Bilateral Adrenalectomy in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

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Context: Management of congenital adrenal hyperplasia (CAH) involves suppression of the hypothalamic–pituitary–adrenal axis using supraphysiological doses of exogenous glucocorticoids. This can pose a challenge, with Cushing syndrome a frequent complication of adequate suppression. Bilateral adrenalectomy, with subsequent replacement of glucocorticoids and mineralocorticoids at physiological doses, has been proposed as an alternative therapeutic strategy.

Objective: To review the outcomes after bilateral adrenalectomy for CAH.

Data Sources: A systematic search of PubMed/MEDLINE and Web of Science, identifying relevant reports published up to 10 January 2018.

Study Selection: Case reports or case series were included if they reported individual patient data from patients with CAH who had undergone bilateral adrenalectomy.

Data Extraction: Information regarding the following was extracted: first author, country, sex, age at adrenalectomy, year of adrenalectomy, diagnosis, molecular abnormality, pre- and postoperative biochemistry, pre- and postoperative medications, pre- and postoperative body mass index, indication for adrenalectomy, surgical technique, gross and microscopic adrenal characteristics, follow-up duration, and short- and long-term postoperative outcomes.

Data Synthesis: We identified 48 cases of bilateral adrenalectomy for CAH, with patients aged from 4 months to 56 years at surgery. The most common indication for surgery was the inability to control hyperandrogenism/virilization and/or Cushing syndrome (n = 30; 62%). Most patients (n = 34; 71%) reported symptomatic improvement postoperatively, with some cases of short-term (n = 5; 10%) and long-term (n = 13; 27%) adverse outcomes.

Conclusions: Bilateral adrenalectomy for CAH appears to be a reasonable therapeutic option for carefully selected patients who have had unsatisfactory outcomes with conventional medical management. **(*J Clin Endocrinol Metab* 103: 1767–1778, 2018)**

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by loss of function of the enzymes required for adrenal steroidogenesis. Of all cases, 95% to 99% will be due to deficiency of 21-hydroxylase (21OHD), leading to impaired synthesis of cortisol and, to a varying extent, of aldosterone, with subsequent accumulation of adrenal steroid precursors, including 17-hydroxyprogesterone (17OHP) and androgens

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Abbreviations: 11OHD, 11β-hydroxylase deficiency; 21OHD, 21-hydroxylase; 17OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HCE, hydrocortisone equivalent; HPA, hypothalamic–pituitary–adrenal; SV, simple virilizing; SW, salt-wasting; TART, testicular adrenal rest tumor.

(1–4). CAH is classified into classic and nonclassic forms, with the classic form further subdivided into salt-wasting (SW) and simple virilizing (SV) phenotypes. Genotype and phenotype correlate well, with particular mutations strongly associated with each of the classic and nonclassic phenotypes (5, 6).

Less common causes of CAH include 11β-hydroxylase deficiency (11OHD) and 17α-hydroxylase deficiency, both resulting in mineralocorticoid excess, with androgen and estrogen deficiencies also present in the latter. Additionally, even rarer variants such as 3β-hydroxysteroid dehydrogenase deficiency exist (2, 7).

Administration of exogenous glucocorticoids was demonstrated in 1950 to be effective in reducing adrenal androgen production (8). Suppression of the hypothalamic–pituitary–adrenal (HPA) axis with glucocorticoid therapy remains standard management, with the addition of mineralocorticoid therapy when required (2, 9, 10). However, management can often prove frustrating for clinicians and patients, because the glucocorticoid doses required for adequate HPA axis suppression are frequently supraphysiological, leading to iatrogenic Cushing syndrome (11–13).

Bilateral adrenalectomy has been proposed as an alternative to conventional medical therapy, with proponents advocating the relative simplicity of managing adrenal insufficiency without the requirement for HPA axis suppression (14, 15). Concerns have been raised, however, about long-term complications, including the risk of subsequent adrenal crises and the development of gonadal adrenal rest tumors (11, 16). The aim of the present systematic review and meta-analysis was to clarify the outcomes of bilateral adrenalectomy in the management of CAH.

Methods

Search strategy

A systematic search of PubMed/MEDLINE and Web of Science was conducted to identify relevant reports published up to 10 January 2018 using the following search terms: "congenital adrenal hyperplasia," "21-hydroxylase deficiency," "11-beta-hydroxylase deficiency," "11β-hydroxylase deficiency," "CYP21A2," "3βHSD," "17α-hydroxylase," "CYP11B1," "P450 oxidoreductase deficiency," "lipoid adrenal hyperplasia," "side chain cleavage enzyme deficiency," and "adrenalectomy." No limits were placed on language, country, or publication date. Reports were initially screened by title for relevance and then by abstract, with full-text articles of potentially relevant reports reviewed. The reference lists of the retrieved full-text studies were scanned to identify additional relevant reports. Two of us (D.M. and H.F.) conducted the literature search independently, and the included and excluded articles were agreed on by consensus with reference to the criteria described in the next section.

Study selection and data extraction

Case reports or case series reporting bilateral adrenalectomy performed in individuals with CAH were included. Reports were excluded if data for patients with CAH were only presented as an aggregate with data from patients undergoing adrenalectomy for other indications. Review articles, editorials, and meeting abstracts were also excluded, as were reports of unilateral adrenalectomy. If a single case was described in multiple reports, all reports were reviewed to ensure the maximum detail of the case had been obtained.

The following information was extracted from each report: first author, country, sex, age at adrenalectomy, year of adrenalectomy, diagnosis, molecular abnormality, pre- and postoperative biochemistry, pre- and postoperative medications, pre- and postoperative body mass index, indication for adrenalectomy, surgical approach, gross and microscopic adrenal characteristics, follow-up duration, and short- and long-term postoperative outcomes. The use of a quality assessment (*e.g.*, the Newcastle-Ottawa Scale; available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was considered inappropriate because these instruments had not been developed to study case reports or series. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (17).

Statistical analysis

Values for the biochemical variables were converted to SI units. Glucocorticoid doses were converted to the daily hydrocortisone equivalent (HCE) using growth-retarding equivalents (hydrocortisone 20 mg equals cortisone acetate 25 mg equals prednisolone 4 mg equals dexamethasone 0.25 mg) (18). Differences between the mean pre- and postoperative variables, including medications (daily HCE and fludrocortisone), biochemical variables (17OHP, adrenocorticotropic hormone, androstenedione, testosterone), and body mass index were analyzed using the paired *t* test, or Wilcoxon signed-rank test when values were not normally distributed. Statistical significance was defined as $P < 0.05$. All analyses were performed using Rcmdr (R Commander; R package, version 2.4-1; in R version 3.4.2) (19, 20).

Results

The systematic search identified 300 potentially relevant records. Another five were identified through review of the reference lists. After removal of duplicates, 254 records were screened for eligibility, identifying 32 relevant articles for inclusion (Fig. 1), reporting 48 cases of bilateral adrenalectomy to treat CAH (14, 16, 21–54) (Table 1).

Preoperative characteristics

The preoperative characteristics of the patients who underwent bilateral adrenalectomy are detailed in Supplemental Table 1. Patient age at bilateral adrenalectomy ranged from 4 months to 56 years, with fairly even numbers undergoing surgery in childhood or adolescence (age ≤18 years; n = 26) compared with adulthood (n = 22). Most operations were performed in females, with only a few

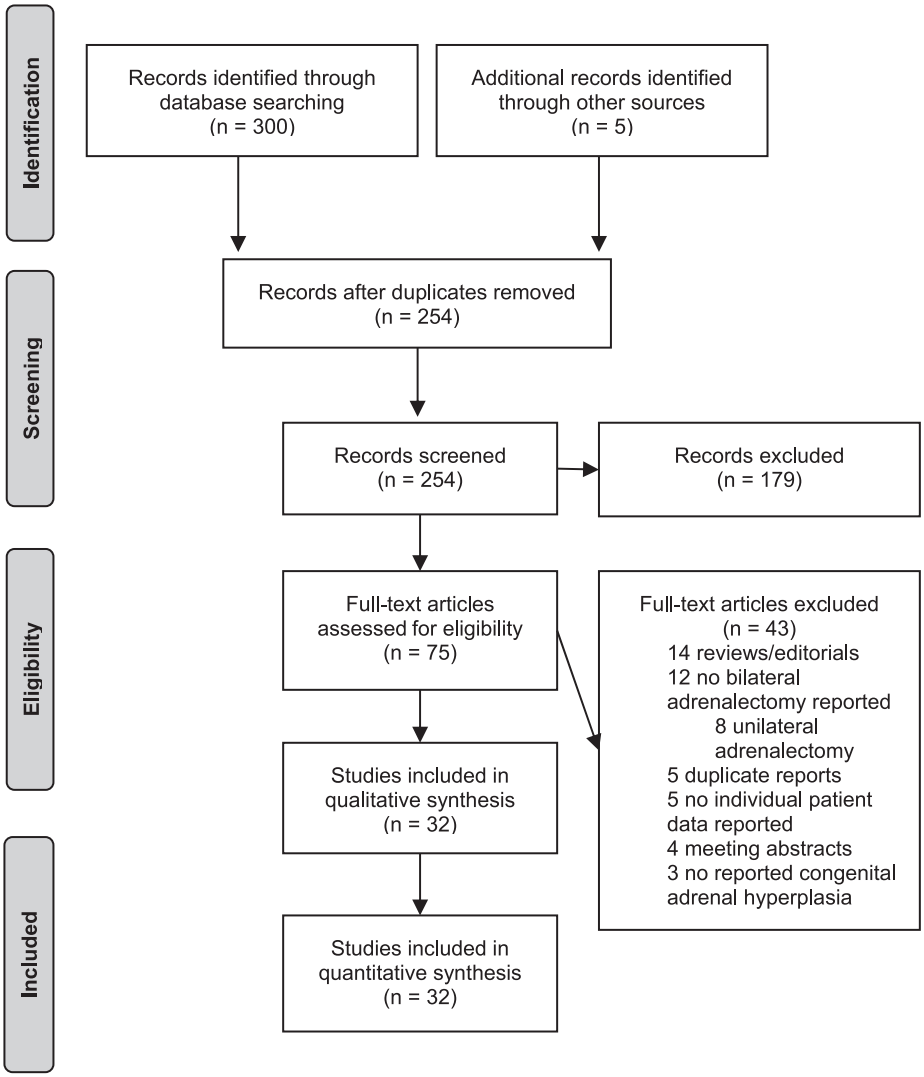

Figure 1. Flowchart illustrating the procedure for article inclusion and exclusion in a meta-analysis of bilateral adrenalectomy for CAH. A systematic search of PubMed/MEDLINE and Web of Science up to 10 January 2018, with manual searching of reference lists, identified 32 relevant reports of bilateral adrenalectomy in patients with CAH.

reported cases in males. Seven patients had 11OHD, with the remainder having 21OHD.

Indications for adrenalectomy

The most common primary indication for bilateral adrenalectomy was symptoms of hyperandrogenism or virilization (n = 25; 52%) (14, 16, 21, 24–32, 35, 39, 42). Five of these patients had received a trial of antiandrogen therapy before bilateral adrenalectomy, with one patient intolerant of treatment (16), and failure to achieve clinical or biochemical control of hyperandrogenism in the remaining four patients (16, 25, 30, 41). One woman from the latter group also desired fertility (41).

Iatrogenic Cushing syndrome was also a common primary indication (n = 10; 21%) (14, 15, 23, 32, 34, 44, 53), with 14 patients (29%) having both hyperandrogenism and Cushing syndrome listed as indications for surgery (16, 23–27, 31, 32, 34, 41). These indications accounted for a greater proportion of children and adolescents undergoing bilateral adrenalectomy (n = 21; 81%) compared with adults (n = 9; 41%; $P = 0.004$).

Infertility was the indication for bilateral adrenalectomy in three women (6%) (16, 41). Eight patients (17%) underwent adrenalectomy because of bilateral adrenal enlargements causing mass symptoms or concern for tumor formation; five of these patients had a history of nonadherence with medical therapy (35, 45, 46, 48, 49). Also, a 51-year-old man reported adherence but had not undergone biochemical monitoring for many years (51), and one patient was not previously known to have CAH and was therefore not receiving medical therapy (52). Five patients (10%), all with 11OHD, had undergone bilateral adrenalectomy for management of refractory hypertension (38, 43, 50). A 3-year-old girl with SW 21OHD underwent bilateral adrenalectomy as a prophylactic measure owing to concerns of disease severity

Table 1. Meta-Analysis of 48 Individuals With CAH Who Underwent Bilateral Adrenalectomy

	All Cases (n = 48)		Children/Adolescents (n = 26)		Adults (n = 22)	
Variable	**n (%)**	***P* Value**	**n (%)**	***P* Value**	**n (%)**	***P* Value**
Sex						
Female	35 (73)		22 (85)		13 (59)	
Male	12 (25)		4 (15)		8 (36)	
Not specified	1 (2)		0 (0)		1 (5)	
Mean age, y	20 ± 13		10 (5)		32 (10)	
Diagnosis						
11OHD	7 (15)		3 (12)		4 (18)	
21OHD	41 (85)		23 (88)		18 (82)	
SW	20 (42)		11 (42)		10 (45)	
SV	5 (10)		2 (8)		3 (14)	
Unspecified	16 (33)		10 (38)		5 (23)	
Indication for adrenalectomy[a]						
Hyperandrogenism/virilization	25 (52)		20 (77)		5 (23)	
Iatrogenic Cushing syndrome	19 (40)		12 (46)		7 (32)	
Adrenal mass/tumor	8 (17)		1 (4)		7 (32)	
Hypertension	5 (10)		2 (8)		3 (14)	
Infertility	3 (6)		0 (0)		3 (14)	
Prophylaxis	1 (2)		1 (4)		0 (0)	
Surgical technique						
Open	14 (39)		5 (28)		8 (47)	
Laparoscopic	22 (61)		13 (72)		9 (53)	
Median adrenal weight, g						
Left	26 (11.6, 382)		14 (7.0, 25)		36 (15.0, 298)	
Right	19.75 (9.09, 42.5)		10 (7.0, 17)		41 (9.85, 43.5)	
Median follow-up duration, mo	27 (14, 72)		27 (10, 84)		26 (21, 56)	
Early postoperative complications	5 (16)		1 (4)		4 (18)	
Stroke	1		1		0	
Hypertensive crisis	1		0		1	
Hypotension[b]	1		0		1	
Ileus[b]	1		0		1	
Wound	1		0		1	
Persistent tachycardia	1		0		1	
Long-term outcomes						
Symptomatic improvement	34 (71)		20 (77)		14 (64)	
Adrenal crisis[c]	8 (17)		5 (19)		3 (14)	
Ectopic ART[c]	5 (10)		5 (19)		0 (0)	
Live births	4 (8)		0 (0)		4 (18)	
Pituitary microadenoma[c]	2 (4)		2 (8)		0 (0)	
Mortality	1 (2)		1 (4)		0 (0)	
Ovarian carcinoma	1 (2)		1 (4)		0 (0)	
Chronic incision site pain	1 (2)		0 (0)		1 (5)	
Mean daily HCE, mg		0.02		0.35		0.03
Preoperative	38 ± 17		41 (21)		37 (14)	
Postoperative	26 ± 9		29 (13)		25 (5.8)	
Mean daily fludrocortisone dose, μg		1		0.42		0.40
Preoperative	163 ± 102		192 (156)		146 (53)	
Postoperative	147 ± 104		189 (147)		123 (62)	
Median 17OHP, nmol/L		< 0.001		0.12		0.008
Preoperative	60.0 (25.9, 158.0)		60.0 (27.9, 95.5)		68.4 (25.9, 249)	
Postoperative	5.4 (1.5,14.78)		8.4 (2.0, 20.9)		5.0 (0.6, 6.0)	
Median ACTH, pmol/L		0.44		0.5		0.88
Preoperative	90.25 (24.0, 119.3)		124 (78.0, 127)		89.5 (15.3, 98.0)	
Postoperative	234 (131.4, 684.4)		556 (278, 848)		157 (36.1, 245)	
Median androstenedione, nmol/L		< 0.001		0.02		0.13
Preoperative	13.5 (5.7, 34.0)		22.5 (6.2, 63.5)		9.52 (4.76, 18.9)	
Postoperative	0.55 (0.35, 2.69)		0.55 (0.30, 1.6)		1.0 (0.35, 2.7)	
Median testosterone, nmol/L		0.02		0.25		0.16
Preoperative	13.4 (5.4, 20.2)		18.5 (14.2, 20.3)		8.33 (3.85, 17.6)	
Postoperative	1.74 (0.35, 5.21)		3.50 (0.35, 5.20)		1.31 (0.65, 7.80)	

(*Continued*)

Table 1. Continued

Variable	All Cases (n = 48)		Children/Adolescents (n = 26)		Adults (n = 22)	
	n (%)	*P* Value	n (%)	*P* Value	n (%)	*P* Value
Median DHEAS, umol/L		0.06		0.13		1
Preoperative	1.1 (0.4, 1.2)		0.8 (0.3, 9.8)		1.06[d]	
Postoperative	0 (0, 0.2)		0.01 (0, 0.1)		0.41[d]	
Median DHEA, nmol/L		0.5				0.5
Preoperative	2.7 (2.6, 2.8)		NR		2.7 (2.6, 2.8)	
Postoperative	1.2 (1.0, 3.7)		6.3[d]		1.0 (1.0, 1.1)	
Mean BMI, kg/m^2		0.01				0.01
Preoperative	29 (6.3)		26 (7.6)		30 (5.6)	
Postoperative	27 (4.9)		NR		27 (4.9)	

Data presented as n (%), mean ± standard deviation, or median (quartile 1, quartile 3).

Abbreviations: ACTH, adrenocorticotropic hormone; ART adrenal rest tissue; BMI, body mass index; NR, not reported.

[a]Total percentage does not equal 100 because multiple indications were present in some cases.

[b]Both complications occurred in the same patient.

[c]Multiple events occurred in one patient.

[d]Values available for only one patient.

associated with her genotype (deletion/R356W) (22); this occurred after the death of an older sibling, who also had SW 21OHD, at the age of 18 months.

Postoperative results

The median follow-up duration after adrenalectomy was 27 months. Details regarding surgical approach and postoperative outcomes are presented in Supplemental Table 2. One patient did not return for postoperative follow-up examinations (45).

Operative technique and early postoperative complications

Bilateral adrenalectomy was performed laparoscopically in 22 cases and using an open approach in 14; the remainder of cases did not report the surgical approach. Also, the indications for surgical approach were not reported. The adrenal glands were enlarged in all patients for whom size was reported, including four cases of giant bilateral myelolipoma, with the largest reported tumor weighing 5.8 kg (46).

Five patients experienced early postoperative complications. A 16-year-old boy with 11OHD, who had undergone laparoscopic bilateral adrenalectomy for refractory hypertension, had three episodes of transient ischemic attack involving the territory of the middle cerebral artery. He had no residual neurologic deficit (38). Another patient with 11OHD developed a postoperative hypertensive crisis after laparoscopic adrenalectomy (54). One study reported persistent sinus tachycardia after open bilateral adrenalectomy in a 40-year-old man (49), and one study reported superficial wound infection after laparoscopic bilateral adrenalectomy in a 19-year-old woman (32). A 51-year-old man developed postoperative ileus with hypotension after adrenalectomy performed for large bilateral adrenal myelolipomas; the surgical approach was not reported (51).

Mortality

One study reported a patient death after bilateral adrenalectomy (21). In the earliest reported case, bilateral adrenalectomy was performed as a staged procedure, with right adrenalectomy at age 4 months, followed by left adrenalectomy at age 5 months. The infant died 1 month after left adrenalectomy of pneumonia. Death was preceded by the development of hyperpigmentation.

Medical therapy

The mean daily HCE was reduced by 12 mg (from 38 mg to 26 mg; 32%; $P = 0.02$) after adrenalectomy (Table 1). The mean daily fludrocortisone dose was unchanged.

Biochemical parameters

The median 17OHP was reduced by 91% after bilateral adrenalectomy [Table 1; Fig. 2(a)]. Androstenedione was 96% lower postoperatively [Fig. 2(b)], and testosterone was reduced by 87% [Fig. 2(c)]. No substantial change was found in adrenocorticotropic hormone [Fig. 2(d)], dehydroepiandrosterone (DHEA) or DHEA sulfate (DHEAS) levels postoperatively (Table 1).

Impact on symptoms

Most patients (74%) reported symptomatic improvement after adrenalectomy (Table 1). This included improvements in features of hyperandrogenism, recommencement of menses or onset of menarche, increased growth velocity, and improvements in Cushingoid features, in particular, weight loss. The mean body mass

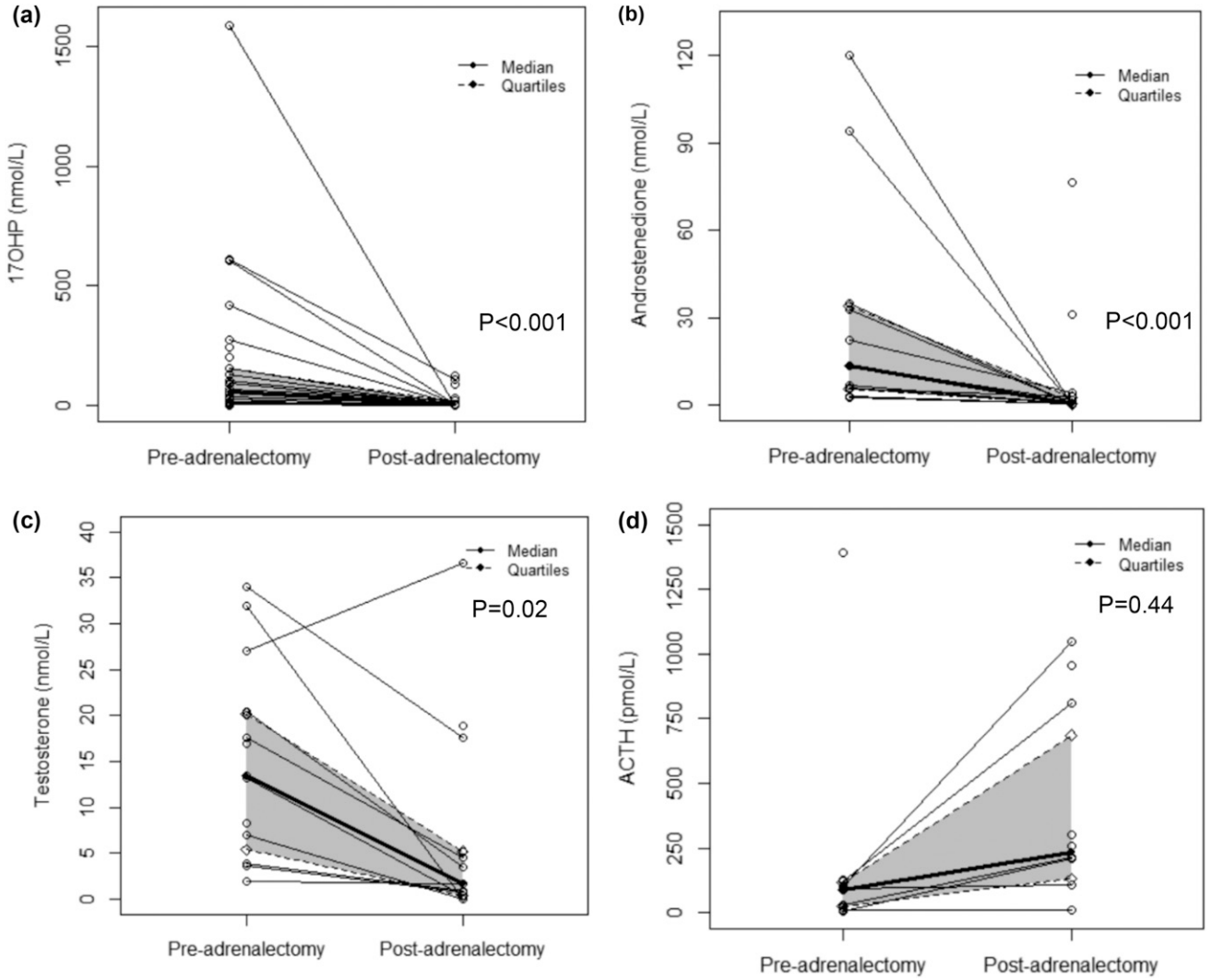

Figure 2. Biochemical parameters before and after bilateral adrenalectomy performed in patients with CAH. The meta-analysis of 48 patients with CAH who had undergone bilateral adrenalectomy demonstrated postoperative reductions in (a) 17OHP ($P < 0.001$), (b) androstenedione ($P < 0.001$), and (c) testosterone ($P = 0.02$), with (d) no statistically significant change in adrenocorticotropic hormone (ACTH; $P = 0.44$). Shaded areas indicate interquartile ranges.

index was reduced from 29 kg/m^2 preoperatively to 27 kg/m^2 postoperatively ($P = 0.01$). Ten case reports specifically reported patient or parental satisfaction and/or improvements in body image (14, 22, 23, 31, 32, 39, 44) but more detailed accounts of psychological outcomes were not provided.

Of the five patients undergoing bilateral adrenalectomy for treatment of hypertension (all with 11OHD), three had remission of hypertension and were able to cease antihypertensive agents (43, 50); left ventricular hypertrophy, demonstrated by echocardiography, was also decreased postoperatively in two of these patients. The remaining two patients required ongoing hypertensive therapy (38). Of these two patients, one had a reduction in the required antihypertensive therapy; however, details of the postoperative antihypertensive therapy for the other patient were not reported.

Fertility

Three women underwent bilateral adrenalectomy for management of primary infertility (16, 41); all three of these women subsequently conceived. One additional case of pregnancy was reported after bilateral adrenalectomy performed because of difficulty controlling hyperandrogenism (42). All offspring were reportedly healthy at delivery.

Adrenal crises

Eight patients (17%) developed adrenal crises after adrenalectomy (Table 1; Supplemental Table 2) (14, 16, 32, 33, 35, 37). This corresponded to 14.8 adrenal crises per 100 patient-years. Five of the eight patients were children or adolescents (14, 16, 33, 35, 37). The adrenal crises in four patients were precipitated by infection (14, 16, 32), and one patient developed an adrenal crisis after extraction

of a wisdom tooth (33); details regarding the precipitant in the remaining three patients were not reported.

Most of the affected patients experienced a single episode in the reported follow-up period, with no subsequent crises after adjustment of the glucocorticoid dosage and emphasis on sick day management. One woman experienced three reported episodes of crisis after adrenalectomy, with no clearly identified precipitant (16). She had been reported to have intermittent adherence to medical therapy before bilateral adrenalectomy, and this pattern was suspected to have continued postoperatively. One other woman, who had undergone bilateral adrenalectomy at 16 years for treatment of hyperandrogenism, also experienced an adrenal crisis after adrenalectomy in the setting of variable adherence to medical therapy. This patient had had a history of drug abuse and nonadherence to therapy before adrenalectomy, with multiple preoperative episodes of adrenal crisis (35, 37).

Two girls, aged 1.3 and 8.1 years at bilateral adrenalectomy, experienced adrenal crises complicated by hypoglycemic seizures. Both instances occurred in the setting of infection, with the younger girl having a nonspecific febrile illness and the elder having acute gastroenteritis (14). Neither child had any further reported episodes of crisis. The elder subsequently developed epilepsy with an ongoing need for antiepileptic therapy.

Ectopic adrenal rest tumors

Five patients required subsequent surgery to remove ectopic adrenal rest tumors (26, 28, 29, 33, 35). Four cases occurred in girls aged 10 to 16 years at adrenalectomy, presenting with recurrence of hyperpigmentation and features of hyperandrogenism and/or amenorrhea (Supplemental Table 2). The interval to presentation ranged from 1 to 16 years after adrenalectomy. Three of the five patients were known to have had poor adherence to glucocorticoid therapy (26, 28, 35). The lesions in four patients were ovarian or paraovarian, with two of these patients having bilateral lesions (29, 35); these patients all had underlying 21OHD. One case occurred in a boy with 11OHD (karyotype 46XX) who had undergone bilateral adrenalectomy at age 15 years for management of refractory hypertension (33); five adrenal rest tumors in the abdomen and pelvis were removed 1 year after adrenalectomy.

No cases of new testicular adrenal rest tumors (TARTs) in male patients were reported. Two patients with known TARTs before adrenalectomy had a reduction in the size of the TARTs after adrenalectomy (38, 48).

Other long-term outcomes

One girl developed ovarian carcinoma after bilateral adrenalectomy performed at age 6 years for rapid bone age advancement and difficulties in controlling hyperandrogenism (24). At age 14 years, high daily doses of glucocorticoids were required for suppression of adrenal androgens. Magnetic resonance imaging and ultrasonography demonstrated a right adnexal cystic mass, and cancer antigen 125 was elevated at 144 ng/mL (reference range, 0 to 34 ng/mL). Complete remission was achieved after right salpingo-oophorectomy and systemic chemotherapy.

Two girls, aged 10 and 16 years at adrenalectomy, developed pituitary microadenoma (26, 37). Both of these patients had also developed ovarian adrenal rest tissue, with pituitary magnetic resonance imaging performed in the setting of increasing hyperandrogenism. One of these girls had a demonstrated history of poor adherence to therapy (37). No studies reported any case of pituitary macroadenoma.

A 40-year-old man who had undergone adrenalectomy via an open transabdominal approach reported chronic pain at the incisional site, which responded well to an intercostal nerve block (49).

Discussion

The present systematic review, identifying 48 cases of bilateral adrenalectomy performed for treatment of CAH, is the largest and most complete review of the reported data to date. Additionally, to the best of our knowledge, ours is the first study to provide quantitative analysis of patient characteristics and outcomes.

The results of our systematic review have confirmed the safety of the procedure, with low rates of perioperative morbidity for both open and laparoscopic approaches. We identified only a single episode of postoperative mortality, which occurred in an infant after bilateral adrenalectomy performed >65 years ago (21). With advances in perioperative management in recent decades, it appears that the risk of mortality is very low. Perioperative morbidity was also low, with no evidence of long-term sequelae. These results are consistent with those from a previous systematic review of bilateral adrenalectomy performed as treatment of Cushing syndrome in 1320 adults, which reported perioperative mortality and morbidity of 3% and 18%, respectively (55). Although no large series of perioperative outcomes after bilateral adrenalectomy in the pediatric population has been reported, to the best of our knowledge, complications have been uncommon in reported series of children undergoing adrenalectomy, including several cases of bilateral adrenalectomy (56, 57).

Bilateral adrenalectomy was most frequently performed to ameliorate hyperandrogenic symptoms and/or Cushing syndrome. For these indications, it appears to be

an effective therapy, with improvement in symptoms for most patients, in addition to reductions in 17OHP, testosterone, and androstenedione. Improvement in hyperandrogenism enables reduction of glucocorticoid doses, with the postoperative average daily HCE 12 mg lower than the required preoperative doses. Reduced glucocorticoid exposure will potentially minimize the risk of developing long-term adverse effects of iatrogenic Cushing syndrome identified in individuals with CAH, including obesity, type 2 diabetes, osteoporosis, and cardiovascular disease (2, 4, 12, 13, 18, 58–62). Only five cases had reportedly received a trial of antiandrogen therapy before bilateral adrenalectomy; it seems reasonable that medical options should first be exhausted before bilateral adrenalectomy is performed.

The outcomes were universally favorable when bilateral adrenalectomy was performed to improve fertility, with all these women achieving the live birth of healthy infants. Fertility has been shown to be generally decreased in both women and men with CAH (4, 62–65), and bilateral adrenalectomy can be used in selected cases to improve fertility when other measures have not been successful. The presence of ectopic adrenal rest tumors can also affect fertility, especially in the testes (64, 66). However, this did not appear to occur after adrenalectomy in the men and women who remained adherent to glucocorticoid therapy.

Bilateral adrenalectomy was also effective for the treatment of refractory hypertension in those with 11OHD, with all patients for whom the outcome was known able to either reduce or cease antihypertensive therapy. Blood pressure and the increased cardiovascular risk in those with 11OHD can be difficult to control (7), making this another scenario for which bilateral adrenalectomy can be used in selected cases when other measures have not been successful.

A previous review by Van Wyk *et al.* (14) described the outcomes of 18 patients who had undergone bilateral adrenalectomy. Their study population predominantly included children and adolescents, with only five cases of adrenalectomy in patients aged >18 years. In contrast, our study had fairly even proportions of adults and younger patients. Moreover, our systematic review included almost three times the number of individuals.

Adrenal crisis is the most common cause of death in patients with CAH and is, therefore, an outcome of particular interest (67). In patients with CAH receiving medical treatment, 33% will have experienced an episode by adolescence, with the incidence increasing to 57% by adulthood (68, 69). The proportion of patients experiencing an adrenal crisis was 17% postoperatively in the present meta-analysis, equivalent to 14.8 adrenal crises per 100 patient-years. This is greater than the previously reported rate of 5.8 per 100 patient-years (69); however, the rate in our meta-analysis is likely an overestimate owing to the high number of patients (15 of 48, nearly one third of patients) for whom the follow-up duration was not reported. The rate of adrenal crisis in the series by van Wyk *et al.* (14) was substantially higher (28%) compared with our review (17%), which might be attributable to the greater proportion of children and adolescents in their study. It has been demonstrated that adrenal crises are more common in younger patients (70–72). In our systematic review, the occurrence of adrenal crises was evenly distributed between adult and pediatric patients; however, the children were more severely affected, including one requiring long-term antiepileptic therapy after a hypoglycemic seizure (14). This might provide a rationale for delaying bilateral adrenalectomy, when being considered as a therapeutic option, until later adolescence or adulthood to minimize the risk of the development of a severe adrenal crisis and associated sequelae.

Bilateral adrenalectomy results in the loss of adrenalin production from the adrenal medulla, which could be expected to result in a greater risk of hypoglycemia, especially when combined with low or deficient glucocorticoid replacement. Hypoglycemia was reported in only two patients, both with SW CAH (14). In addition, adrenalin deficiency attenuates the symptoms of hypoglycemia, such as pallor and tremor; thus, hypoglycemia might not be easily observed clinically. Adrenalin production in the adrenal medulla is already compromised in CAH, with the degree of deficiency related to the severity of the enzyme deficiency (59, 73, 74). Bilateral adrenalectomy, therefore, might not cause a large difference in capacity to produce adrenalin in patients with SW CAH. In contrast, patients with SV CAH might experience a larger difference, although no cases in patients with SV CAH were reported.

With the exception of a single patient who had a known history of poor adherence to therapy before adrenalectomy, adrenal crisis occurred only once in each affected patient, with no further episodes after glucocorticoid dose adjustment and patient or parental education. This underlines the importance of carefully determining the dose to achieve adequate glucocorticoid replacement postoperatively and appropriate patient and parental education on sick day management of glucocorticoid therapy (75). Given that patients with CAH receiving suppressive glucocorticoid therapy, who have not undergone bilateral adrenalectomy, require plans for sick day management including stress glucocorticoid dosing (11), concerns regarding the risk of adrenal crisis after bilateral adrenalectomy do not appear sufficient to prohibit this therapeutic option for appropriate patients.

Activation of ectopic adrenal rest tissue is also a serious long-term concern. It occurred in five individuals in our review, leading to recurrence of hyperandrogenism in four girls and the need for further surgery. The series by Van Wyk (14) did not report any patients with confirmed ectopic adrenal rest tissue. However, this was the presumed underlying cause for eight patients with significantly elevated levels of steroid precursors after adrenalectomy (14). The clinical and biochemical features, therefore, require ongoing monitoring after adrenalectomy, with prompt initiation of appropriate investigations in those where there is any suspicion. This outcome occurred exclusively in younger patients, adding further weight to the argument to delay bilateral adrenalectomy until adulthood, if feasible. A history of poor adherence to glucocorticoid replacement regimens before bilateral adrenalectomy was a common feature in patients developing both adrenal crises and ectopic adrenal rest tissue activation. Therefore, this is a potentially important consideration when determining the suitability of bilateral adrenalectomy in this subset of patients.

Of note was the unexpected observation that the TARTs present in two men before undergoing bilateral adrenalectomy decreased in volume postoperatively. Neither man had been taking glucocorticoid therapy regularly before bilateral adrenalectomy and likely had good adherence postoperatively, as demonstrated by the absence of a postoperative adrenal crisis. The increased glucocorticoid exposure postoperatively thus appears to have contributed to the regression of the TARTs.

The reported case of ovarian carcinoma was a concerning finding, especially at the young age of 14 years (24). Because it was a single case, this appears to be a very rare outcome and was possibly a chance finding. Increasing androgen production in the preceding period might have been caused by the carcinoma, which, as with the activation of ectopic adrenal rest tissue, underscores the importance of prompt assessment in patients with recurrence of hyperandrogenism after bilateral adrenalectomy.

Pituitary microadenomas were uncommon in our review, and, reassuringly, no pituitary macroadenoma developed, alleviating concerns of sequelae such as mass effect or an effect on the secretion of other pituitary hormones.

Patients with 11OHD were overrepresented in our systematic review, comprising 15% of cases undergoing bilateral adrenalectomy compared with the reported 0.2% to 8% of overall cases of CAH (7). Most of these patients (five of seven) had undergone bilateral adrenalectomy for management of refractory hypertension. With the exception of the youngest patient, all had hypertensive end-organ complications, including stroke, retinopathy, and left ventricular hypertrophy. This indicates that a substantial proportion of patients with 11OHD will have hypertension that cannot be adequately controlled by medical methods and causes substantial morbidity, providing a strong argument for consideration of bilateral adrenalectomy in this scenario.

The levels of DHEA and DHEAS were not significantly lower postoperatively in our meta-analysis, although our analysis was limited by these values only being reported for a few cases. In women with adrenal insufficiency, low DHEA levels have been postulated as contributing to reduced quality of life and libido, with conflicting results regarding improvement of these measures with replacement therapy (76, 77). Patients with CAH already have low levels of DHEA and DHEAS compared with the expected values for age (12, 58, 78, 79). Thus, bilateral adrenalectomy might not lead to a reduction of any clinical significance. It is reasonable to address this issue after adrenalectomy, just as for patients with adrenal insufficiency for other reasons, and to consider DHEA therapy on an individualized basis in patients with persistent and seriously impaired quality of life and libido despite optimization of conventional glucocorticoid and mineralocorticoid therapy (76, 77). Women who have undergone bilateral adrenalectomy for control of hyperandrogenism might, however, be reluctant to begin androgen replacement therapy for fear that features of hyperandrogenism might recur.

Although our systematic review was the largest to date, it was still limited by small numbers, because bilateral adrenalectomy appears to have been seldom performed for this rare condition. Our results were also inherently limited by the absence of a control population. A potential bias was present in the reporting of favorable outcomes, with no single outcome uniformly reported across all cases. The techniques for performing biochemical measurements were seldom reported, and substantial variability across centers and time is likely. Our search also did not identify any cases of bilateral adrenalectomy performed for rarer forms of CAH, with all reported cases in patients with either 21OHD or 11OHD. Our results are, therefore, potentially not generalizable to patients with other forms of the disease. However, the strengths of our study included its size, because it is the largest review of bilateral adrenalectomy for CAH to date, with 48 identified cases. To the best of our knowledge, ours is also the first quantitative analysis of both short- and long-term outcomes for patients with CAH who have undergone bilateral adrenalectomy. The search was not limited by language, publication date, or CAH type.

Conclusion

The present systematic review and meta-analysis have demonstrated improvement in clinical and biochemical

parameters after bilateral adrenalectomy for CAH, along with the safety of the procedure, indicating this is a reasonable therapeutic option for appropriately selected patients with unsatisfactory outcomes with conventional medical therapy. Care must be taken to emphasize the importance of appropriate management of glucocorticoid therapy, especially in the setting of intercurrent illness. Long-term monitoring for the recurrence of features of hyperandrogenism is essential, with their occurrence indicating possible activation of ectopic adrenal rest tissue, which should prompt appropriate biochemical and imaging assessments.

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