	**107 µg/24h (295 nmol/24 hours)**
Normal range	<63 pg/mL (<13.9 pmol/L)	<25 µg/dL (<690 nmol/L)	<50 µg/24h (<138 nmol/24 hours)

Abnormal values are shown in bold font. Values in parentheses are International System of Units.

Abbreviations: NA, not available; UFC, urinary free cortisol.

Case 2

Metyrapone was maintained at 250 mg 4 times daily with no complications (Table 2, Fig. 2). BP was monitored every 3 to 4 weeks in our center and at every obstetric checkup, and potassium levels were measured every 3 to 4 weeks. The patient went into labor at 39 weeks and, due to lack of progression, had an unplanned cesarean section, delivering a healthy baby girl. The patient opted to stop metyrapone 36 hours before delivery and did not receive perioperative stress dose glucocorticoids. The newborn was monitored in the newborn intensive care unit for 1 day without evidence of adrenal insufficiency.

Outcome and Follow-up

Case 1

Postpartum, the patient continued metyrapone 250 mg 3 times daily and was able to taper off nifedipine, maintaining normal BP levels. She has since maintained clinical and biochemical stability without comorbidities on metyrapone at 250 mg in the afternoon and 500 mg at bedtime and metformin 1 g BID. Follow-up has shown normal UFC and LNSC values—27 µg/24 hours (75 nmol/24 hours) and 0.027 µg/dL (0.74 nmol/L), respectively—and stable pituitary MRI findings. She has a stable weight, regular menses, and a most recent hemoglobin A1c of 5.4% (NRR: < 5.7%). The twins, now 2.5 years old, are healthy and thriving.

Case 2

Four days postpartum, metyrapone was resumed. The patient was admitted 1 week later for 1 day with postpartum preeclampsia, managed with labetalol and magnesium. The metyrapone dose was increased to 5 times daily, with successful discontinuation of antihypertensive medications 3 weeks later; although the patient experienced labile BPs off treatment for 1 year postpartum, subsequently resolving. Due to a temporary metyrapone shortage, ketoconazole was added and metyrapone was decreased to BID. Five months postpartum, her UFC was well controlled at 26 µg/24 hour (72 nmol/24 hour) on metyrapone 250 mg BID and ketoconazole 200 mg in the morning and

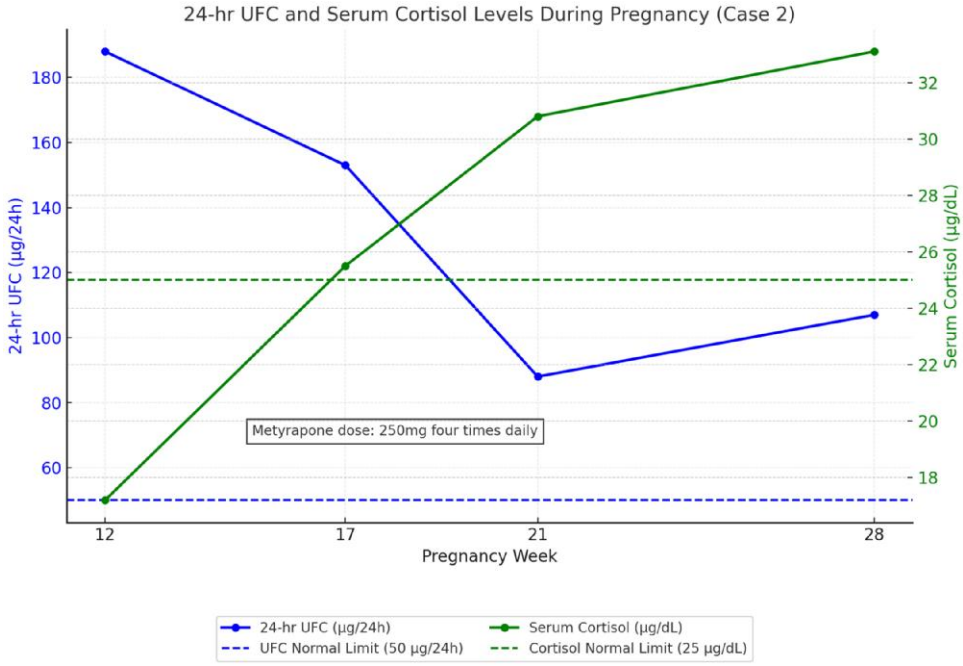

Figure 2. Shows the 24-hour UFC and serum cortisol levels during pregnancy for case 2. Dashed lines indicate the upper limit of normal for 24-hour UFC and serum cortisol in nonpregnant women. The metyrapone dose was maintained at 250 mg 4 times daily throughout pregnancy.

Abbreviation: UFC, urinary free cortisol.

300 mg in the evening. The patient has been doing well and is currently on ketoconazole 200 mg in the am and 400 mg in the pm, and her 5-year-old child shows normal development.

Discussion

We describe, for the first time, 2 patients with CD treated preconception and throughout pregnancy with the cortisol synthesis inhibitor metyrapone. CD in pregnancy is rare, as hypercortisolemia impairs the hypothalamic-pituitary-ovarian axis, leading to menstrual disturbances and infertility [1]. In 2021, Sridharan et al published the largest systematic review of patients with CD during pregnancy, involving 62 pregnancies in 55 patients, with CD diagnosed before pregnancy in 26 (44.4%) cases [4]. Among these, 9 patients received exclusive medical treatment, with 7 diagnosed before conception. Metyrapone was used in 3 of the 9 cases, with daily doses ranging from 500 to 1000 mg. In all cases, metyrapone was initiated during pregnancy: case 1 from the second trimester until delivery, case 2 from weeks 14 to 18 as a bridge to surgery, and case 3 from week 24 until delivery. Other treatment options included cabergoline (pregnancy category B and used during pregnancy for patients with prolactinoma), ketoconazole (considered teratogenic and has antiandrogenic effects), or cyproheptadine, without significant adverse effects reported [4, 5]. Since then, 9 additional cases of CD in pregnancy have been documented, but only 2 involved medical therapy [6-12]. In 1 case, metyrapone was introduced after 12 weeks of gestation, while in the other, cabergoline was administered to a patient diagnosed with CD before conception [7, 8]. Only 4 reported cases demonstrated continuous medical therapy throughout gestation, all using cabergoline [2].

While guidelines recommend BLA before conception for patients with CD controlled with medical therapy [13], the current cases suggest that metyrapone can be considered in CD management throughout gestation without serious side effects. Nevertheless, these cases provide only anecdotal data, as metyrapone crosses the placenta and is classified as pregnancy category C with unknown teratogenic potential [6]. Of note, no pharmacotherapy is FDA approved for CS during pregnancy. Other CS therapies, excluding mifepristone, which is an abortifacient, include pasireotide, osilodrostat, and levoketoconazole, which have not been used in reported cases during pregnancy, and their use is not recommended [1].

Despite favorable outcomes in our cases, this treatment had several challenges. One limitation is the interpretation of biochemical results and treatment benchmarks. Physiologic alterations in pregnancy include elevated cortisol-binding protein, free cortisol levels, and plasma ACTH, due to placental CRH, activating the hypothalamic-pituitary-adrenal axis [14]. In normal pregnancies, UFC levels typically increase 2- to 3-fold, while LNSC levels may remain normal, although data on this are limited [15]. Suppression of cortisol by dexamethasone is blunted during pregnancy, complicating the assessment of disease activity and treatment response [4, 6].

For disease monitoring, UFC and LNSC levels are used, although LNSC may be superior, as cortisol's diurnal rhythm is thought to be preserved in pregnancy [4, 6]. Guidelines suggest a cut-off of 1.5× above the upper limit of normal for UFC in the context of adrenal steroidogenesis inhibitors [13]. Nevertheless, optimal target ranges remain inconclusive, and it is unclear if UFC values correlate directly with clinical outcomes. Our cases demonstrate this point: case 1 had favorable clinical outcomes despite normal UFC levels and metyrapone dose reductions, while case 2 had positive outcomes despite UFC levels above the upper limit of normal in the setting of stable doses.

Another concern is the potential for metyrapone to elevate BP and increase the risk for preeclampsia. Metyrapone inhibits 11β-hydroxylase, leading to 11-deoxycorticosterone accumulation, a mineralocorticoid with hypertensive effects [4]. In both cases, our patients remained normotensive during pregnancy but developed hypertension in the immediate postpartum period, with the second case developing postpartum preeclampsia, successfully managed with antihypertensive medication and magnesium. In both cases, hypertension resolved spontaneously.

Metyrapone can also cause accumulation of adrenal androgen precursors, manifesting as acne and hirsutism in nonpregnant women; however, androgen levels have been reported to remain normal [16]. In pregnant women, there is a theoretical risk of fetal virilization, but no documented cases exist [7]. The rise in androgen levels during normal pregnancy and the lack of established reference ranges make the clinical value of monitoring them questionable [17]. In both our cases, there were no androgenic effects in the mothers or infants.

A multidisciplinary approach is recommended for CS management during pregnancy, involving maternal-fetal medicine specialists, pediatricians, and endocrinologists to ensure close monitoring, especially for GDM, hypertension, preeclampsia, and fetal growth. Individualized care is necessary, considering disease etiology, severity, and related comorbidities. During labor and delivery, appropriate corticosteroid stress dosing is advised, and postpartum care must include monitoring for neonatal adrenal insufficiency. While no significant adverse effects were observed in our cases, long-term data on metyrapone use throughout pregnancy are limited, Further research is needed to understand its safety profile and establish optimal dosing strategies.

Learning Points

- While not FDA approved for pregnancy, cortisol synthesis inhibition with metyrapone represents a viable option for managing CD throughout pregnancy when surgical intervention is contraindicated or declined, although careful monitoring and dose optimization are essential.
- Management should be individualized according to CS etiology, severity, ongoing trimester, and associated comorbidities.
- A multidisciplinary approach is essential for optimal maternal and fetal outcomes, involving close collaboration between maternal-fetal medicine, endocrinology, and pediatrics teams, due to an elevated risk of GDM, hypertension, preeclampsia, fetal growth restriction, and preterm labor.
- Metyrapone therapy requires careful monitoring and dose adjustments due to its potential hypertensive effects, highlighting the importance of regular blood pressure monitoring and assessment for preeclampsia, even in the postpartum period.
- Further investigation is required on the optimal UFC and LNSC levels that should be targeted in each trimester.

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Contributors

All authors made individual contributions to authorship. E.B.G. was involved in the diagnosis and management of the patients and manuscript submission. A.T. and E.B.G. were responsible for manuscript drafting, revision, and submission. All authors reviewed and approved the final draft.

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E.B.G. reports serving as an investigator for research grants to MSKCC from Recordati, Sparrow, and Xeris and serving as an occasional consultant to HRA Pharma, Sparrow, Xeris, and Lundbeck. A.T. does not report a conflict.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from both patients.

Data Availability Statement

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

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