ISSN: 2378-3397

Ogolo et al. Int J Surg Res Pract 2025, 12:173
DOI: 10.23937/2378-3397/1410173
Volume 12 | Issue 1
Open Access

International Journal of
Surgery Research and Practice

ORIGINAL ARTICLE

Perioperative Dynamics of Serum Cortisol in Pituitary Adenoma Resection: Impact of Tumour Size and Surgical Approach

DE Ogolo[1,2*], Ndukuba KO[2], Akwada OR[2], Okwunodulu O[1], CA Ndubuisi[1], WC Mezue[1] and SC Ohaegbulam[1]

[1]*Memfys Hospital Enugu, Enugu State, Nigeria*

[2]*Division of Neurosurgery, Department of Surgery, Alex Ekwueme Federal University Teaching Hospital, Ebonyi State*

***Corresponding author:** *Dr. Donald Ogolo, Memfys Hospital Enugu, Enugu State, Nigeria*

Abstract

Background: Perioperative cortisol levels following pituitary tumour surgery are pivotal in the postoperative endocrine landscape. The interplay between tumour size, preoperative hormonal status, surgical approach, and subsequent management significantly influences cortisol dynamics. Understanding these intricacies is crucial for optimizing patient outcomes and ensuring hormonal balance during the critical perioperative period. This study aims to evaluate the perioperative dynamics of serum cortisol in patients undergoing transcranial and transsphenoidal resection of pituitary adenoma, and the relationship of pituitary tumour size on preoperative serum cortisol levels.

Results: In this retrospective cohort study, data from 64 patients with histologically confirmed pituitary adenoma resected within four years were analyzed. Exclusions were based on the absence of histology or early morning fasting serum cortisol levels. Among the cases, 39 were males and 25 females. The transcranial approach was used in 40 patients (62.5%), and the transsphenoidal approach in 24 patients (37.5%). Preoperative normal serum cortisol levels were observed in 35 patients (54.7%), while severe hypocortisolemia was noted in 17 patients (26.6%). Tumour size greater than 1 cm was significantly associated with preoperative hypocortisolemia (cortisol < 140 nmol/L) in 86.2% of patients compared to those with tumours less than 1 cm ($p = 0.0374$). No significant association was found between the surgical approach and postoperative cortisol levels ($p = 0.1083$). Additionally, there was no relationship between subnormal cortisol levels and the development and duration of postoperative diabetes insipidus ($p = 0.4389$ and 0.741, respectively).

Conclusions: This study demonstrated that a pituitary macroadenoma predicts preoperative hypocortisolism. However, increasing tumour size beyond 1 cm did not correlate with worsening trend in preoperative hypocortisolism. Furthermore, there was no significant correlation between the surgical approach and the development of postoperative hypocortisolism. These findings suggest that while tumour size is an important factor in preoperative hormonal status, the choice of surgical method does not significantly impact postoperative cortisol dynamics.

Keywords

Perioperative cortisol, Pituitary adenoma, Macroadenoma, Transsphenoidal, Transcranial, Surgical approach

List of Abbreviations

ACTH: Adrenocorticotrophic Hormone; MRI: Magnetic Resonance Imaging

Introduction

Pituitary tumours account for 15% of all intracranial tumours, with pituitary adenomas accounting for 85% of these [1-3]. Patients undergoing resection of a pituitary tumour are usually administered glucocorticoid therapy under certain circumstances, including those with biochemically confirmed low or subnormal levels of cortisol preoperatively as well as those with equivocally low cortisol levels preoperatively. Additionally, stress doses are sometimes administered intraoperatively

Citation: Ogolo DE, Ndukuba KO, Akwada OR, Okwunodulu O, Ndubuisi CA, et al. (2025) Perioperative Dynamics of Serum Cortisol in Pituitary Adenoma Resection: Impact of Tumour Size and Surgical Approach. Int J Surg Res Pract 12:173. doi.org/10.23937/2378-3397/1410173

Accepted: January 28, 2025; **Published:** January 30, 2025

when such levels are below normal preoperatively. Considering the low safety profile of glucocorticoids in terms of side effects, it is imperative that administration is indicated.

Cortisol is a steroid hormone synthesized from the zona fasciculata of the adrenal gland under the influence of adrenocorticotropic hormone (ACTH) secreted by the anterior pituitary gland and corticotropin-releasing hormone in the paraventricular nucleus of the hypothalamus [4-6]. Amongst the important functions of cortisol within the body include mediating immune responses, regulating glucose and protein metabolism, inflammatory response as well as stress response [7], including surgical stress and stress from pathological entities. Thus, low cortisol levels can negatively impact a patient's ability to withstand a disease process as well as to successfully go through a surgical process with lower intraoperative and postoperative complications. Similarly, a supranormal level of serum cortisol can be associated with several adverse effects.

Most supranormal serum cortisol levels (hypercortisolism) in neurosurgery are found in the setting of functional, secreting pituitary macroadenomas (Cushing's disease) [8-10]. In such situations, excessive secretion of ACTH from a functional pituitary tumour results in supranormal stimulation of a normal adrenal gland to produce high amounts of cortisol.

The physiological levels of cortisol follow a circadian rhythm, varying throughout the day with peak levels occurring during the morning hours from 7 a.m. to 9 a.m. [4,11]. This phenomenon, known as the cortisol awakening response, is characterized by a 38-75% increase in the basal levels of serum cortisol shortly after morning awakening, and it is said to occur in about 77% of normal individuals [11,12]. After its peak, the serum cortisol levels continually decrease throughout the day and troughs around midnight, and subsequently start to build up until its peak within the morning hours. These rhythms however differ individually. Individuals more active deep into the night or who have sleep disorders at night have been shown to have a much-delayed peak cortisol levels in the following morning [13-15]. Conversely, those who have a much earlier wake-up time, (such as morning shift workers with wake-up between 4 a.m. to 5.30 a.m.) have a greater and more prolonged cortisol awakening response [15,16]. Cortisol levels also increase during fasting [17].

Occasionally and rarely, non-functioning pituitary adenomas can cause hypocortisolism or secondary adrenal insufficiency, especially in apoplexy [18-20]. In such circumstances, production of ACTH is interrupted by haemorrhage and necrosis of the gland. More commonly in neurosurgery, hypocortisolism may follow injury to the pituitary gland during resection of a pituitary adenoma [21], or a surgery involving a pathology within the sellar region.

Before a pituitary surgery, it is imperative that all patients undergo an endocrinologic assessment. Part of this assessment involves an evaluation of the status of their hypothalamic-pituitary-adrenal axis. Serum morning cortisol is regarded as most accurate test for hypocortisolism in such patients, and 24-hour urine free cortisol for hypercortisolism [22]. To assess for axis recovery in patients on exogenous steroids, the dose of the exogenous steroid is typically skipped the night before and a fasting early morning cortisol is assessed next day. Conversely, it is required that cortisol levels are optimized prior to surgery. This improves the ability of the patient to withstand the stress of surgery. Cortisol test for optimization of the patient for surgery however does not require skipping the previous night dose because the objective of this test is not to assess for axis recovery which might take a longer time to recover. Moreover, most axis failures result from suppression of the pituitary function by the pathology or complications of the pathology. Thus, recovery will depend largely on excision of the offending pathology. If such preoperative cortisol is low, the protocol in the author's centre is to either administer an intraoperative stress dose of the steroid intraoperatively, in cases of emergency, or to administer orally in elective cases while monitoring for adverse effects of steroid use including steroid induced diabetes and infections.

While several studies have evaluated cortisol levels following transsphenoidal surgeries, very few have assessed the effects of the transcranial approach, as well as the dynamics of preoperative and postoperative cortisol levels following transsphenoidal and transcranial surgeries. This study thus aims to evaluate the perioperative dynamics of serum cortisol in patients undergoing transcranial and transsphenoidal resection of pituitary adenoma, as well as the relationship of pituitary tumour size on preoperative serum cortisol levels.

Methods

This was a retrospective cohort study assessing perioperative cortisol dynamics on all patients with histologically confirmed pituitary adenoma following surgical resection at the study location within a four-year period, following due institutional ethical approval and consent. Data was obtained from patient case notes and operative records. Data obtained included patient biodata, surgical approach utilized, pituitary tumour size, development of post-operative diabetes insipidus, and pre-operative early morning fasting serum cortisol done at first clinic visit, as well as day one or two post-operative early morning fasting serum cortisol levels.

Inclusion criteria included all patients who underwent surgical resection for an eventual histologically confirmed pituitary adenoma, with measurement of early morning fasting serum cortisol. Patients without histology of pituitary adenoma or early morning fasting serum cortisol were excluded. Obtained data was collated and analysed by descriptive and inferential statistics. P value < 0.05 was regarded as statistically significant.

Results

A total of 64 cases of histologically confirmed pituitary adenoma were seen within the period (Table 1). Males accounted for 60.9% and females accounted for 39.1%, giving a male to female ratio of 1.6:1. Pituitary adenoma was most seen in patients between 46- to 60-year-old (42.2%), followed by the 31- to 45-year-old group (29.7%). Giant pituitary adenoma (> 4 cm in size) was the commonest (48.4%) while pituitary microadenoma (< 1 cm) accounted for the least (6.3%) (Table 1). Transcranial approach was carried out in 40 patients (62.5%) while the transsphenoidal approach was utilized in 24 patients (37.5%). Preoperative normal cortisol (140-700 nmol/L) was observed in 54.7% of cases while severe hypocortisolemia (< 80 nmol/L) was observed in 26.6% (Table 1).

Table 1: Patient demographics, tumour size, surgical approach, and preoperative fasting cortisol levels.

	Frequency
Sex	
Male	39
Female	25
Age (years)	
0-15	0
16-30	5
31-45	19
46-60	27
61-75	10
> 75	3
Pituitary tumour size	
< 1 cm	4
1-4 cm	29
> 4 cm	31
Surgical Approach	
Transcranial	40 (62.5%)
Transsphenoidal	24 (37.5%)
Preoperative cortisol (fasting early morning) at first clinic visit post radiologic diagnosis	
< 80 nmol/L	17 (26.6%)
80-140 nmol/L	12 (18.8%)
140-700 nmol/L	35 (54.7%)

The relationship of the tumour size to pre-operative cortisol levels was evaluated using Fischer test. A tumour size > 1 cm was significantly associated with pre-operative hypocortisolaemia (cortisol < 140 nmol/L) in 86.2% of patients who presented with hypocortisolism compared to tumours < 1 cm (p = 0.0374) (Figure 1). After a size of 1 cm, there was no direct association between the size of an adenoma and the likelihood of worsening hypocortisolaemia.

Early morning fasting cortisol levels were done on the second post-operative day. Two broad surgical approaches were used - transcranial and trans-sphenoidal approaches. The effect of the surgical approach utilized on post-operative cortisol levels was analyzed using chi square test. There was no relationship between surgical approach and post-operative cortisol levels (p = 0.1083) (Figure 2).

Furthermore, the relationship between the presence of pre-operative serum cortisol levels and the subsequent development of diabetes insipidus post-operatively was evaluated using Fischer exact test. There was no relationship between both subnormal cortisol levels (< 140 nmol/L) and normal cortisol levels (140-700 nmol/L), and the development of diabetes insipidus post-operatively (p = 0.4389) (Figure 3).

The preoperative and post-operative cortisol levels are shown in Table 2. Most patients with pituitary adenoma had normal cortisol values both preoperatively and postoperatively.

Similarly, there was no established relationship between post-operative serum cortisol levels and the duration or length of post-operative diabetes insipidus (p = 0.741) (Figure 4).

Discussion

This study noted a male dominance of pituitary adenoma compared to the female sex, with males accounting for nearly twice as much as females with pituitary adenoma (1.6:1) (Table 1). Many literatures done within Europe and Middle East had observed greater female preponderance, especially during child-bearing age (18-45 years) [23-25]. This might be because sex incidence in pituitary adenomas is dependent on several factors. Some studies have shown that female sex is more positively associated with microadenomas and prolactinomas while macroadenomas and endocrine-inactive and growth hormone adenomas were more prevalent amongst the male sex [24-

Table 2: Peri-operative cortisol levels.

Cortisol levels (nmol/L)	**Pre-operative cortisol (at first clinic visit post-radiologic diagnosis)**	**Post-operative cortisol (day 1-2 post-surgery)**
< 80	17 (26.6%)	6 (9.4%)
80-140	12 (18.8%)	12 (18.8%)
> 140-700	35 (54.7%)	46 (71.9%)

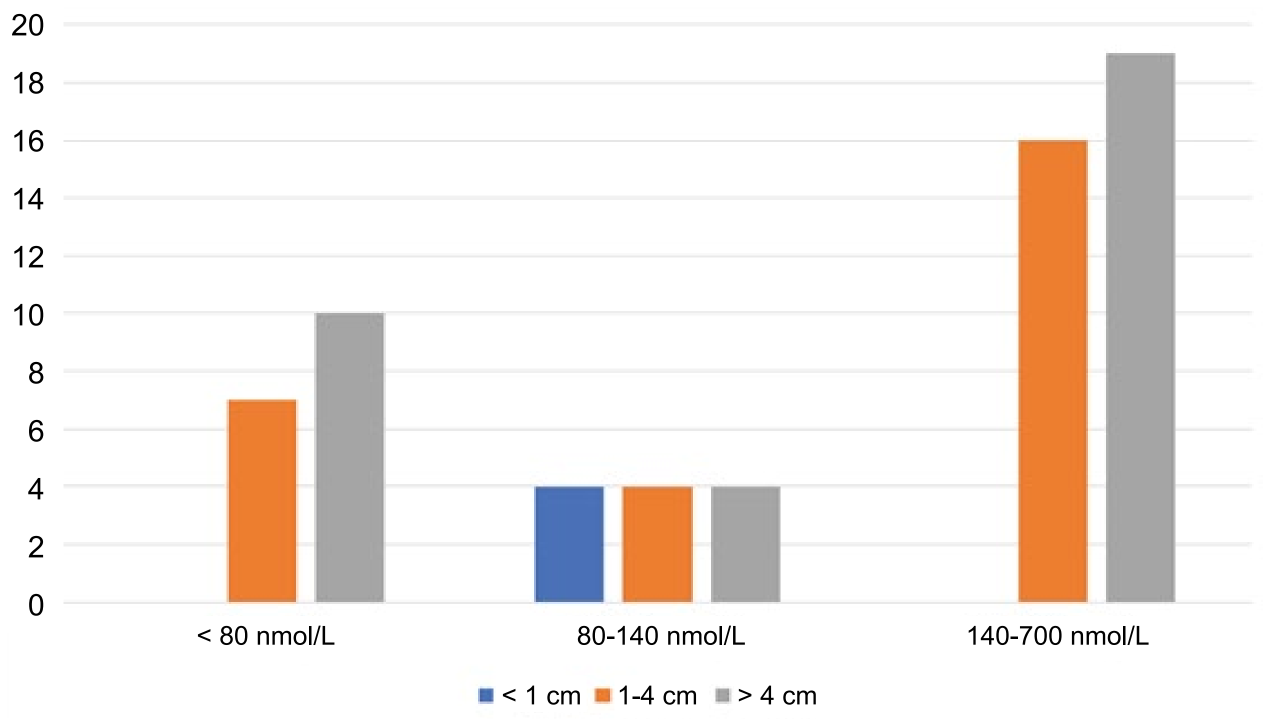

Figure 1: Relationship of tumour size to preop cortisol.

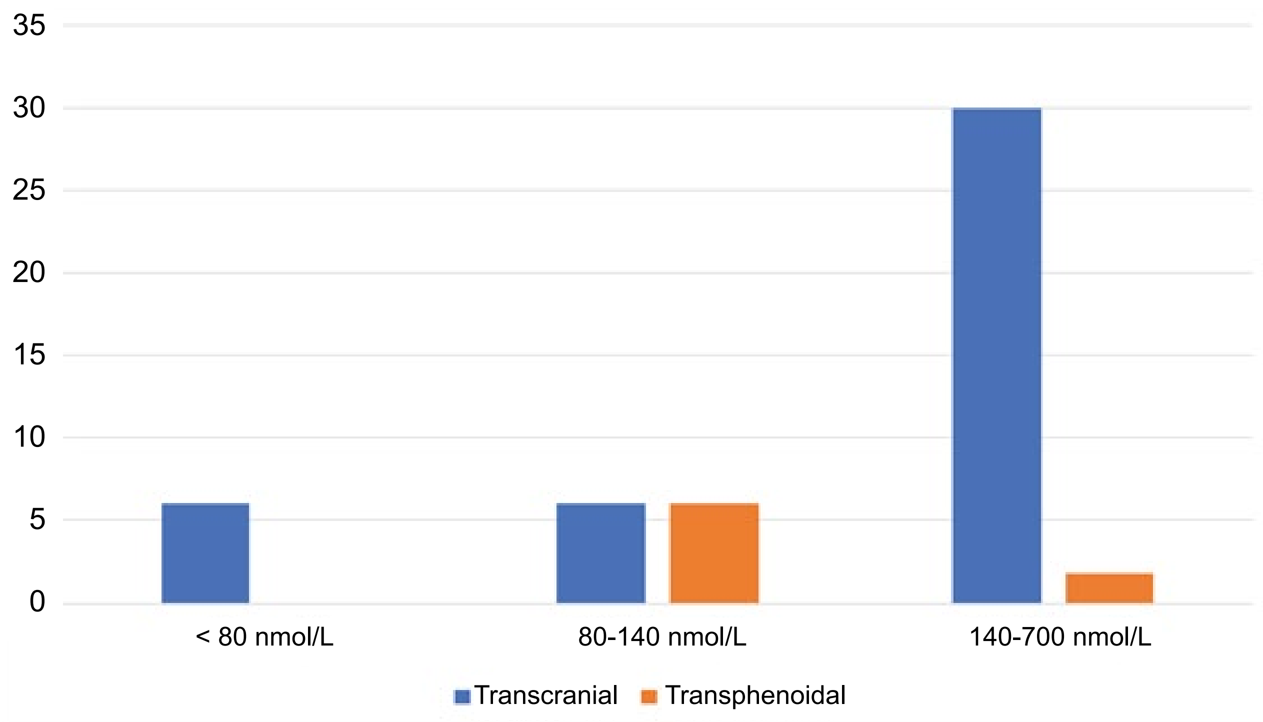

Figure 2: Relationship of surgical approach to post-operative cortisol (on Day 2).

26]. Furthermore, microadenomas are usually discovered incidentally or produce symptoms by being endocrinologically active rather than by mass effect as observed with macroadenomas. Hormone over-activity during reproductive age might also account for early overt expression of microadenomas within the female sex during child-bearing years, and earlier presentation for diagnosis. Similar studies had shown near equal frequency between both sexes outside the reproductive years of the female sex [27,28]. In contrast to several literatures, this study demonstrated a higher incidence of macroadenomas than microadenomas. This can be attributed to the fact that most microadenomas in these studies were discovered incidentally, or at autopsy for other unrelated pathologies [29]. Autopsy studies had shown about 25% of people have undiagnosed microadenomas [29,30].

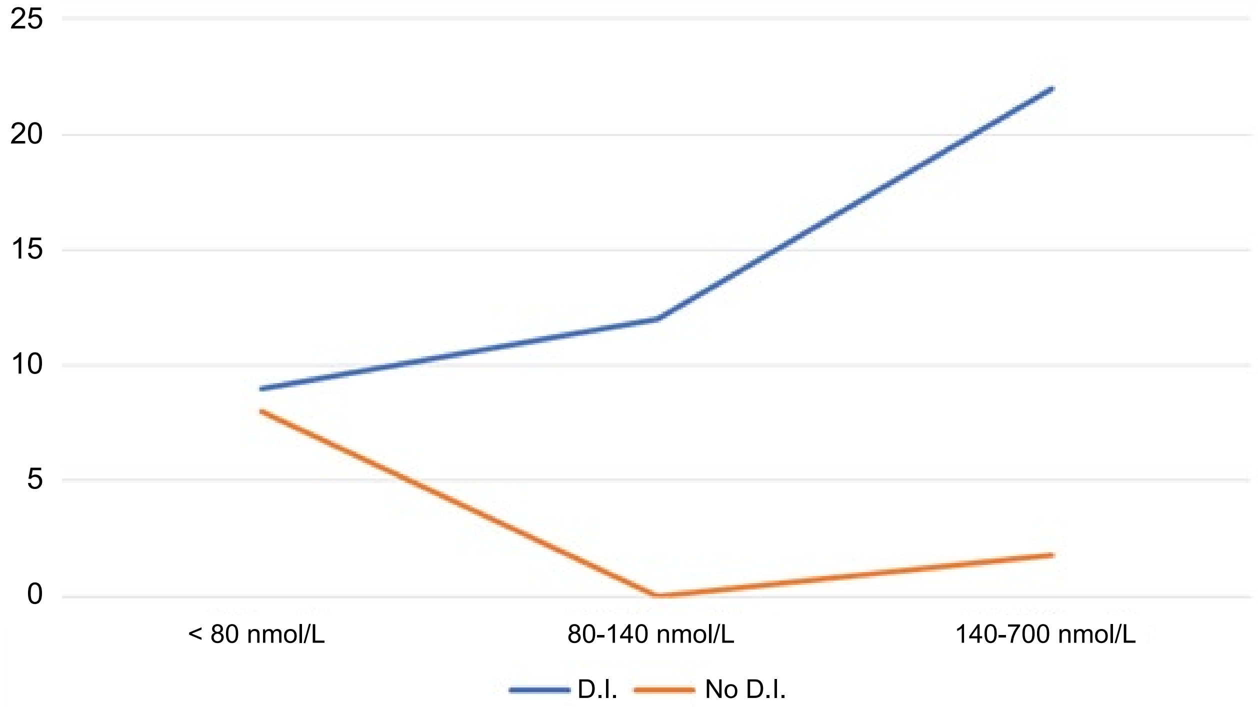

Figure 3: Relationship between preoperative cortisol levels and development of post-operative diabetes insipidus.

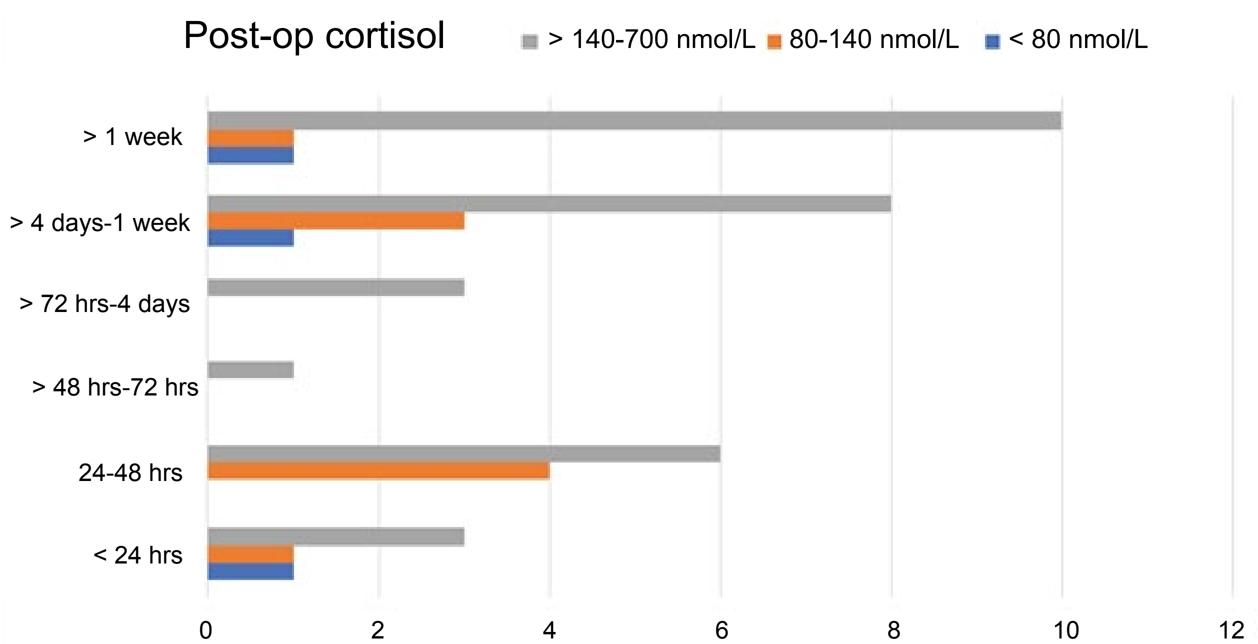

Figure 4: Relationship between post-op serum cortisol and length of post-op diabetes insipidus.

Approximately 10% of the healthy population have also been demonstrated to harbour a microadenoma on MRI scan [23]. Moreover, microadenomas typically come to the fore due to hormonal dysfunctions it elicits. Most of such patients are treated medically for unrelated problems with low index of suspicion for a pituitary tumour aetiology. The overt symptoms that relate to the pituitary aetiology might only occur when the tumour becomes large enough to cause visual disturbances or problems related to compression of the structures within and around the sellar. Thus, though the symptoms of a pituitary microadenoma presents comparatively earlier, these might not be appropriately tackled until it grows large enough to elicit typical sellar pathology symptoms. Giant adenomas were the most frequently seen size of adenomas (Table 1). They are a class of pituitary macroadenomas whose extent goes far beyond the normal confines of the pituitary region within the sellar, or more objectively, whose diameter exceeds 4 cm [23]. Majority of pituitary adenomas in this study were seen in ages 45-60 years (Table 1). Most studies done globally however place the highest occurrence within the 4th decade of life [25,26]. These studies however demonstrate a greater preponderance of microadenomas which are the commonest type of pituitary adenomas seen in such young age groups. Macroadenomas however, which accounted for the commonest adenomas seen in this study, are commonly seen in the older age groups [25].

Approaches used in surgeries for pituitary tumours depends on several factors including patient preference, degree of pneumatization of the sphenoid sinuses, the relationship of the tumour to adjacent neurovascular structures, tumour size, surgeon skill, among other factors. Transsphenoidal approach might be an ideal approach for a patient with completely intrasellar tumour with no surrounding neurovascular attachments, and with a well pneumatized sphenoid sinus. The greater number of transcranial approaches observed in this study (64.5%) arose from these potential factors. The maximal goal was maximal tumour resection.

Cortisol plays a vital role in stress responses to neurological pathologies and cranial surgeries. Pathologies affecting the hypothalamo-pituitary-adrenal axis affects the dynamics of cortisol elaboration peri-operatively. Majority of patients (54.7%) with histologically confirmed pituitary adenoma had normal serum fasting cortisol (140-700 nmol/L) at their first clinic visit following radiologic diagnosis of the sellar region tumour. Majority of those with hypocortisolemia had severe hypocortisolemia (26.6%) at similar visits. This latter finding can be explained by the fact that most of these patients, especially those who had not been diagnosed earlier at a different facility before referral to our facility, had not yet commenced steroids. Some of the patients who had been placed on exogenous steroids prior to referral to our facility but who presented with low fasting cortisol had huge tumour burdens which suppressed pituitary function and blunted the effects of such exogenous cortisol. Such patients eventually required intravenous doses of cortisol to adequately optimize the cortisol for surgery. Additionally, a few of these patients had been on prolonged cortisol replacement therapy from their previous referral facility while concomitantly delaying presentation to our facility and thus, delaying definitive treatment. Thus, the role of these prolonged exogenous steroids as culprits in suppressing the corticotropin-ACTH-cortisol axis and ultimately deflating serum cortisol levels cannot be ruled out in such instances.

In this study, the tumour size was demonstrated to have significant relationship to the preoperative cortisol levels. This was in keeping with other studies which demonstrated similar findings [31,32]. This can be attributed to mass effect of the tumour on normal functioning corticotrophs. When compared to a microadenoma (tumour size < 1 cm), a macroadenoma (tumour size > 1 cm) was significantly more associated with lower pre-operative serum cortisol levels. However, the influence of tumour size on preoperative cortisol level was lost after tumour sizes > 1 cm. Thus, a macroadenoma > 4 cm for instance, was not associated with lower serum cortisol levels than a macroadenoma size of 2 cm.

The majority of patients (71.9%) displayed normal postoperative fasting cortisol levels (> 140-700 nmol/L), while a smaller proportion showed low cortisol levels (9.4%, < 80 nmol/L), and 18.8% exhibited borderline values (80-140 nmol/L). These values indicated the extent of hormonal axis recovery following tumour resection, assessed on the second day post-surgery with the omission of the previous night's post-operative steroid therapy dose. Several factors may influence postoperative axis recovery. Occasionally, axis recovery can be prolonged and not immediate, especially in instances of a previous longstanding pathology. Besides, surgical manipulation of the hypothalamo-pituitary axis can delay recovery. Furthermore, the degree of preoperative suppression from steroid therapy can further delay recovery. Most of these patients had their cortisol levels preoperatively optimized to normal or borderline values prior to surgery. Borderline values, especially in cases of emergencies were supplemented with stress doses. This fairly accounted for the findings of higher frequencies of normal and borderline postoperative cortisol values obtained in this study.

Furthermore, this study demonstrated no significant associated between surgical approach and postoperative cortisol levels. The transsphenoidal route has severally been described as a relatively minimally invasive approach. It involves far less manipulation of brain tissue, utilizes a largely extradural approach, and involves lesser time for surgery in skilled hands. Thus, the stress of surgery would be expected to induce lower post-operative cortisol levels than with the more invasive and extensive transcranial route. However, the dynamics of serum cortisol in the presence of a pituitary tumour is quite different. Effect of Surgical approach on postoperative cortisol can be largely blunted by several other factors, more importantly, tumour size and volume, preoperative hormonal status. Thus, a patient with a macroadenoma and low preoperative cortisol levels on correction would be expected to have low postoperative levels. In this study, most patients had normal preoperative cortisol levels, either due to a non-functional non-corticotrophic tumour, a microadenoma or from ongoing correction with exogenous steroids. Thus, the findings of a non-significant association between the route of surgery and postoperative cortisol levels could have been blunted by these factors. Additionally, the development of post-operative diabetes insipidus or the length and duration of diabetes insipidus was not related to preoperative or postoperative levels of serum cortisol respectively.

Conclusion

This study demonstrated that a pituitary macroadenoma was predictive of preoperative hypocortisolism. However, progressively increasing tumour size after 1 cm was not predictive of a worsening trend in preoperative hypocortisolism. Furthermore, there was no significant correlation between surgical approach and the development of post-operative hypocortisolism. There was also no significant relationship between pre-operative hypocortisolism and development of postoperative diabetes insipidus, or between post-operative cortisol and duration of post-operative diabetes insipidus.

Declarations

Ethical approval and consent to participate

This study was conducted following due ethical approval from Memfys hospital ethical committee.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to strict patient confidentiality but are available from the corresponding author on reasonable request.

Competing interest

No competing interest.

Funding

None.

Authorship contributions

Ogolo D.E: Conceptualization, formulation, software, formal analysis, investigation, writing-original draft preparation, visualization; Ndukuba KO: Formal analysis, supervision; Akwada OR: Supervision, analysis; Okwunodulu O: Supervision; Ndubuisi CA: Supervision; Mezue WC: Supervision; Ohaegbulam SC: Supervision.

Acknowledgement

Not applicable.

References

1. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe H Jr, et al. (2007) Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 156: 203-216.
2. Tohti M, Li J, Zhou Y, Hu Y, Yu Z, et al. (2015) Is peri-operative steroid replacement therapy necessary for the pituitary adenomas treated with surgery? A systematic review and meta analysis. PLoS One 10: e0119621.
3. Thapar K, Kovacs K, Laws E (1995) The classification and molecular biology of pituitary adenomas. Adv Tech Stand Neurosurg 22: 3-53.
4. Ramamoorthy S, Cidlowski JA (2016) Corticosteroids: Mechanisms of action in health and disease. Rheum Dis Clin North Am 42: 15-31.
5. Angelousi A, Margioris AN, Tsatsanis C, Feingold KR, Anawalt B, et al. (2020) ACTH Action on the Adrenals. Endotext.
6. Thau L, Gandhi J, Sharma S (2023) Physiology, cortisol. Treasure Island (FL): StatPearls Publishing.
7. Oakley RH, Cidlowski JA (2013) The biology of the glucocorticoid receptor: New signaling mechanisms in health and disease. J Allergy Clin Immuno 132: 1033-1044.
8. Brue T, Castinetti F (2016) The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis 11: 135.
9. Chaudhry HS, Singh G (2023) Cushing syndrome. StatPearls [Internet] Treasure Island (FL) StatPearls Publishing.
10. Kairys N, Anastasopoulou C, Schwell A, Haddad LM (2023) Cushing disease (Nursing). StatPearls [Internet] Treasure Island (FL) StatPearls Publishing.
11. Wust S, Wolf J, Hellhammer DH, Federenko I, Schommer N, et al. (2000) The cortisol awakening response-normal values and confounds. Noise Health 2: 79-88.
12. Fries E, Dettenborn L, Kirschbaum C (2009) The cortisol awakening response (CAR): Facts and future directions. Int J Psychophysiol 72: 67-73.
13. Lindholm H, Ahlberg J, Sinisalo J, Hublin C, Partinen M, et al. (2012) Morning cortisol levels and perceived stress in irregular shift workers compared with regular daytime workers. Sleep Disord 2012: 789274.
14. Hirotsu C, Tufik S, Andersen ML (2015) Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Sci 8: 143-152.
15. Federenko I, Wüst S, Hellhammer DH, Dechoux R, Kumsta R, et al. (2004) Free cortisol awakening responses are influenced by awakening time. Psychoneuroendocrinology 29: 174-184.
16. Backhaus J, Junghanns K, Hohagen F (2004) Sleep disturbances are correlated with decreased morning awakening salivary cortisol. Psychoneuroendocrinology 29: 1184-1191.
17. Højlund K, Wildner-Christensen M, Eshøj O, Skjaerbaek C, Holst JJ, et al. (2001) Reference intervals for glucose, beta-cell polypeptides, and counterregulatory factors during prolonged fasting. Am J Physio Endocrino Metab 280: E50-E58.
18. Mattke AF, Vender JR, Anstadt MP (2002) Pituitary apoplexy presenting as addisonian crisis: after coronary artery bypass grafting. Tex Heart Inst J 29: 193-199.
19. Blasco AML, Portuondo ESG, Martínez AR (2014) Pituitary adenoma as a rare form of secondary adrenal insufficiency. A Case Report. MediSur 12: 118-124.
20. Hsu C-C, Lin H-D, Huang C-Y, Chiang Y-L (2022) Unusual manifestations of adrenal insufficiency: A case report of hypopituitarism and Well's syndrome after apoplexy of a silent pituitary gonadotropic adenoma. Medicine 101: e29274.
21. Butenschoen VM, von Werder A, Bette S, Schmette V, Schwendinger N, et al. (2022) Transsphenoidal pituitary adenoma resection: Do early post-operative cortisol levels predict permanent long-term hypocortisolism?. Neurosurg Rev 45: 1353-1362.

22. Chandler WF (2009) Treatment of disorders of the pituitary gland: Pearls and pitfalls from 30 years of experience. Clin Neurosurg 56: 18-22.

23. Jane JA Jr, Catalino MP, Laws ER Jr, Feingold KR, Anawalt B (2000) Surgical treatment of pituitary adenomas. Endotext [Internet].

24. Mindermann T, Wilson CB (1994) Age□related and gender□related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 41: 359-364.

25. Aljabri KS, Bokhari SA, Assiri FY, Alshareef MA, Khan PM (2016) The epidemiology of pituitary adenomas in a community-based hospital: A retrospective single center study in Saudi Arabia. Ann Saudi Med 36: 341-345.

26. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, et al. (2006) High prevalence of pituitary adenomas: A cross-sectional study in the province of Liege, Belgium. J Clini Endocrinol Metab 91: 4769-4775.

27. Robinson N, Beral V, Ashley J (1979) Incidence of pituitary adenoma in women. Lancet 2: 630.

28. Annegers J, Coulam C, Abboud C, Laws E Jr, Kurland L (1978) Pituitary adenoma in Olmsted County, Minnesota, 1935--1977. A report of an increasing incidence of diagnosis in women of childbearing age. Mayo Clin Proc 53: 641-643.

29. Tomita T, Gates E (1999) Pituitary adenomas and granular cell tumors: Incidence, cell type, and location of tumor in 100 pituitary glands at autopsy. Am J Clin Pathol 111: 817-825.

30. Costello RT (1936) Subclinical adenoma of the pituitary gland. Am J Patho 12: 205-216.1.

31. Zhao M, Li K, Niu H, Zhao Y, Lu C (2023) Perioperative hormone level changes and their clinical implications in patients with pituitary adenoma: A retrospective study of 428 cases at a single center. Front Endocrinol 14: 1286020.

32. Staby I, Krogh J, Klose M, Baekdal J, Poulsgaard L, et al. (2021) Pituitary function after transsphenoidal surgery including measurement of basal morning cortisol as predictor of adrenal insufficiency. Endocr Connect 10: 750-757.