Case Report

Persistent vs Recurrent Cushing’s Disease Diagnosed Four Weeks Postpartum

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1. Introduction

Despite a relatively high prevalence of Cushing’s syndrome (CS) in women of reproductive age, it is rare for pregnancy to occur in patients with active disease [1]. Hypercortisolism leads to infertility through impairment of the hypothalamic-gonadal axis. Additionally, while Cushing’s disease (CD) is the leading etiology of CS in nonpregnant adults, it is less common in pregnancy, accounting for only 30–40% of the CS cases in pregnant women [2]. It has been suggested that in CD there is hypersecretion of both cortisol and androgens, impairing fertility to a greater extent, while in CS of an adrenal origin, hypersecretion is almost exclusively of cortisol with minimal androgen production [3]. Regardless of the cause, active CS in pregnancy is associated with a higher maternal and fetal morbidity, hence, prompt diagnosis and treatment are essential.

Pregnancy is considered a physiological state of hypercortisolism, and the peripartum period is a common time for women to develop CD [3, 4]. A recent study reported that 27% of reproductive-age women with CD had onset associated with pregnancy [4]. The high rate of pregnancy-associated CD suggests that the stress of pregnancy and peripartum pituitary corticotroph hyperstimulation may promote or accelerate pituitary tumorigenesis [4–6]. During pregnancy, the circulating levels of corticotropin-releasing hormone (CRH) in the plasma increase exponentially as a result of CRH production by the placenta, decidua, and fetal membranes rather than by the hypothalamus. Unbound circulating placental CRH stimulates pituitary ACTH secretion and causes maternal plasma ACTH levels to rise [4]. A review of the literature reveals many studies of CD onset during the peripartum period, but CD recurrence in the peripartum period has only been
reported a handful of times [7–10]. Of these, most cases 
recurred during pregnancy. CD recurrence in the imme-
diate postpartum period has only been reported once [7]. Below,
we report for the first time a case of CD recurrence that
occurred 4 weeks postpartum, with a documented dormant
disease throughout pregnancy.

2. Case Presentation

A 30-year-old woman initially presented with prediabetes,
weight gain, dorsal hump, abdominal striae, depression,
lower extremity weakness, and oligomenorrhea with a
recent miscarriage 10 months ago. Diagnostic tests were
consistent with CD. Results included the following: three
elevated midnight salivary cortisols: 0.33, 1.38, and 1.10 μg/
dL (<0.010–0.090); 1 mg dexamethasone suppression test
(DST) with cortisol 14 μg/dL (<1.8); elevated 24 hr urine
cortisol (UFC) measuring 825 μg/24 hr (6–42); ACTH
35 pg/mL (7.2–63.3). MRI of the pituitary gland revealed a
left 4 mm focal lesion (Figure 1(a)). After transphenoidal
resection (TSA), day 1, 2, and 3 morning cortisol values
were 18, 5, and 2 μg/dL, respectively. Pathology did not
show a definitive pituitary neoplasm. She was rapidly tri-
trated off hydrocortisone (HC) by six weeks postresection.
Her symptoms steadily improved, including improved energy levels, improved mood, and resolution of striae. She
resumed normal menses and conceived unexpectedly around 3 months post-TSA. Hormonal evaluation com-
pleted a few weeks prior to her pregnancy indicated no recurrence: morning ACTH level, 27.8 pg/mL; UFC, 5 μg/
24 hr; midnight salivary cortisol, 0.085 and 0.014 μg/dL.
Her postop MRI at that time did not show a definitive adenoma (Figure 1(b)). During pregnancy, she had a
normal oral glucose tolerance test at 20 weeks and no other
sequela of CD. Every 8 weeks, she had 24-hour urine
cortisol measurements. Of these, the highest was 93 μg/
24 hr at 17 weeks and none were in the range of CD (Table 1). Towards the end of her 2nd trimester, she started
to complain of severe fatigue. Given her low 24 hr urine
cortisol level of 15 μg/24 hr at 36 weeks gestation, she was
started on HC. She underwent a cesarean section at 40 weeks gestation for oligohydramnios and she subsequently
delivered a healthy baby boy weighing 7.6 pounds with
APGAR scores at 1 and 5 minutes being 9 and 9. HC was
discontinued immediately after delivery. Around four
weeks postpartum she developed symptoms suggestive for
CD. Diagnostic tests showed an elevated midnight salivary
cortisol of 0.206 and 0.723 μg/dL, and 24-hour urine cor-
tisol of 400 μg/24 hr. MRI pituitary illustrated a 3 mm
adenoma in the left posterior region of the gland, which was
thought to represent a recurrent tumor (Figure 1(c)). A
discrete lesion was found and resected during repeat TSA.
Pathology confirmed corticotroph adenoma with MIB-
1 < 3%. On postoperative days 1, 2, and 3, the cortisol levels
were 26, 10, and 2.8 μg/dL, respectively. She was tapered off
HC within one month. Her symptoms improved only slightly and she continued to report weight gain, muscle
weakness, and fatigue. Three months after repeat TSA, biochemical data showed 1 out of 2 midnight salivary
cortisols elevated at 0.124 μg/dL and elevated urine cortisol
of 76 μg/24 hr. MRI pituitary demonstrated a 3 × 5 mm left
enhancement, concerning for residual or enlarged persis-
tent tumor. Subsequent lab work continued to show a
biochemical excess of cortisol, and the patient was started
on metyrapone but reported no significant improvement of
her symptoms and only mild improvement of excess
cortisol. After a multidisciplinary discussion, the patient
made the decision to pursue bilateral adrenalectomy, as she
refused further medical management and opted against
radiation given the risk of hypogonadism.
3. Discussion

The symptoms and signs of Cushing’s syndrome overlap with those seen in normal pregnancy, making diagnosis of Cushing’s disease during pregnancy challenging [1]. Potential mechanisms of gestational hypercortisolemia include increased systemic cortisol resistance during pregnancy, decreased sensitivity of plasma ACTH to negative feedback causing an altered pituitary ACTH setpoint, and non-circadian secretion of placental CRH during pregnancy causing stimulation of the maternal HPA axis [5]. Consequently, both urinary excretion of cortisol and late-night salivary cortisol undergo a gradual increase during normal pregnancy, beginning at the 11th week of gestation [2]. Cushing’s disease is suggested by 24-hour urinary-free cortisol levels greater than 3-fold of the upper limit of normal [2]. It has also been suggested that nocturnal salivary cortisol be used to diagnose Cushing’s disease by using the following specific trimester thresholds: first trimester, 0.25 μg/dL; second trimester, 0.26 μg/dL; third trimester 0.33, μg/dL [11]. By these criteria, our patient had no signs or biochemical evidence of CD during pregnancy but developed CD 4 weeks postpartum.

A recent study by Tang et al. proposed that there may be a higher risk of developing CD in the peripartum period, but did not test for CD during pregnancy, and therefore was not able to definitively say exactly when CD onset occurred in relation to pregnancy [4]. Previous literature suggests that there may be a higher risk of ACTH-secreting pituitary adenomas following pregnancy as there is a significant surge of ACTH and cortisol hormones at the time of labor. This increased stimulation of the pituitary corticotrophs in the immediate postpartum period may promote tumorigenesis [6]. It has also been suggested that the hormonal milieu during pregnancy may cause accelerated growth of otherwise dormant or small slow-growing pituitary corticotroph adenomas [4, 5]. However, the underlying mechanisms of CD development in the postpartum period have yet to be clarified. We highlight the need for more research to investigate not only the development, but also the risk of CD recurrence in the postpartum period. Such research would be helpful for family planning.

4. Conclusion

Hypothalamic-pituitary-adrenal axis activation during pregnancy and the immediate postpartum period may result in higher rates of CD recurrence in the postpartum period, as seen in our patient. In general, more testing for CS in all reproductive-age females with symptoms suggesting CS, especially during and after childbirth, is necessary. Such testing can also help us determine when CD occurred in relation to pregnancy, so that we can further understand the link between pregnancy and CD occurrence, recurrence, and/or persistence. Learning about the potential mechanisms of CD development and recurrence in pregnancy will help us to counsel these reproductive-age women who desire pregnancy.

Abbreviations

CD: Cushing’s disease
TSA: Transsphenoidal resection
DST: Dexamethasone suppression test
ACTH: Adrenocorticotropic hormone
MRI: Magnetic-resonance imaging
HC: Hydrocortisone
CTH: Corticotroph-releasing hormone
HPA: Hypothalamic-pituitary-adrenal.

Data Availability

The data used to support the findings of this study are included within the article.

Additional Points

Note. Peripartum refers to the period immediately before, during, or after pregnancy and postpartum refers to any period after pregnancy up until 1 year postdelivery.

Disclosure

This case report is a follow up to an abstract that was presented in ENDO 2020 Abstracts. https://doi.org/10.1210/jendso/bvaa046.2128.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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