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Pregnancy-associated Cushing's disease? An exploratory retrospective study

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Abstract

Purpose In most clinical series of Cushing's disease (CD), over 80% of patients are women, many of whom are of reproductive age. The year following pregnancy may be a common time to develop CD. We sought to establish the incidence of CD onset associated with pregnancy.

Methods A retrospective review was conducted for patients with biochemically-proven CD. Demographics, clinical history, biochemistry, imaging, pathology, and outcomes were reviewed. Pregnancy-associated CD was defined as symptom onset within 1 year of childbirth.

Results Over 10 years, 77 patients including 64 women (84%), with CD underwent endonasal surgery. Of the 64 women, 64% were of reproductive age (15–45 years) at the time of diagnosis, and 11 (27%) met criteria for pregnancy-associated CD. Of these 11 women, median number of pregnancies prior to onset of CD was 2 (range 1–4) compared to zero (range 0–7) for 30 other women with CD onset during reproductive age ($p = 0.0024$). With an average follow-up of 47 ± 34 months, sustained surgical remission rates for woman with pregnancy-associated CD, other women of reproductive age, and women not of reproductive age were 91%, 80% and 83%, respectively. The average lag-time from symptom onset to diagnosis for women with pregnancy-associated CD was 4 ± 2 years.

Conclusions In this exploratory study, over one quarter of women of reproductive age with CD appeared to have symptomatic disease onset within 1 year of childbirth. This relatively high rate of pregnancy-associated CD suggests a possible causal relationship related to the stress of pregnancy and pituitary corticotroph hyperactivity in the peripartum period. This possible association suggests a heightened degree of clinical suspicion and biochemical testing for CD may be warranted after childbirth. Further study of this possible link between pregnancy and CD is warranted.

Keywords Pregnancy · Peripartum · Cushing's disease · Hypercortisolemia · Pituitary adenoma · Corticotrophs

Abbreviations

ACTH	Adrenocorticotrophic hormone
CD	Cushing's disease
CRH	Corticotroph releasing hormone
DNA	Deoxyribonucleic acid
HPA	Hypothalamic–pituitary–adrenal
IPSS	Inferior petrosal sinus sampling
MRI	Magnetic resonance imaging

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Introduction

Cushing's disease (CD) is an endocrinopathy caused by an adrenocorticotrophic hormone (ACTH) secreting pituitary adenoma, which disproportionately affects women over men, with most studies noting over 80% of those with CD are women and a majority of women are of reproductive age. The resultant hypercortisolemia of CD typically leads to a myriad of signs and symptoms which may include progressive weight gain, diabetes mellitus, hypertension, metabolic syndrome, osteoporosis, coagulopathy, cognitive decline, as well as psychiatric complaints of anxiety and depression. If left untreated, CD is associated with high rates of mortality largely due to hyperglycemia, hypertension, and resultant cardiovascular complications [1–8]. Anecdotal evidence suggests a higher incidence of CD immediately following

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pregnancy, in the peripartum period. However, establishing the diagnosis of CD is potentially problematic in this subset of patients as cortisol levels during normal pregnancy often reach those found in CD, and many of the normal changes of pregnancy are a result of physiologic hypercortisolemia [9]. The failure of the physical changes of pregnancy-related hypercortisolemia to resolve after delivery of the newborn may be misidentified as "normal" by both patients and their health care providers, allowing CD to persist undiagnosed, often for an extended period of time.

In this retrospective review of our clinical cohort of patients with CD, we attempt to determine if there is an association between pregnancy and CD. Awareness of this possible association may allow for a prompter diagnosis of CD in women following pregnancy and more timely treatment, potentially precluding the excessive morbidity and disability of CD in women who may have maximal physical, emotional and psychological demands on them in the early years of child-rearing.

Methods

Chart review

All patients with biochemically-diagnosed CD treated at Providence Saint John's Health Center in Santa Monica, CA, from July 2007 through December 2017 were identified. We collected information regarding the patients' demographics, clinical history, laboratory studies, imaging, pathology and outcomes. Men and adolescent females under age 15 years were excluded, as were patients who had questionable diagnosis of CD with biochemical inconsistency and no ACTH-staining adenoma found after gland exploration. We grouped the remaining women into three subsets: (1) women with pregnancy-associated CD—defined as symptom-onset within 1 year of pregnancy that was explicitly linked to the pregnancy by the patient's own recollection of her pregnancy and subsequent symptoms related to CD, (2) women of reproductive age—defined as age 15–45 years, in whom CD onset was not associated temporally with pregnancy within the past year, and (3) women not of reproductive age at time of CD onset [10]. In a minority of patients in whom accurate timing of onset of CD symptoms relative to pregnancy was unclear based on detailed clinical notes, such patients were contacted directly for their additional input and recollection. This retrospective study was approved by the institutional review board at Providence Saint John's Health Center.

The diagnosis of CD was determined in all patients based on a combination of clinical signs and symptoms, as well as biochemical assays including elevated midnight salivary cortisol levels, elevated 24–h urinary free cortisol concentration, elevated ACTH levels, loss of diurnal variation in serum cortisol levels, or failure to suppress ACTH production after 1 mg dexamethasone administration. Inferior petrosal sinus sampling (IPSS) was performed in patients who satisfied the criteria for ACTH-dependent Cushing's syndrome without a visible lesion on gadolinium-enhanced sellar MRI including a dynamic post-gadolinium spoiled gradient recalled acquisition in the steady-state sequence. Additionally, in the great majority of patients, immunohistochemical staining for ACTH within a histologically proven pituitary adenoma was used to confirm the diagnosis.

As previously described, all patients with biochemically-confirmed CD underwent endonasal surgery with either an endoscope-assisted, or since 2010 a fully endoscopic approach, with the goal of selective adenomectomy, or in patients without a clear adenoma identified, a thorough gland exploration through multiple incisions, and in some cases partial or total hemihypophysectomy [11, 12]. Early biochemical remission was defined as symptomatic subnormal cortisol levels (≤ 5 µg/dl) within 48 h of surgery. These patients were discharged from the hospital on appropriate glucocorticoid replacement (typically hydrocortisone 20 mg every morning and 10 mg in the late afternoon), with a gradual taper off glucocorticoids over 6–12 months as the adrenal axis recovery is monitored. Surgical remission was defined as those who experience secondary physiologic adrenal insufficiency following surgical management alone, while total remission rates were calculated based on remission achieved using multimodal treatment including medical management, radiation therapy, and adrenalectomy.

Statistical analysis

The study population was divided into the three aforementioned groups based on reproductive age and pregnancy-associated disease onset. A Kruskal–Wallis Rank Sum test was performed to compare continuous variables including age, duration of symptoms, adenoma size and imaging, and laboratory studies. Categorical variable such as pregnancy status and remission were compared using Fisher's exact tests. For comparison of medians, the Mann–Whitney U test was performed. A p-value ≤ 0.05 was considered significant.

Results

Table 1 shows demographic information, pre- and post-operative laboratory studies, pathology findings, treatments, and outcomes of the 64 women with CD. In total, these 64 women comprised 84% of the cohort (16% were men). Of these women, 41 (65%) were of reproductive age, and of these, 11 (27%) had pregnancy-associated CD. Overall, 28% (n = 18) had prior surgery for CD, including 36% (n = 4) of women with pregnancy-associated CD, 43% (n = 13) of the

Table 1 Patient demographics, laboratory and radiographic findings, treatment, and outcome stratified by reproductive age and pregnancy or not pregnancy-associated CD

	All women	Not reproductive age	Reproductive age, not pregnancy-associated	Pregnancy-associated	p-value
Demographics					
Patients (n)	64	23 (36%)	30 (47%)	11 (17%)	
Child bearing age (n)	41 (65%)	0	30	11	
Median (range) number of pregnancies prior to CD dx	N/A	N/A	0 (0–7)	2 (1–4)	**0.0024**
Age at disease onset (years)	38 ± 14	52 ± 11	31 ± 8	29 ± 5	**< 0.001**
Age at surgery (years)	42 ± 13	55 ± 11	35 ± 8	34 ± 5	**< 0.001**
Time to diagnosis (years)	4 ± 4	3 ± 2	5 ± 4	4 ± 2	0.17
Prior surgery (n)	18 (28%)	1 (4%)	13 (43%)	4 (36%)	**0.05**
Laboratory studies					
Pre-op					
Plamsa ACTH (pg/ml)	139 ± 461	76 ± 51	210 ± 666	78 ± 33	0.15
Ref range 7–60 pg/ml[c]					
24-h urine free cortisol (μg)	215 ± 208	220 ± 220	212 ± 212	217 ± 173	0.68
Ref range < 45 μg					
Salivary cortisol (ng/ml)	193 ± 174	232 ± 190	151 ± 116	219 ± 219	0.67
Ref range 50–170 ng/ml[d]					
Serum cortisol (μg/dl)	25 ± 12	29 ± 14	22 ± 10	25 ± 7	0.38
Ref range 10–20 μg/dl[c]					
Post-op					
Serum cortisol (μg/dl)	3.0 ± 3.3	3.6 ± 4.1	3.0 ± 2.6	1.9 ± 2.6	0.12
Imaging and pathology findings					
Visible adenoma	53 (83%)	19 (83%)	23 (77%)	11 (100%)	0.35
Invasive adenoma	20 (31%)	6 (26%)	11 (37%)	3 (27%)	0.88
Macroadenoma[a] (n)	14 (22%)	4 (17%)	6 (20%)	4 (36%)	0.87
ACTH-staining (n)	50 (89%)	17 (94%)	22 (81%)	10 (100%)	0.29
Treatment					
Surgical resections median (range)	1 (1–5)	1 (1–3)	2 (1–5)	1 (1–3)	0.32
Radiosurgery (n)	3 (5%)	1 (4%)	2 (7%)	0	0.99
Medical management (n)	9 (14%)	3 (13%)	6 (20%)	0	0.45
Bilateral adrenalectomy (n)	3 (5%)	0	3 (10%)	0	0.30
Outcome					
Surgical remission (n)	53 (83%)	19 (83%)	24 (80%)	10 (91%)	1
Remission after multimodal treatment (n)	57 (89%)	20 (87%)	27 (90%)	10 (91%)	1
Follow-up (mos)	47 ± 34	50 ± 38	50 ± 34	29 ± 20	0.29

p-value ≤ 0.05 considered statistically significant are in bold

N/A data not available

[a]Macroadenoma defined as maximal diameter ≥ 10 mm

[b]A.M. levels

[c]Midnight lab collection

remaining women of reproductive age, and in one patient (4%) not of reproductive age.

In comparing the number of pregnancies prior to onset of CD, data was available in the cohort of woman of reproductive age. Of 11 women with pregnancy-associated CD, median number of pregnancies pre-CD was 2 (range 1–4); of 29 of 30 women of reproductive age not pregnancy-associated, median number of pregnancies pre-CD was zero (range 0–7), p = 0.0024. Specifically of these 29 women, 19 (66%) had no pregnancies and 10 (34%) had one or more pregnancies. The exact time course between pregnancy and CD onset in the ten patients who did have at least one pregnancy prior to onset of CD was unable to

be reliably determined in these patients but was more than a year prior to onset of CD.

As shown in Table 2, the 11 women with pregnancy-associated CD ranged in age from 17 to 37 years (average 29 ± 5 years) at symptom onset and underwent their first or only surgery for CD at age 34 ± 5 years, on average. The lag-time or delay in diagnosis from symptom onset to diagnosis of CD was 4 ± 2 years in the women with pregnancy-associated CD.

As shown in Table 1, in comparing the women with and without pregnancy-associated CD, there were no significant differences in pre-operative biochemical data including average highest plasma ACTH level, 24-h urinary free cortisol levels or salivary cortisol levels.

Pre-operative MRI findings were also similar across the three groups including rate of MRI visibility, microadenoma versus macroadenoma and mean tumor size in those with visible adenomas. Based on imaging and intra-operative findings, the rate of tumor invasiveness into the cavernous sinus was also similar across groups.

Surgical Outcomes and Sustained Remission

Overall 83% (n = 53) of all women had remission with surgery alone, although 33% required more than one surgery at our institution. By cohort, sustained surgical remission rates for woman with pregnancy-associated CD, other women of reproductive age, and women not of reproductive age were 91%, 80% and 83%, respectively. Remission rates for patients undergoing first-time versus redo surgery were 87% and 83%, respectively. Of the 11 (17%) women who did not go into remission following surgery, 27% (n = 3) had MRI invisible adenomas, and 73% (n = 8) had invasive adenomas into the cavernous sinus, sellar floor, clivus, or through the diaphragm sella, and 45% (n = 5) had prior surgery at outside institutions. Of the 11 patients who did not have remission following surgery, 4 (36%) ultimately achieved remission of their CD with additional therapies including medical management, stereotactic radiosurgery, and/or bilateral adrenalectomies, for an overall sustained remission rate using all therapies of 89% with an average follow-up period of 47 ± 34 months, however, two of three patients who had bilateral adrenalectomies ultimately developed Nelson's syndrome.

Recurrences were documented in 3%. To date, none of the ten women with pregnancy associated CD and early remission have had a recurrence. Two of these ten have gone on to have subsequent successful pregnancies.

Case examples

Case 1

A 31-year-old woman presented several months after the delivery of her first child with progressive weight gain, easy bruising, stress fractures, and increase in both arm and abdominal striae. She had gained over 35 kg in the peripartum period despite exercising and dietary measures and in retrospect, became clearly concerned with her progressive weight gain within a few months of childbirth. Her endocrine work-up revealed 24-h urinary free cortisol levels of 125 and 138 μg (normal < 45 μg), plasma ACTH of 104 pg/ml (normal < 60 pg/ml), and an abnormal low-dose dexamethasone suppression test. An MRI of her pituitary gland revealed a 11 × 10 × 9 mm pituitary adenoma (Fig. 1). Fifteen months after delivery of her child, she underwent endoscopic endonasal adenoma removal with pathology confirming an ACTH-staining corticotroph pituitary adenoma. She went into early remission and was weaned off of hydrocortisone approximately 1 year after surgery. She had a subsequent second uneventful pregnancy and has remained in clinical and biochemical remission nearly 6 years after adenoma removal.

Case 2

A 38-year-old woman presented after giving birth to her only child, having gained nearly 20 kg in the peripartum period and was unable to lose weight despite maintaining a healthy lifestyle. She also complained of hair loss, purple abdominal striae, dysmenorrhea, and refractory hypertension. She clearly dated the onset of this inability to lose weight and other symptoms within a year of childbirth, though had a prolonged 7-year course of ongoing hypertension and weight gain, prior to definitive diagnosis with CD. Her endocrinological work-up revealed plasma ACTH levels of 105.7 pg/ml (normal < 60 pg/ml), morning serum cortisol of 22.6 μg/dl (normal < 20 μg/dl), 24-h urine free cortisol of 118 μg (normal < 45 μg). Both high and low-dose dexamethasone suppression testing was performed with a post-suppression cortisol level of 2 μg/dl. MRI revealed a 10 × 9 × 4 mm pituitary adenoma which was removed via an endoscopic endonasal approach. Pathology confirmed an ACTH-staining pituitary adenoma. Post-operatively she had early and then sustained remission, and was weaned off hydrocortisone replacement during the subsequent year. Post-operatively she had a significant 10 kg weight loss and resolution of her hypertension, which was sustained for 3 years after surgery without evidence of recurrence at last follow-up.

Table 2 Patients with pregnancy-associated Cushing's disease

Pt	Age (years)		History		Pregnancies (n)		Tumor characteristics		Treatment	Outcome		
	Symptom onset	First surgery	Diagnosis delay (y)	Prior surgery	Before CD	After CD Tx	Tumor size (mm)	ACTH-staining	Adjuvant Tx	Early remission	Sustained remission	Follow-up (m)
1	26	35	9	No	2	0	5	Yes	No	Yes	Yes	18.6
2	30	31	1	Yes	2	0	2	No	No[a]	No	No	2.0
3	17	19	2	Yes	1	1	5	Yes	No	Yes	Yes	67.0
4	25	31	6	Yes	1	0	3	Yes	No	Yes	Yes	9.0
5	36	38	2	Yes	3	0	7	Yes	No	Yes	Yes	62.8
6	29	31	2	No	1	1	10	Yes	No	Yes	Yes	23.3
7	31	38	7	No	1	0	10	Yes	No	Yes	Yes	44.3
8	37	41	4	No	1	0	10	Yes	No	YES	Yes	18.4
9	28	30	2	No	3	0	6	Yes	No	Yes	Yes	35.0
10	32	36	4	No	4	0	6	Yes	No	Yes	Yes	27.7
11	29	32	3	No	3	0	10	Yes	No	Yes	Yes	15.0
Mean	29 ± 5	34 ± 5	4 ± 2	4 (36%)	2 (med)	0 (med)	7 ± 3	10 (91%)	0	10 (91%)	10 (91%)	29 ± 20

Adjuvant therapy includes radiation therapy, medical management, and adrenalectomy

AM morning, *CD* Cushing's disease, *Med* median, *Tx* treatment, *UFC* urine free cortisol

[a]Bilateral adrenalectomies were recommended in this patient but she was lost to follow-up

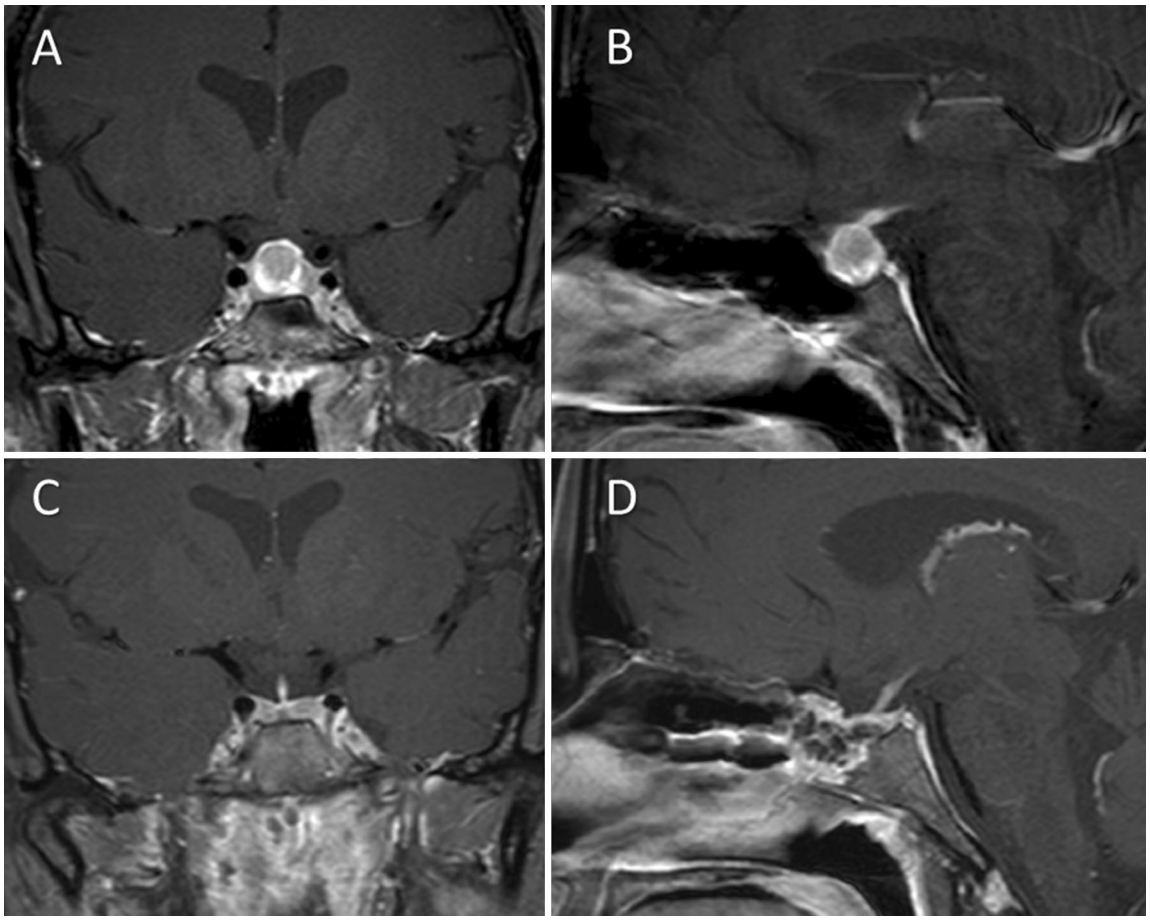

Fig. 1 Case 1 example: pre and post-operative post-gadolinium sellar MRI of 31-year old woman with ACTH-secreting adenoma. Pre-operative coronal and sagittal images (**a, b**) show 11 mm hypo-enhancing adenoma. 3-months after endonasal endoscopic selective adenomectomy, coronal and sagittal images (**c, d**) show gross total tumor removal with restoration of pituitary gland contour. The patient has remained in remission for almost 6 years since her surgery with normal pituitary gland function

Discussion

The pituitary gland and HPA during pregnancy

Changes in the pituitary gland and endocrine function are normal during pregnancy. Anatomically, the pituitary gland increases nearly 1.5 times in size, often extending into the suprasellar space towards the optic chiasm [13, 14]. During normal gestation, the number of corticotrophic pituicytes does not change, in contrast with gonadotrophs, somatotrophs, and lactotrophs, but there is a relative increase in maternal hypothalamic–pituitary–adrenal (HPA) axis activity. Expectedly, total and free cortisol, urinary free cortisol, plasma 17-hydroxycorticosteroids, and corticosteroid-binding globulin (CBG) levels are elevated [14, 15].

Mechanisms of increased corticotroph stimulation during pregnancy

After a transient drop in plasma cortisol levels due to a negative feedback loop, cortisol levels gradually increase throughout gestation, beginning at the 11th week and plateauing in the third trimester [15, 16]. There are several theories regarding the etiology of gestational hypercortisolemia including the increased anti-glucocorticoid effects of elevated progesterone, systemic cortisol resistance, an altered pituitary ACTH set point, and placental ACTH secretion [16]. Plasma ACTH levels also increase steadily throughout pregnancy, reaching their peak levels during labor, suggestive of a source that is outside of normal feedback control [15, 17]. One possible source is the noncircadian secretion of placental corticotroph releasing hormone (CRH) that occurs

during pregnancy that can stimulate the maternal HPA axis. This correlates with an increased placental ACTH, and glucocorticoids that act in a feed-forward manner to increase placental CRH throughout pregnancy. However, the systemic effects of increased placental CRH are thought to be limited by maternal CRH binding globulin, which decreases in the final weeks of pregnancy, increasing the active levels of CRH in the mother, such that placental CRH is a major stimulus of the HPA axis later in gestation [17].

Can pregnancy promote tumorigenesis or stimulate a pre-existing corticotroph adenoma?

Essentially, normal human gestation is accompanied by a dramatic increase in the activity of the maternal HPA axis. Placental production of CRH, increased sensitivity of pituitary corticotrophs to CRH (both placental and maternal), and decreased sensitivity of the pituitary corticotrophs to cortisol's negative feedback inhibition, all contribute to the rise of maternal plasma ACTH and, in turn, cortisol. Both hormones typically reach plasma levels consistent with those found in patients with CD and experience a final significant surge at the time of labor [9, 18]. This increased stimulation of the pituitary corticotrophs during gestation and the immediate post-partum period may somehow promote tumorigenesis resulting in a higher risk of ACTH-secreting pituitary adenomas and CD following pregnancy [18].

Alternatively, it is also quite possible that many of these women (including others of reproductive age but not diagnosed within a year of pregnancy) had small slow-growing or event dormant corticotroph pituitary adenomas that were stimulated by the hormonal milieu during pregnancy. Given that the median number of pregnancies in the pregnancy-associated CD cohort was 2, repeated "exposure" to the stress of pregnancy may also be an important factor.

It is also important to note that in the women of reproductive age and not-pregnancy associated CD, that two-thirds of this cohort (19 patients) had no pregnancies prior to their diagnosis of CD. This fact (and that men too can develop CD) strongly supports the concept that the hormonal demands and changes associated with pregnancy may be just one possible factor among many that ultimately leads to a clinically significant corticotroph adenoma.

However, one study looking at the change in corticotroph adenomas during gestation in 11 women with Nelson's syndrome after bilateral adrenalectomies, found that in 20 pregnancies across the group, adenoma growth rate as measured by serial MRI and plasma ACTH levels was overall similar in the pre-pregnancy, pregnancy and post-pregnancy time-periods [19]. While this study may suggest that pregnancy itself plays no significant role in corticotroph tumor progression in patients with Nelson's syndrome, it is a relatively small retrospective study of patients who had already progressed to overt CD, and may thus not be entirely relevant to the question being posed in the present study. Clearly, further study of the possible connection between CD and pregnancy is warranted.

Another possible explanation of the association between CD and pregnancy is simply that patients are more likely to remember the onset of their CD symptoms in relation to a landmark life event such as pregnancy and childbirth, which leads to long-term physical changes in most women, irrespective of Cushing's status.

Is the association between pregnancy and CD non-random?

This study found that over one-fourth of all women of reproductive age presented with CD onset within 1 year of child birth. Based on United States Census data and The World Bank, the average woman in the United States had 1.8–2.1 births during our study period (2007–2017), assuming roughly 92 weeks of gestation and the subsequent peripartum period (1 year) per child, the average woman spends 166–193 weeks, or 10.3–12.0% of her reproductive years in the peripartum and post-partum period [20]. In contrast, we found 27% of our patients of reproductive age experienced peripartum CD onset, suggesting a nonrandom or possibly causal relationship between pregnancy and CD, with a greater than twofold increased risk of a woman developing CD within 1 year of pregnancy.

Clinical implications

Our findings in this exploratory study, while preliminary and with a relatively small patient cohort, suggest a heightened degree of clinical suspicion of pregnancy-associated CD may be warranted in women following childbirth. It was in fact weight gain or failure to lose weight post-pregnancy, which was the most frequent complaint and presentation in our patients with pregnancy-associated CD, and which often lead to an eventual diagnosis of CD. As such, appropriate biochemical testing may be indicated in women who 6–18 months after pregnancy, are still unable to lose the weight of pregnancy, continue to gain weight, have new, persistent or more refractory hypertension and diabetes mellitus, and/or other classical stigmata of CD.

Study limitations

Weaknesses of this study include its retrospective nature and the subjective nature of the onset of CD symptoms, based largely on the patient's recollection of symptom onset. Using objective diagnosis of CD as a starting point

for these patients was impractical because as previously discussed, one of the difficulties in this population is the appropriate identification of physical changes as signs and symptoms of hypercortisolemia overlap significantly with pregnancy. Another weakness of this report is the general definition of "reproductive age" as 15–45 years, as opposed to a patient-specific determination of menarche and menopause. In female patients around the age of menopause who develop CD, it is difficult to determine which, CD or menopause, is the cause of the amenorrhea, so a relatively arbitrary cutoff was used, though consistent with the age range typically utilized in the obstetric literature [10]. Additionally, there was lack of potentially important clinical data across the three cohorts of women such as timing of onset of hypertension, diabetes mellitus, metabolic syndrome and progressive weight gain. Having such data would have been useful to help determine if women may have had "subclinical" corticotroph adenomas pre-existing that were aggravated by the stress of pregnancy or alternatively if pregnancy itself was a potentially dominant stimulant to onset of CD. In an ideally designed study to determine if pregnancy is a potentiator or risk factor for CD, a more detailed childbirth history for all women is required as well as more details on signs and symptoms of CD onset relative to pregnancy. It would be helpful also to perform wider-scale studies on women with CD, determining the number of pregnancies and live births prior to onset of pregnancy to see if fertility and frequency of pregnancy can be correlated with incidence of Cushing's.

Conclusion

CD disproportionately affects women of reproductive age. In this small exploratory study, over one quarter of such women appeared to have had disease onset within 1 year of pregnancy. This increased incidence of pregnancy-associated CD suggests a potentially causal relationship between the stress of pregnancy and peripartum pituitary corticotroph hyperstimulation that may ultimately promote or accelerate tumorigenesis. If this association of CD with pregnancy is in fact nonrandom and pregnancy is in some way a potentiator of the development of clinically overt CD, a heightened degree of clinical suspicion and biochemical testing for CD may be warranted in women after childbirth. Such added vigilance and awareness may ultimately allow some CD patients to be diagnosed and treated sooner, and help maximize quality of life and minimize disability for these women during their reproductive years.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest to disclose.

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