Pregnancy After Pituitary Surgery Does Not Influence the Recurrence of Cushing's Disease

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Abstract

Purpose: Pregnancy is associated with the activation of the hypothalamus-pituitary-adrenal axis, which can cause a misdiagnosis of Cushing's syndrome. The aim of this study is to evaluate the impact of pregnancy after pituitary surgery on the recurrence rate in Cushing's disease (CD) patients.

Methods: This was a retrospective study in a tertiary center. Between 1990 and 2020, 355 CD patients underwent pituitary surgery. Of those included, 113 female patients who were ≤ 45 years old (median age of 32 years, 14-45), PS remission, a follow up of ≥ 6 months (median of 122 months, 6-402) and an available obstetric history. Recurrence was defined as the diagnosis of Cushing's syndrome via at least two altered first-line methods. The patients were divided into two subgroups according to pregnancy: no pregnancy or pregnancy prior to CD diagnosis (NP/PP) and pregnancy after CD pituitary surgery (PA).

Results: Overall, recurrence occurred in 43 out of 113 patients (38%). A higher recurrence rate was seen in the PA subgroup (11/22, 50%), but there was no significant difference between the NP/PP subgroup (32/91, 35%). No difference in survival-free recurrence (SFR) was found between NP/PP and PA subgroups. The lower SFR was related to a higher PS plasma ACTH and normal pituitary at pathological analyses.

Conclusions: There was no difference in the recurrence rate in patients according to pregnancy history. Other studies with higher numbers of patients are needed to confirm these data.

Introduction

Transsphenoidal selective adenomectomy by an experienced pituitary surgeon is the optimal treatment option for Cushing's disease (CD) in adult and pediatric patients [1].

Overall, the CD has a post-surgical (PS) remission rate of approximately 80%, including approximately 80–85% for microadenomas and a lower rate for macroadenomas (approximately 60%) [1–4].

However, long-lasting remissions decrease in the follow-up due to a significant recurrence rate. Therefore, the term “remission” is preferable to “cure” in PS CD patients.

The recurrence rate is approximately 15–25% within 5–10 years of an initially successful surgery [2, 3, 5].

Among unfavorable prognosis factors for recurrence are a PS serum cortisol (Fs) $> 2-5 \mu\text{g/dL}$, a high PS ACTH, an early recovery of hypothalamus-pituitary-adrenal (HPA) axis function with a short period of need for glucocorticoid replacement, an absence of a return of the circadian rhythm of cortisol secretion and positive responses of ACTH and/or serum cortisol to PS desmopressin/CRH stimulation [6–7].

It had been previously demonstrated that pregnancy is associated with the following: activation of the HPA axis; serial increases in ACTH and cortisol as a result of CRH and ACTH placental production; and maximal levels of cortisol during the third trimester [8–10].

Based on the knowledge that gestation constitutes a state of "hypercortisolism" and considering the clinical observation that several recurrent CD episodes occur after pregnancy, the aim of this study is to evaluate the impact of pregnancy history in recurrence rate in CD PS patients.

Material And Methods

Patients

We performed a retrospective study in a tertiary hospital with 355 patients whose diagnosis confirmed CD and who were admitted between 1990 and 2020. All patients had transsphenoidal surgery, with a minimum follow-up of six months (median of 83 months, 6–415). Overall, the remission rate was 69.3% (246/355), and 76 patients (30.9%) presented with recurrence in the follow-up.

For this study, inclusion criteria were women ≤ 45 years old with postoperative remission and obstetric history available. Of the 355 patients initially evaluated, 113 met these criteria, with a median age of 32 years (14–45). The Ethical and Research Committees of our institution approved the study.

All the patients were seen by two of the authors at least at the diagnosis, before surgery and over the study.

The diagnosis of ACTH-dependent CS was based on typical clinical features and standard hormonal criteria. Additionally, desmopressin had been used in cases of doubtful or discordant methods for CS diagnosis [11].

Differential diagnosis of ACTH-dependent CS was achieved by pituitary MRI, the response to human or ovine CRH, a high-dose dexamethasone suppression test (HDDST) and a bilateral inferior petrosal sinus sampling (BIPSS) in cases of equivocal or negative MRI for a pituitary lesion suggestive of adenoma [12].

The diagnosis of CD was confirmed by histological features which were identified as pituitary adenoma with ACTH immunostaining in the majority of cases. In the remaining patients without ACTH immunostaining, the diagnosis of CD was established by postsurgical remission and/or by a central to peripheral ACTH gradient in the BIPSS. Only two pathologists performed all pathological analyses during the study period.

Post-surgical remission was defined as a low ($< 5 \mu\text{g/dL}$) or undetectable Fs levels 18–24 h after the last dose of oral cortisone acetate or hydrocortisone, which were collected in the fifth postoperative day (mean), clinical for adrenal insufficiency, need for glucocorticoid replacement, disappearance of clinical of hypercortisolism and normal urinary cortisol – 24h (UC) levels (after glucocorticoid withdraw) for a minimum of six months of pituitary surgery. A post-surgical desmopressin test was used to predict recurrence risk [6].

Recurrence was defined as the reappearance of clinical symptoms and signs of hypercortisolism and at least two first-line methods pointing to the activity of CD after more than six months post-surgery.

Pituitary surgery was done by one neurosurgeon from 1982–1999 and by another two neurosurgeons after 2000 (VASC and GOS). The mean follow-up of patients was 122 months (range 6–402).

The obstetric history was collected personally during outpatient visits (MCM) or through telephone or email contacts (LML, MJBT and MCM), emphasizing the number and timing of pregnancies in relation to CD diagnosis, history of maternal and fetal complications and newborn data (size and weight).

Hormone assays

Serum cortisol was measured by fluoroimmunoassay in an AutoDelfia System (Wallac, Perkin Elmer, Turku, Finland) with an intra-assay (IA) variation coefficient (VC) of 8.2% and an inter-assay (IE) VC of 7.5%, and a sensitivity of 1 µg/dL until February 2009. From this date on, Fs was measured by a chemiluminescence assay (CLA) (DPC, Siemens, Los Angeles, CA, USA) with an IA-VC of 7.4% and an IE-VC of 8.6% with the same sensitivity of 1 µg/dL. For the measurement of UC without extraction, we used the same assays for Fs. Until June 2010, nocturnal salivary cortisol (NSC) was measured by radioimmunoassay (DPC, Siemens, Los Angeles, CA, USA) with an IA- and IE-VC of < 20% with the sensitivity of 0.1 µg/dL. From this date on, an ELISA (Salimetrics®, LLC, State College, PA, USA) was used with an IA- and IE-VC < 6.3% with the sensitivity of 0.016 µg/dL. From 1992–2002 and from 2003–2007, ACTH was measured by an immunoradiometric method (CIS bio International, Gif/Yvette, France) with an IE-VC < 14% and a sensitivity of 16 pg/mL. From 2002–2003, ACTH was measured by a CLA (Nichols Advantage, CA, USA) with an IE-VC < 12.6% and a sensitivity of 10 pg/mL. After 2007, another CLA (DPC, Siemens, Los Angeles, CA, USA) was used with an IA-VC of 4.9% and an IE-VC of 6.1% with a sensitivity of 5 pg/mL.

Statistical analysis

The chi-square test was conducted to verify the association between categorical variables in contingency tables, and Fisher's exact test was adopted in 2x2 tables whenever at least one expected frequency was less than 5.

For normally distributed variables, the analysis of variance was used to verify association between continuous data and categorical variables with three categories, and the Student t-test was used for variables with two categories. For non-normally distributed variables, the Mann-Whitney U test was used to verify associations between continuous data, and the Kruskal-Wallis test was used for categorical variables with two categories. The Shapiro-Wilk test was conducted to verify normal distributions for continuous variables.

The follow-up time was considered as the period of months between the date of pituitary surgery or until the date of death or the last date with information for censored cases (alive patients or lost for the follow up).

The Kaplan-Meier method was used to estimate the overall survival probability and the log-rank test to compare survival curves.

The level of significance of 5% was considered for all statistical tests. Statistical computer software STATA® 10.0 (StataCorp LLC, College Station, Texas, USA) was used to conduct all statistical analysis.

Results

Patient subgroups according to pregnancy history

The selected patients were divided into two subgroups according to their obstetric history: no-pregnancy or pregnancy prior to CD diagnosis (NP/PP) and pregnancy after CD surgery (PA) (Table 1).

Table 1
Patient subgroups according to pregnancy history

Parameter	NP/PP	PA	<i>p</i>
Number (%)	91 (80.5)	22 (19.5)	NA
Age: years (mean ± SD) *	31.7 ± 7.6	27.2 ± 6.5	0.011[#]
Fs 800 h: µg/dL (mean ± SD) *	23.2 ± 8.0	32.3 ± 40.0	0.843
NSC: ng/dL (mean ± SD) *	617.4 ± 574.8	2695.6 ± 5973.8	0.393
UC: µg/24 h (mean ± SD) *	694.4 ± 472.8	2276.5 ± 7236.2	0.602
ACTH: pg/mL (mean ± SD) *	73.3 ± 50.5	91.6 ± 67.3	0.282
MRI (visible lesions): micro/macro (n) *	54 / 28	11 / 6	0.928
MRI: maximum diameter, mm (mean ± SD) *	9.1 ± 4.1	9.0 ± 4.2	0.955
PS Fs 800 h: µg/dL (mean ± SD)	2.2 ± 2.4	2.7 ± 2.3	0.738
PS ACTH: pg/mL (mean ± SD)	10.1 ± 9.2	5.0 ± 2.2	0.347
PS desmopressin: Fs, µg/dL (mean ± SD)	2.7 ± 4.0 (n = 35)	3.1 ± 4.4 (n = 7)	0.999
PS glucocorticoid use: months (mean ± SD)	12.4 ± 7.6	9.3 ± 9.0	0.062
Pathology: adenoma ACTH+/normal pituitary	73 / 10	13 / 4	0.250
Follow up: months (mean ± SD)	124.3 (83.7)	187.7 (112.6)	0.013^{&}
Recurrence: %	35	50	> 0.05
Time of recurrence: months (mean ± SD)	67.1 ± 53.7	60.6 ± 46.0	0.896
*At diagnosis of ACTH-dependent Cushing's syndrome; NP, no pregnancy; PP, previous pregnancy to Cushing's disease diagnosis; PA, pregnancy after pituitary surgery; Fs, serum cortisol (Reference [R]: 5–25 µg/dL); NSC, nocturnal salivary cortisol (R: <120 ng/dL); UC, urinary cortisol (R: 30–300 µg/24 h); ACTH, R: <60 pg/mL; MRI, magnetic resonance imaging; PS, post-surgical; [#] <i>p</i> -value by Student's t-test; ^{&} <i>p</i> -value by Mann-Whitney test; NA, not appreciable; SD, standard deviation			

The majority of laboratory and imaging data at diagnosis and the in post-surgical time were similar between two subgroups, except by a lower age at diagnosis and a higher follow up in the PA subgroup.

Postsurgical and long-term outcome

Of the 113 patients included in this study, 43 patients (38%) had a recurrence, with a median of 48 months (8-240) after pituitary surgery.

The patients who recurred were slightly younger at Cushing's diagnosis (29.0 ± 7.0 vs. 31.9 ± 7.7 years-old, $p = 0.047$), presented a larger follow-up PS time (173.9 ± 92.2 vs. 113.7 ± 86.3 months, $p = 0.001$) and a higher number of sinus cavernous invasion (Table 2). Although the higher percentage of pregnancies after surgery in recurrence patients, the survival-free recurrence curve was not different between two subgroups according to pregnancy history (Fig. 1). A lower survival-free recurrence was related to higher PS plasma ACTH more than 68.2 pg/mL at 5th PS Day and normal pituitary at pathological analyses (data not shown).

Table 2
Postsurgical and long-term outcome for all patients (n = 113)

Parameter	Remission	Recurrence	<i>p</i>
Number (%)	70 (62.0)	43 (38.0)	NA
Age: years (mean $\pm$ SD) *	31.9 ± 7.7	29.0 ± 7.0	0.047[#]
Fs 800 h: $\mu\text{g/dL}$ (mean $\pm$ SD) *	25.7 ± 22.8	23.5 ± 8.3	0.812
NSC: ng/dL (mean $\pm$ SD) *	1089.3 ± 2845.8	546.1 ± 675.7	0.251
UC: $\mu\text{g/24 h}$ (mean $\pm$ SD) *	1121.9 ± 3968.8	775.6 ± 562.9	0.474
ACTH: pg/mL (mean $\pm$ SD) *	74.9 ± 59.9	79.8 ± 39.7	0.099
MRI (visible lesions): micro/macro (n) *	43 / 18	22 / 16	0.199
MRI: maximum diameter (mm) (mean $\pm$ SD) *	8.8 ± 4.3	9.5 ± 3.8	0.272
MRI: sinus cavernous invasion (n) *	0	4	0.029^{&}
PS Fs: $\mu\text{g/dL}$ (mean $\pm$ SD)	2.0 ± 1.8	2.8 ± 3.2	0.173
PS ACTH: pg/mL (mean $\pm$ SD)	8.4 ± 8.1	14.2 ± 10.6	0.053
PS desmopressin: Fs: $\mu\text{g/dL}$ (mean $\pm$ SD)	1.7 ± 2.9	4.7 ± 5.2	0.070
PS glucocorticoid use: months (mean $\pm$ SD)	12.3 ± 7.7	11.2 ± 8.2	0.565
Pathology: adenoma ACTH+/normal pituitary (n)	60 / 7	26 / 7	0.145
Follow up: months (mean $\pm$ SD)	113.7 ± 86.3	173.9 ± 92.2	0.001^{**}
Pregnancy: number of patients (n)	39	28	0.969
Pregnancy: previous PS/after PS (n)	28 / 11	17 / 11	0.341
*At diagnosis of ACTH-dependent Cushing's syndrome; Fs, serum cortisol (Reference [R]: 5–25 $\mu\text{g/dL}$); NSC, nocturnal salivary cortisol (R: <120 ng/dL); UC, urinary cortisol (R: 30–300 $\mu\text{g/24 h}$); ACTH, R: <60 pg/mL; MRI, magnetic resonance imaging; PS, post-surgical; ** <i>p</i> -value by Mann-Whitney test; [#] Student's t-test; ^{&} Fisher's test; NA, not appreciable; SD, standard deviation			

Obstetric and delivery history

Of 113 patients of this study, 67 patients (59.3%) have a positive history of pregnancy, and most of them were pregnant prior to CD diagnosis (67.2%).

Overall, there were 135 pregnancies in 67 patients, 2.0 per patient. There is no difference in a number of pregnancies per patient, maternal weight gain, type of delivery (normal or cesarean), delivery time (term or premature), newborn weight and newborn size, between remission and recurrence patients (Table 3).

Table 3
Postsurgical and long-term outcomes in relation to pregnancy history (n = 67)

Parameter	Remission	Recurrence	<i>p</i>
Pregnancy: number of patients (n)	39	28	0.969
Pregnancy: number per patient (mean $\pm$ SD)	2.0 $\pm$ 0.7	2.0 $\pm$ 0.8	0.969
Weight gain during pregnancy: kg (mean $\pm$ SD) *	13.3 $\pm$ 7.9	13.1 $\pm$ 6.1	0.726
Delivery: normal/cesarean: % *	39.3 / 60.7	22.7 / 77.3	0.213
Delivery time: term/premature: % *	87.1 / 12.9	90.0 / 10.0	0.999
Newborn weight: g (mean $\pm$ SD) *	3196.7 $\pm$ 817.9	3224.5 $\pm$ 405.0	0.891
Newborn size: cm (mean $\pm$ SD) *	48.9 $\pm$ 2.7	49.5 $\pm$ 2.8	0.976
Maternal complications: n *	8	5	NA
Fetal/Newborn complications: n *	4	7	NA
*Data from pregnancy/newborn closer to CD diagnosis or recurrence; NA, not appreciable; SD, standard deviation			

Considering data from pregnancy/newborn closer to CD diagnosis or recurrence, the maternal complications occurred in 13 patients, 8 in remission and 5 in recurrence cases; complications included arterial hypertension of pregnancy, preeclampsia, gestational diabetes mellitus, fetal macrosomia and panic syndrome.

Fetal complications occurred in 11 cases, 4 in remission and 7 in recurrence cases; complications included neonatal jaundice, prematurity, neonatal hypoxia, oligodramnious and small-for-gestational-age fetus.

Discussion

To date, there is no single factor to predict the recurrence of CD in the long-term follow-up of patients. Previous studies showed that several factors, such as PS serum cortisol, PS ACTH, recovery of the HPA

axis/return of the circadian rhythm of cortisol secretion, the extent of glucocorticoid replacement, early responses of ACTH and/or serum cortisol to secretagogues, among others [6, 7], can contribute to a recurrence. This fact can be explained by the rarity of the disease, the heterogeneity of studies, studies with a small number of patients and/or short time of follow-up and lack of consensus for recurrence criteria diagnosis. However, even patients with “rigid” criteria of remission and “low risk” can present a recurrence in the long-term follow-up with a non-negligible frequency.

This study is the first to evaluate the influence of pregnancy on the recurrence rate in a group of reproductive-age female CD patients that initially show post-surgical remission (n = 113). This group recurred at a rate of 38%, with a median of 48 months (range 8-240) after pituitary surgery, similar to a recurrence rate of overall patients, 30.9% (76/246). This relative higher recurrence rate in comparison to mean of literature may be explained by the great long-term surveillance, 30 years, in our study.

Even though the patients having pregnancy after pituitary surgery presented a higher recurrence rate of 50%, there was no significant difference in relation to other subgroup (NP/PP) according to the survival-free recurrence curve. This higher recurrence rate in the PA could be due to the subgroup being younger and having had longer follow-up time than the other.

Other parameters at diagnosis and PS periods for predicting recurrence were analyzed in this study. Recurrence patients showed a higher sinus cavernous invasion. Additionally, the lower survival-free recurrence was related to higher PS plasma ACTH more than 68.2 pg/mL at 5th PS Day and normal pituitary at pathological analyses.

We decided to study the influence of pregnancy on the recurrence rate of post-surgical CD patients because in our clinic experience, we occasionally observe early recurrence in patients some months after pregnancy, even in patients considered “low risk”. We suggest that hormonal changes that occur during the pregnancy may stimulate putative tumor cell remnants. There is no similar study in the literature. However, one interesting study analyzed the impact of pregnancy on progression of corticotropic tumor after bilateral adrenalectomy in 11 patients with 20 pregnancies, and it concluded that pregnancy does not accelerate corticotropic tumor growth and ACTH increase in Nelson’s syndrome [13].

A healthy pregnancy is considered a transient physiologic state of ‘hypercortisolism’ [14]. There is a state of increased HPA axis function, leading to increased circulating cortisol and ACTH levels, reaching values in the range seen in Cushing’s syndrome (CS). These changes may lead to a misdiagnosis of CS during this period, with clinical features mimicking those seen in patients with CS. However, these changes lack the specific clinical manifestations of CS [9].

The mechanisms of ACTH increase during normal pregnancy are not fully elucidated, but they may include placental synthesis and the release of biologically active corticotropin-releasing hormone (CRH) and ACTH, pituitary desensitization to cortisol feedback, or enhanced pituitary responses to corticotropin-releasing factors, such as vasopressin and CRH [9, 10]. conditions that could stimulate the remnants of corticotropic tumor cells and cause CD recurrence.

On the other hand, the CRH-binding protein is elevated during the first two trimesters of pregnancy, but it decreases considerably in the final trimester, and bioavailable plasmatic CRH is consequently elevated [10, 15, 16].

CD in pregnancy is a rare phenomenon with few cases reported in the literature, and most of them are ACTH-independent [10]. CD is associated with fetal morbidity and mortality. When untreated, fetal mortality is nearly 20%, and treatment reduces but does not abolish this adverse outcome. Maternal morbidity includes hypertension, hyperglycemia, and eclampsia [17].

This study had some limitations that could influence the results. This study was retrospective and had a relatively small number of patients in each subgroup. Obstetric history was collected through telephone or email contacts in a portion of patients. However, we believe that the final number of included patients and quality of data were appropriate to perform this study.

We conclude that in our cohort, there was no difference in the recurrence rate in female patients according to pregnancy history. However, other studies with higher numbers of patients are necessary to confirm these data.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lia Mesquita Lousada, Mariuxi Jacqueline Borja Tapia and Marcio Carlos Machado. The first draft of the manuscript was written by Lia Mesquita Lousada and Marcio Carlos Machado and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The Ethical and Research Committees of our institution approved the study. For this type of study, formal consent is not required.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards.

Consent to participate

The Ethical and Research Committees of our institution approved the study. For this type of study, formal consent is not required.

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Figures

Figure 1

Recurrence-free survival curve according to pregnancy occurrence

PS, pituitary surgery