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## ORIGINAL ARTICLE

WILEY

## Adrenal

# Service evaluation suggests variation in clinical care provision in adults with congenital adrenal hyperplasia in the UK and Ireland

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## Abstract

**Background:** Congenital adrenal hyperplasia (CAH) encompasses a rare group of autosomal recessive disorders, characterised by enzymatic defects in steroidogenesis. Heterogeneity in management practices has been observed internationally. The International Congenital Adrenal Hyperplasia registry (I-CAH, <https://sdmregistries.org/>) was established to enable insights into CAH management and outcomes, yet its global adoption by endocrine centres remains unclear.

**Design:** We sought (1) to assess current practices amongst clinicians managing patients with CAH in the United Kingdom and Ireland, with a focus on choice of glucocorticoid, monitoring practices and screening for associated co-morbidities, and (2) to assess use of the I-CAH registry.

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**Measurements:** We designed and distributed an anonymised online survey disseminated to members of the Society for Endocrinology and Irish Endocrine Society to capture management practices in the care of patients with CAH.

**Results:** Marked variability was found in CAH management, with differences between general endocrinology and subspecialist settings, particularly in glucocorticoid use, biochemical monitoring and comorbidity screening, with significant disparities in reproductive health monitoring, notably in testicular adrenal rest tumours (TARTs) screening ( $p = .002$ ), sperm banking ( $p = .0004$ ) and partner testing for CAH ( $p < .0001$ ). Adoption of the I-CAH registry was universally low.

**Conclusions:** Differences in current management of CAH continue to exist. It appears crucial to objectify if different approaches result in different long-term outcomes. New studies such as CaHASE2, incorporating standardised minimum datasets including replacement therapies and monitoring strategies as well as longitudinal data collection, are now needed to define best-practice and standardise care.

#### KEYWORDS

congenital adrenal hyperplasia, I-CAH

## 1 | INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders characterised by enzymatic defects in steroidogenesis. The most common cause is 21-hydroxylase deficiency, due to mutations in the CYP21A2 gene with an approximate prevalence of 1 in 15,000 of the population.<sup>1</sup> Age of symptom onset and phenotype severity is dictated by the degree of enzymatic deficiency. Reduced or absent enzymatic activity results in glucocorticoid deficiency and subsequent ACTH-driven adrenal androgen excess. Mineralocorticoid deficiency is clinically apparent in about two thirds of affected individuals.

The cornerstone of management of patients with CAH is adequate glucocorticoid replacement, with the aim of normalising androgen excess, without resultant supra-physiological glucocorticoid exposure. While the 2018 Endocrine Society guidelines advocate for hydrocortisone in adults with CAH, discordant practices of glucocorticoid prescribing persist between institutions.<sup>2</sup> This reflects a paucity of high quality evidence regarding optimum replacement regimens and associated impact on long-term metabolic morbidity and quality of life.<sup>3-5</sup> This is also applicable across multiple domains of management of patients with CAH.

Several studies have highlighted a tendency towards supra-physiological glucocorticoid replacement, with consequent long-term sequelae including osteoporosis, adverse metabolic profile and reduced patient-reported quality of life.<sup>6-10</sup> However, datasets indicating risk are derived from surrogate measures, with Endocrine Society guidelines advocating metabolic and cardiovascular screening as per general population guidelines.<sup>3</sup> These recommendations have been contentious, with clinicians often implementing routine assessments for associated co-morbidities on an institutional or individualised basis.

Clinical monitoring of patients with CAH relies on careful assessment for symptoms and signs suggestive of glucocorticoid or androgen excess. Traditionally, biochemical assessment has relied on the measurement of serum 17-hydroxyprogesterone (17-OHP) and androstenedione in CAH monitoring.

Outcomes relating to optimal glucocorticoid replacement, frequency and parameters of monitoring, in addition to screening protocols for associated co-morbidities have not been clearly demonstrated in management of CAH. As such, discordant management practices are observed internationally.

The Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) was established in 2003 and assessed the health status of adults living with CAH in the United Kingdom. Non-physiological glucocorticoid replacement, poor metrics of metabolic health and reduced patient-reported quality of life were identified as areas of concern.<sup>7,11,12</sup> The International Congenital Adrenal Hyperplasia Registry (I-CAH Registry) was subsequently developed in an effort to longitudinally assess patient outcomes in CAH, and promote collaboration and networking in patient management, with expansion of research opportunities in CAH.<sup>13-15</sup>

This survey aimed to capture current management practices amongst clinicians managing patients with CAH in the UK and Ireland. Areas of interest included setting of patient care (general or subspecialist clinics), review frequency, monitoring practices and choice of glucocorticoid replacement. We also aimed to assess awareness and use of the I-CAH registry by clinicians. We compared management of CAH amongst those managing patients in a general setting and those reviewing patients in dedicated subspecialist clinics.

## 2 | METHODS

### 2.1 | Online survey

An anonymised online survey was designed and distributed amongst members of the Society for Endocrinology and the Irish Endocrine Society. The questionnaire aimed to assess practices of monitoring and management amongst clinicians providing care for patients with CAH. All respondents gave informed consent before completing the survey. Ethical approval was not required as our survey involved an assessment of routine clinical practice.

The survey assessed setting of management, frequency of clinic review, practices of glucocorticoid prescribing, use of combinations of glucocorticoids, biochemical monitoring, and screening for reproductive health and metabolic co-morbidities. Respondents also responded to questions regarding awareness and use of the I-CAH Registry. The circulated survey is available in its entirety in Supporting Information S1: Appendix 1.

Initial respondent data was subsequently analysed to compare management of CAH in General Endocrinology and dedicated subspecialist clinics.

### 2.2 | Statistical analysis

Descriptive statistics were used in the analysis of data to summarise responses. Where relevant, Chi-square testing was applied to compare variables between the two groups. Statistical significance was taken as achieving a *p*-value of less than .05.

## 2.3 | Results

### 2.3.1 | Survey response

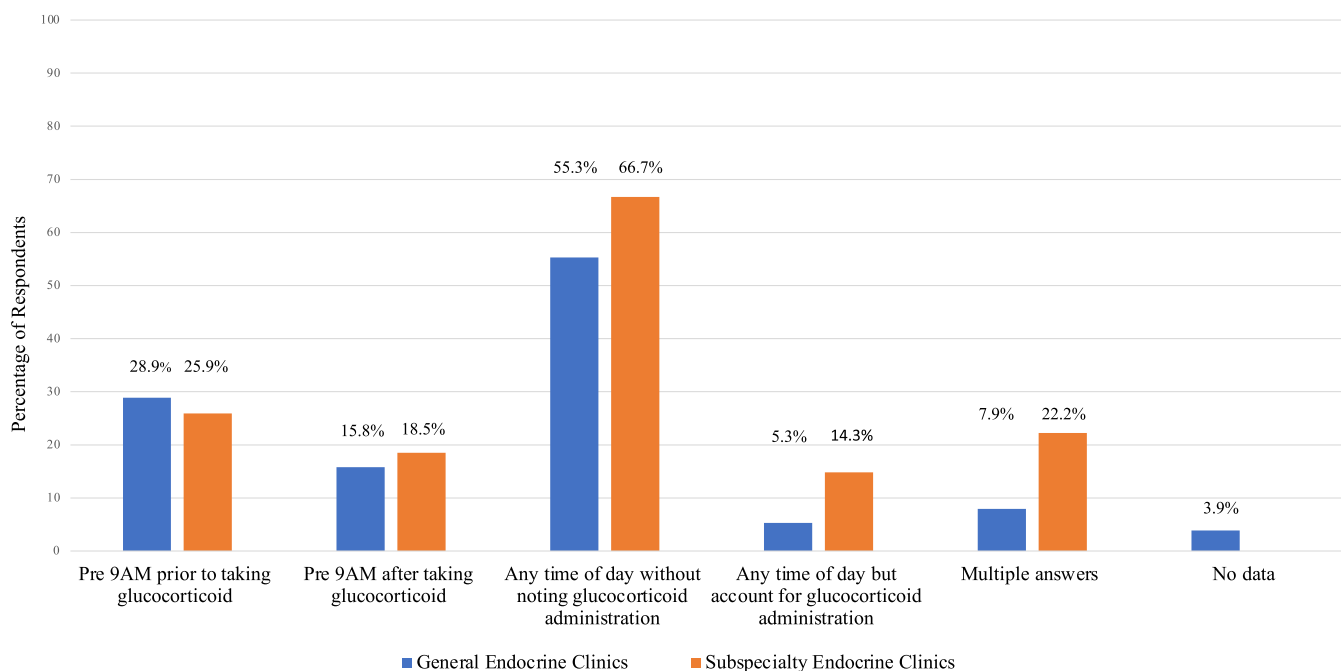
1354 surveys were issued, and there was a response rate of 15% (*n* = 198). Of the 198 survey respondents, 65% (*n* = 128) confirmed they were involved in the management of patients with CAH. Of those, 51% (*n* = 65) continued the survey, responding to subsequent questions regarding management practices.

### 2.3.2 | Setting of management

Of the 65 respondents confirmed to be currently managing patients with CAH, 59% (*n* = 38) reported managing patients with CAH solely in General Endocrinology clinics. The remaining 42% (*n* = 27) reviewed patients in subspecialist clinics, with evidence of multiple clinic review settings amongst respondents amongst this subgroup. The majority of subspecialist clinics were Adrenal, with respondents also reviewing patients in Reproductive Endocrinology clinics. Ten respondents (15%) routinely review patients in dedicated CAH clinics. The median number of patients with CAH managed by each respondent was 20 (interquartile range: 10–50).

### 2.3.3 | Review frequency

Amongst clinicians managing patients in General Endocrinology clinics, 53% (*n* = 20) undertook annual clinical review of patients with CAH. This involved assessment in the outpatient setting for



**FIGURE 1** Routine clinical practice with respect to standard timing of phlebotomy for monitoring biochemistry in patients with CAH. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/ien.15043)]

evidence of androgen excess, and indicators of cortisol over-replacement both clinically and biochemically, with tracking of biometric data including weight, height and blood pressure. This contrasted with 41% ( $n = 11$ ) in the subspecialist setting ( $p = .32$ ). Six monthly review frequency was routine for 34% ( $n = 13$ ) of respondents in the General Endocrinology context, compared to 44% ( $n = 12$ ) of those in subspecialty clinics ( $p = .16$ ). An unspecified clinical review frequency was reported in 13% ( $n = 5$ ) of General Endocrinology clinics, in comparison to 15% ( $n = 4$ ) of subspecialty clinics ( $p = .79$ ). This was inclusive of patient-initiated follow-up.

### 2.3.4 | Timing of samples for biochemical monitoring

Practices of timing of blood sampling for monitoring biochemical parameters relative to last dose of glucocorticoid replacement was assessed (Figure 1). Of clinicians based in General Endocrinology settings, 29% requested early morning bloods (ideally before 09.00) and before taking the morning glucocorticoid dose, compared to 26% of those in subspecialist settings ( $p = .68$ ). Conversely, 16% and 19% of each group reported monitoring bloods were taken early morning but after glucocorticoid dose was administered ( $p = .58$ ). The majority in both groups undertook routine monitoring at any time of day, irrespective of timing of last glucocorticoid replacement, as reported by 55% of clinicians managing patients with CAH in a General Endocrinology clinic, and two-thirds of those reviewing patients in a subspecialist setting ( $p = .31$ ). In 5% of General Endocrinology services, and 15% of subspecialist services, these parameters were assessed at any time, but timing of glucocorticoid dosing was accounted for ( $p = .06$ ). Multiple practices of monitoring were also reported in both groups.

### 2.3.5 | Biochemical monitoring parameters

Biochemical monitoring in CAH management showed similar patterns between general and subspecialist clinics (Table 1, Figure 2). There were no statistically significant differences between settings, except for renin activity which was assessed by 58% ( $n = 22$ ) of respondents in general clinics versus 81% ( $n = 22$ ) in subspecialty services ( $p = .0003$ ). Additionally, assessment of 17 OHP day curve, was monitored by two respondents in the General Endocrinology setting, compared to no subspecialty respondents ( $p = .037$ ). Assessment of 17-OHP was nearly identical in both settings. A smaller percentage of General Endocrinology settings measured androstenedione and testosterone compared with subspecialty clinics; however the difference was statically not significant. DHEA-S monitoring was reported by 53% in General Endocrinology and 44% in subspecialist clinics. ACTH measured by 21% in General Endocrinology clinics and 30% of subspecialist clinics. Differences in use of cortisol day curves, renal function, oestradiol and gonadotropin measurement are demonstrated in Table 1.

### 2.3.6 | Choice of glucocorticoid replacement

A broad range of glucocorticoid replacement practices were employed by respondents across both General Endocrinology and subspecialist settings (Figure 3). Respondents used a variety of treatment regimens within each centre including single type of glucocorticoid, combination therapy or modified-release hydrocortisone preparations.

The majority of centres use hydrocortisone in at least one patient, either as a monotherapy or combination therapy (90% General Endocrinology clinics, 93% in subspecialist services). Within General Endocrinology clinics, 47% reported prescribing prednisolone, compared to 70% of those in subspecialty settings. Dexamethasone prescribing, as a single agent glucocorticoid replacement or as combination therapy for any patient, was reported by 32% of General Endocrinology clinics, compared to 56% of clinicians in subspecialty clinics.

Significantly more respondents in subspecialist centres (48%) were using combination regimens compared to clinicians managing patients in General Endocrinology clinics (16%,  $p < .0001$ ). For those using combination therapies in selected patients, the majority of clinicians use hydrocortisone plus prednisolone with a significant difference between the subspecialty setting (44%) and general endocrinology clinics (5%).

No clinician managing patients in General Endocrinology clinics reported the use of modified release hydrocortisone preparations, whereas 30% of respondents in subspecialty settings described use of modified-release hydrocortisone preparations. We asked respondents specifically regarding prescribing practices in relation to Efmody and Plenadren. Efmody is given as a twice daily hydrocortisone regimen, with the aim of mimicking physiological cortisol production, and enhancing androgen suppression overnight. It employs multiparticulate pharmacokinetics to reproduce this endogenous early morning cortisol rise. Plenadren is administered once daily and consists of an external coating of immediate release hydrocortisone, with an inner core allowing for a more sustained release. Theoretically, this replicates endogenous daytime cortisol profiles to minimise peaks and troughs in dosing regimens, but does not suppress nocturnal androgen production in CAH. A total of 6 respondents (22%) working in subspecialist clinics prescribed Efmody, and 2 respondents confirmed use of Plenadren (7%). Prescription of both Efmody and Plenadren for patients with CAH was described by 1 respondent (3%).

### 2.3.7 | Practices of reproductive health monitoring

Clear differences appear to exist in the monitoring of reproductive health between centres (Table 1). There is a trend towards increased clinical and biochemical reproductive health screening in specialised clinics, with some differences being statistically significant. Routine assessment of testosterone was undertaken by 50% of clinicians in

**TABLE 1** Summary of responses and comparison between general endocrinology clinics and subspecialty settings.

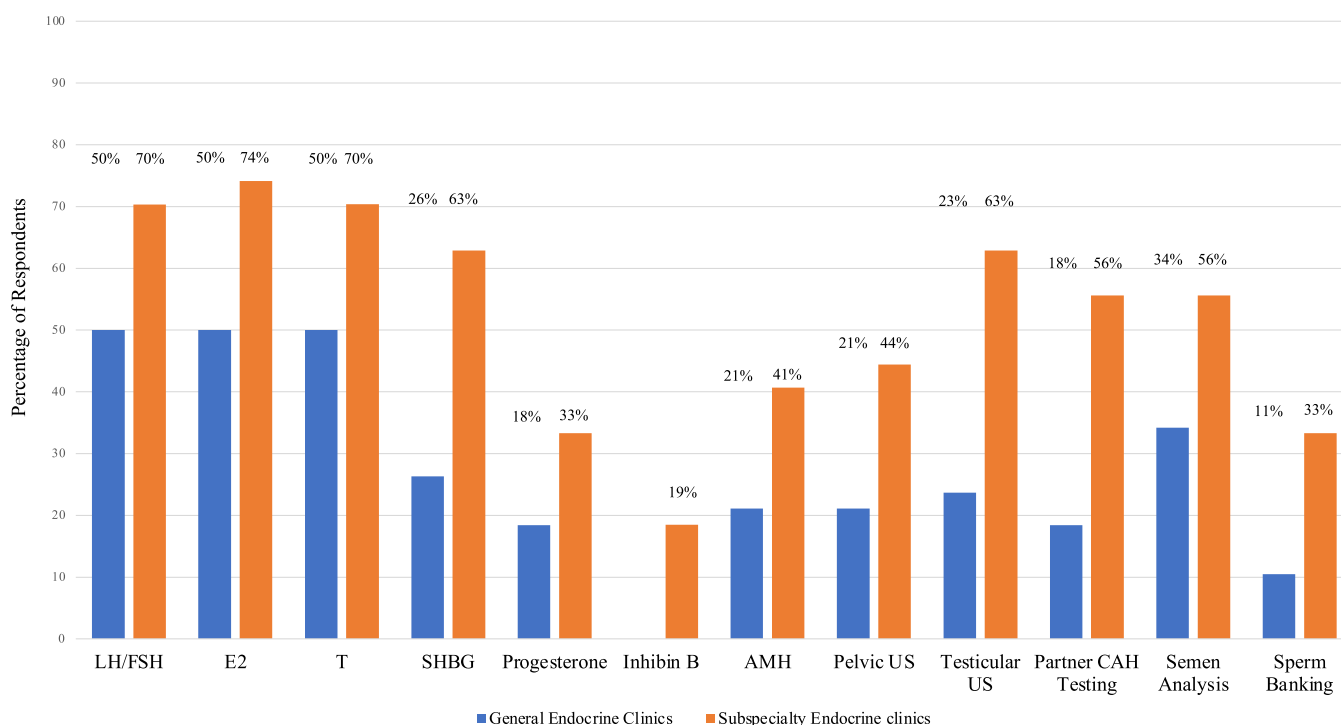
	Respondents <i>n</i> = 65	General endocrinology <i>n</i> = 38	Subspecialty clinic <i>n</i> = 27	Significance GE versus SC
<b>Biochemical monitoring</b>				
17OHP	89% ( <i>n</i> = 58)	90% ( <i>n</i> = 34)	89% ( <i>n</i> = 24)	<i>p</i> = .93
Androstenedione	60% ( <i>n</i> = 39)	53% ( <i>n</i> = 20)	70% ( <i>n</i> = 19)	<i>p</i> = .12
Testosterone	77% ( <i>n</i> = 50)	71% ( <i>n</i> = 27)	85% ( <i>n</i> = 23)	<i>p</i> = .25
DHEA-S	49% ( <i>n</i> = 32)	53% ( <i>n</i> = 20)	44% ( <i>n</i> = 12)	<i>p</i> = .36
Renal function	88% ( <i>n</i> = 57)	84% ( <i>n</i> = 32)	93% ( <i>n</i> = 25)	<i>p</i> = .49
Plasma renin activity	68% ( <i>n</i> = 44)	58% ( <i>n</i> = 22)	82% ( <i>n</i> = 22)	<i>p</i> = .0003
ACTH	25% ( <i>n</i> = 16)	21% ( <i>n</i> = 8)	30% ( <i>n</i> = 8)	<i>p</i> = .20
17-OHP day curve	3% ( <i>n</i> = 2)	5% ( <i>n</i> = 2)	0% ( <i>n</i> = 0)	<i>p</i> = .037
Random cortisol	14% ( <i>n</i> = 9)	16% ( <i>n</i> = 6)	11% ( <i>n</i> = 3)	<i>p</i> = .34
Cortisol day curve	11% ( <i>n</i> = 7)	11% ( <i>n</i> = 4)	11% ( <i>n</i> = 3)	<i>p</i> = .88
Gonadotrophins	55% ( <i>n</i> = 36)	50% ( <i>n</i> = 19)	63% ( <i>n</i> = 17)	<i>p</i> = .20
Oestradiol	52% ( <i>n</i> = 34)	50% ( <i>n</i> = 19)	55% ( <i>n</i> = 15)	<i>p</i> = .62
<b>Glucocorticoid replacement</b>				
Hydrocortisone	91% ( <i>n</i> = 59)	90% ( <i>n</i> = 34)	93% ( <i>n</i> = 25)	<i>p</i> = .79
Mono- or combination tx				
Prednisolone	57% ( <i>n</i> = 37)	47% ( <i>n</i> = 18)	70% ( <i>n</i> = 19)	<i>p</i> = .03
Mono- or combination tx				
Dexamethasone	42% ( <i>n</i> = 27)	32% ( <i>n</i> = 12)	56% ( <i>n</i> = 15)	<i>p</i> = .14
Mono- or combination tx				
Combination regimes	29% ( <i>n</i> = 19)	16% ( <i>n</i> = 6)	48% ( <i>n</i> = 13)	<i>p</i> < .0001
Hydrocortisone + dexamethasone	8% ( <i>n</i> = 5)	8% ( <i>n</i> = 3)	7% ( <i>n</i> = 2)	<i>p</i> = .80
Hydrocortisone + prednisolone	22% ( <i>n</i> = 14)	5% ( <i>n</i> = 2)	44% ( <i>n</i> = 12)	<i>p</i> < .0001
Prednisolone + dexamethasone	3% ( <i>n</i> = 2)	4% ( <i>n</i> = 1)	3% ( <i>n</i> = 1)	0.79
Hydrocortisone + dexamethasone + prednisolone	2% ( <i>n</i> = 1)	3% ( <i>n</i> = 1)	0% ( <i>n</i> = 0)	<i>p</i> = .13
Hydrocortisone only	23% ( <i>n</i> = 15)	34% ( <i>n</i> = 13)	7% ( <i>n</i> = 2)	<i>p</i> < .0001
Prednisolone only	2% ( <i>n</i> = 1)	3% ( <i>n</i> = 1)	0% ( <i>n</i> = 0)	<i>p</i> = .32
Dexamethasone only	2% ( <i>n</i> = 1)	0% ( <i>n</i> = 0)	4% ( <i>n</i> = 1)	<i>p</i> = .04
Modified release hydrocortisone	12% ( <i>n</i> = 8)	0% ( <i>n</i> = 0)	30% ( <i>n</i> = 8)	<i>p</i> = .0007
<b>Reproductive health monitoring</b>				
Testosterone	77% ( <i>n</i> = 50)	50% ( <i>n</i> = 27)	70% ( <i>n</i> = 23)	<i>p</i> = .06
SHBG	42% ( <i>n</i> = 27)	24% ( <i>n</i> = 10)	63% ( <i>n</i> = 17)	<i>p</i> = .007
Progesterone	25% ( <i>n</i> = 16)	18% ( <i>n</i> = 7)	33% ( <i>n</i> = 9)	<i>p</i> = .23
Inhibin B	8% ( <i>n</i> = 5)	0% ( <i>n</i> = 0)	19% ( <i>n</i> = 5)	<i>p</i> = .0007

(Continues)

TABLE 1 (Continued)

	Respondents <i>n</i> = 65	General endocrinology <i>n</i> = 38	Subspecialty clinic <i>n</i> = 27	Significance GE versus SC
AMH	29% ( <i>n</i> = 19)	21% ( <i>n</i> = 8)	41% ( <i>n</i> = 11)	<i>p</i> = .008
Pelvic ultrasound	31% ( <i>n</i> = 20)	21% ( <i>n</i> = 8)	44% ( <i>n</i> = 12)	<i>p</i> = .003
Testicular US - TART	40% ( <i>n</i> = 26)	24% ( <i>n</i> = 9)	63% ( <i>n</i> = 17)	<i>p</i> = .002
CAH partner testing	34% ( <i>n</i> = 22)	18% ( <i>n</i> = 7)	56% ( <i>n</i> = 15)	<i>p</i> < .0001
Semen analysis	43% ( <i>n</i> = 28)	34% ( <i>n</i> = 13)	56% ( <i>n</i> = 15)	<i>p</i> = .016
Sperm banking	20% ( <i>n</i> = 13)	11% ( <i>n</i> = 4)	33% ( <i>n</i> = 9)	<i>p</i> = .0004

Note: Bold values are significant *p* < 0.05.



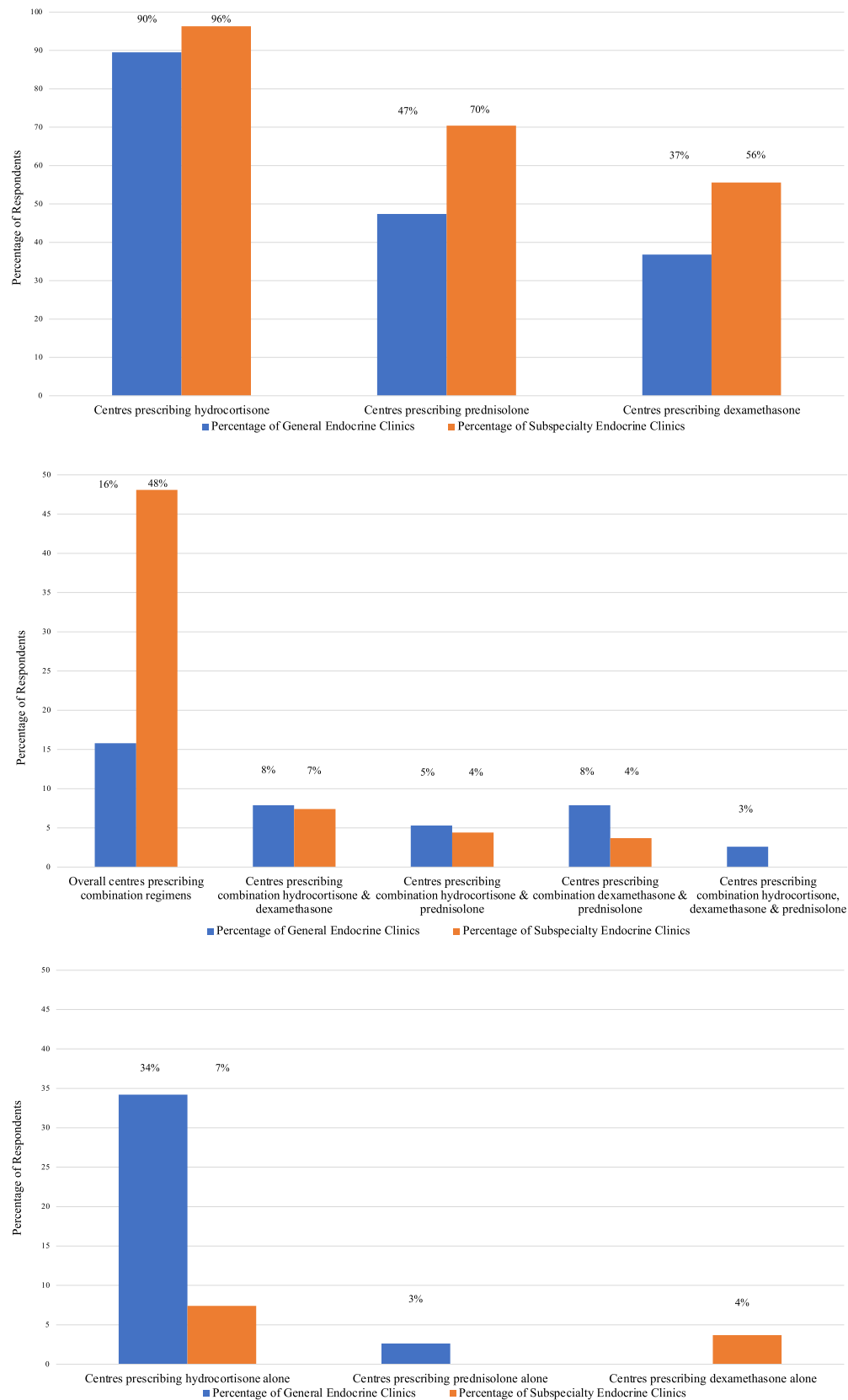
**FIGURE 2** Biochemical practices of monitoring disease activity and treatment efficacy in the setting of both general adult endocrinology clinics and subspecialist adult clinics managing patients with CAH. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]

the General Endocrinology setting, and 70% of those with a subspecialty clinic. In the General Endocrinology context, 18% routinely monitored progesterone as a marker of reproductive health compared to 33% in the subspecialist setting. Inhibin B is assessed by 19% of those in subspecialty clinics, but not by respondents in General Endocrinology settings. Evaluation for TARTs, partner genetic testing, assessment of pelvic ultrasound and AMH levels, and semen analysis and sperm banking were all offered to a significantly greater extent to patients attending subspecialist clinics compared to general clinics (Table 1).

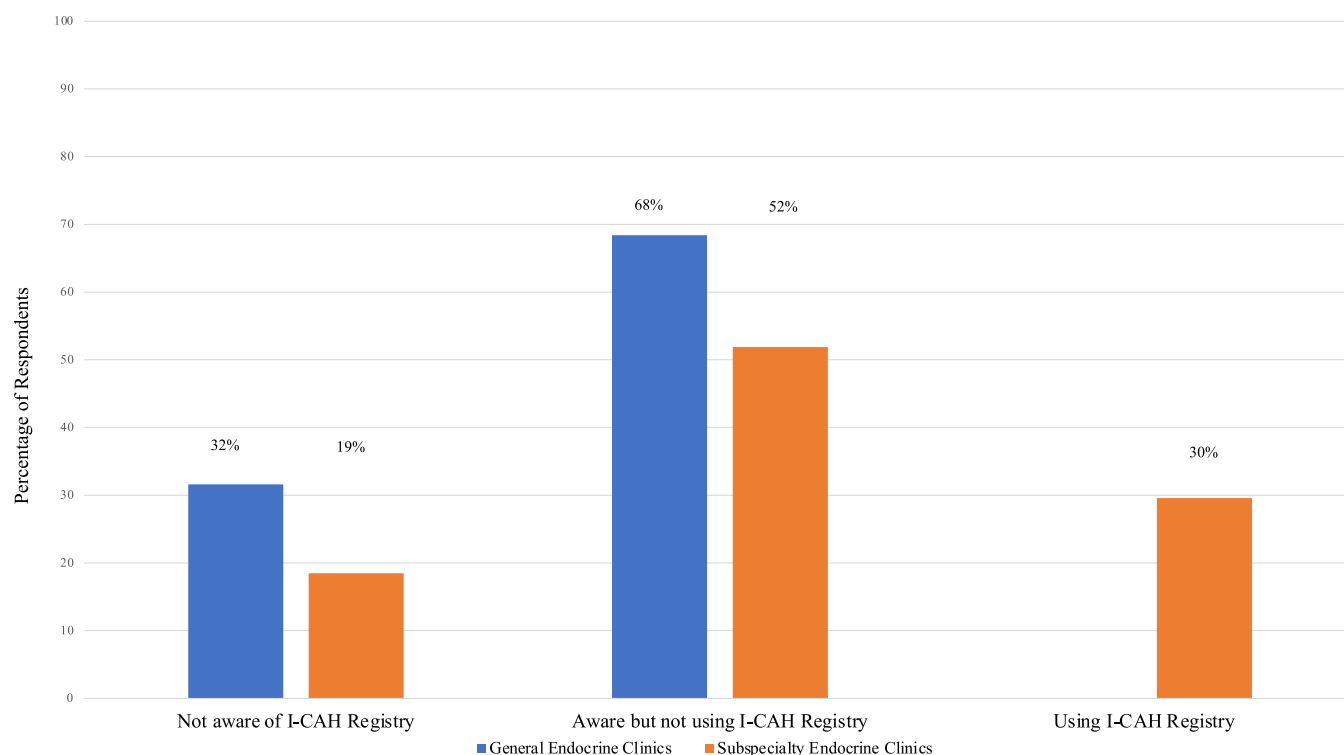
### 2.3.8 | Awareness and use of I-CAH registry

Twelve (32%) clinicians managing patients in a General Endocrinology setting were not aware of the I-CAH registry, in comparison to 19% (*n* = 5) of subspecialty respondents (*p* = .07, Figure 4). Of those aware of the registry, a further 68% (*n* = 26) of respondents in the General Endocrinology setting reported not using it, compared to 52% of those in the subspecialty context (*n* = 14) (*p* = .14). Eight respondents (30%) routinely reviewing patients in subspecialty clinics reported registering patients with the I-CAH registry.





**FIGURE 3** (See caption on next page).



**FIGURE 4** Use of the I-CAH Registry within the UK and Ireland by endocrinologists managing patients with CAH. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/1365-2266.15043)]

### 3 | DISCUSSION

This survey evaluated current management practices of clinicians routinely caring for adult patients with CAH in both the General Endocrinology and subspecialist context. Additionally, we assessed uptake and awareness of the I-CAH registry. Multiple studies have highlighted the heterogeneity of management for patients with CAH due to lack of high-quality randomised control trials demonstrating optimal therapeutic and monitoring strategies in CAH patients.<sup>2,16,17</sup> Our data is in line with previous findings, with respect to demonstrating ongoing variation in practice across multiple domains in both clinical contexts.

Evaluation of data obtained from this questionnaire endeavoured to capture current management practices amongst endocrinologists in a variety of settings within the U.K. and Ireland. Despite distribution via national society communication channels, uptake and subsequent survey completion was low amongst eligible respondents, with a response rate of only 15%. Of those issued the questionnaire, 4.8% completed it in its entirety. Even amongst clinicians currently managing patients with CAH in their service,

there was an attrition rate of 49%. While available data is indicative of diversity in current management practices, there is an acknowledged risk of bias given this low response rate, particularly amongst those managing patients with CAH, who declined to complete the questionnaire. It is possible respondents may be reflective of those with greater experience and caseload of patients with CAH, and could suggest a higher proportion of subspecialist management. As such, it is difficult to ascertain if this data is truly reflective of current management practices in CAH, as greater heterogeneity than demonstrated here may exist in clinical practice.

The I-CAH registry has now been in operation for over a decade, but it is clear that the level of awareness and participation amongst those who were surveyed is limited. The platform has mainly been used in paediatric endocrinology but the number of adult cases has increased over time.<sup>13–15</sup> Awareness of rare disease registries and participation in rare endocrine disease registries have been reported to be variable in expert centres previously.<sup>18</sup> There are several barriers to participating in rare disease registries,<sup>19</sup> but inadequate resources and time as well as not being able to obtain consent from the patient are common reasons.<sup>20</sup> Another common concern raised

**FIGURE 3** Glucocorticoid selection for patients with CAH in both general endocrinology and subspecialty endocrinology clinics. (A) Shows the overall proportion of centres prescribing each glucocorticoid. (B) Shows the rates of combination prescription overall, and individual combination selection across both groups. (C) Highlights single agent steroid prescribing practices in both clinic contexts. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/1365-2266.15043)]

by registry users is the purpose of the data collection exercise and the lack of a real-world minimum data set that may be required for studying specific outcomes.<sup>21</sup> The assessment of real-world data provided by greater use of the I-CAH registry would enable improved assessment of current routine practice, with the aim of comparing practice and ultimately pooled outcomes in patients with CAH on an international scale. Strategies to expand use of the I-CAH Registry include promotion amongst patient advocacy groups, national and international conferences, particularly given reported lack of awareness amongst both subspecialists and General Endocrinologists. Feedback from existing users would be another important avenue to explore current existing barriers to use.

Data from this updated survey of management in CAH in the UK and Ireland highlights ongoing significant heterogeneity in multiple domains of care. The CaHASE study recommended prioritising care in subspecialist clinics,<sup>7</sup> however 59% of respondents were reported undertaking review of CAH patients in General Endocrinology clinics.

Previous findings from CaHASE have highlighted the role of subspecialist input into the management of patients with CAH. Our data demonstrated that 59% of clinicians continue to care for patients with CAH in General Endocrinology clinics. While assessing outcome measures was beyond the scope of this survey, managing complex patients such as individuals with CAH can be challenging. Similarly, amongst subspecialist respondents, there was notable variation in the setting of CAH patient care, with the majority of respondents having more than one subspecialist clinic where patients with CAH were routinely reviewed across Reproductive Endocrinology, Adrenal and dedicated CAH clinics. This is indicative of ongoing heterogeneity in practices of routine review across institutions in the UK and Ireland.

There was no reported difference regarding practices of review frequency, with variable rates of annual and 6 monthly review across both groups. The impact of such variations in practice - including clinic review frequency - warrants further assessment on effect on long-term health in CAH. Increased review frequency could enable closer monitoring of biochemistry and symptoms of over- and undertreatment and subsequent improved titration of treatment regimens. However, this has not been demonstrated in the literature, and consideration should be made regarding impact on resource allocation and potential for impact on health-related anxiety. Longitudinal assessment of real-world data will enable greater understanding of whether review frequency impacts on outcomes in CAH. Furthermore, it would be useful to define objective criteria that would support individualised management and the clinical need for review frequency. A "one-size fits all" approach is unlikely to account for this variability of clinical presentation and associated comorbidities encountered in managing patients with CAH.

The current Endocrine Society guideline for management of CAH advocates for use of hydrocortisone as glucocorticoid replacement.<sup>2</sup> However, the low quality evidence supporting these recommendations has led to a lack of global consensus on optimal glucocorticoid replacement regimens in adults. Our data mirrors that of previous studies, highlighting significant heterogeneity amongst clinicians regarding

choice of glucocorticoid replacement.<sup>3-6,16,22</sup> Our findings are similar to those previously described, with a high proportion of clinicians reporting reliance on hydrocortisone prescribing - either as monotherapy or in combination regimens. We noted high levels of both combination prescribing, and routine use of more potent steroid preparations across both General Endocrinology and subspecialty clinics. Dexamethasone use was high across both clinical settings, despite previous cross-sectional studies suggestive of increased adverse metabolic profiles, and poorer comparative quality of life indices.<sup>11,12,17</sup> Use of higher potency glucocorticoids may also be indicative of more challenging disease control, so it is difficult to ascertain cause and effect in selection of dexamethasone. There was a significant difference between use of combination glucocorticoid replacement and modified-release hydrocortisone preparations in specialist centres compared to General Endocrinology respondents. Modified-release hydrocortisone has been suggested to mimic a more physiological cortisol pattern, and has been associated with greater androgenic suppression and biochemical indices of disease control.<sup>10</sup> This survey suggests patient access to these is limited in General Endocrinology clinics compared to subspecialist ones. Of note, our survey did not assess for practices of reverse circadian prescribing in adults with CAH. Overall, there is limited real-world data to underpin current recommendations regarding glucocorticoid prescribing in CAH; it remains to be seen whether selection of glucocorticoid agent has any meaningful impact on long-term outcomes. Further longitudinal data, such as that provided by the I-CAH registry, would be beneficial to ascertain if difference in practice of steroid prescribing translates to different outcomes.

Overall, monitoring practices in all clinical settings were not in line with current Endocrine Society guidelines.<sup>3</sup> While there was evidence of appropriate use of 17-OHP monitoring in both groups, there were high rates of both ACTH and DHEA-S monitoring, in addition to use of random cortisol, cortisol day curves and 17-OHP day curves by some respondents. These have not been shown as optimal parameters for monitoring in CAH patients, with no demonstrable links to improved outcomes or patient reported quality of life.<sup>23</sup> Apart from measurement of renin activity amongst subspecialty clinics, no other parameters assessed as part of routine biochemical monitoring achieved statistical significance. There was a lack of concordance with guidelines regarding timing of monitoring bloods. Outcomes related to monitoring parameters and adjustments in glucocorticoid dosing based on these have not been demonstrated. As with multiple aspects of care with CAH, an evidence-base examining whether monitoring parameters, and timing of biochemical sampling, results in improvements in long-term outcomes is needed given such variability in clinical practice.

Impact on reproductive health remains an important long-term health sequelae of CAH. Reproductive dysfunction in CAH is complex. In male patients, both TARTs and poor disease control contribute to gonadal suppression, whereas in female patients elevated circulating androgens and altered genital tract anatomy both incur effects on reproductive health.<sup>21,24,25</sup> Prevalence of TARTs in male patients with CAH is estimated at 30-80%, with universal screening recommended due to associated fertility

impact. Development of TARTs may also be representative of underlying poor disease control. While management of reproductive health was not assessed in the CaHASE study,<sup>7</sup> our survey highlights significant differences in multiple aspects of assessment and screening between respondents in general and subspecialist clinical services. This may be suggestive of disparities in care for patients with CAH dependent on their setting of management, and would be an important area of interest in future analysis of real-world data. An additional area for future focus should include patient-reported outcomes regarding reproductive health and sexual function, as this presents as a domain of patient care that warrants greater attention and analysis of longitudinal outcomes. Further documentation of rates of counselling regarding impact on reproductive function, and patient perception of fertility may also be beneficial in provision of patient-centred care.

Our survey results echo previous studies highlighting significant heterogeneity in practices of glucocorticoid prescribing and routine monitoring, in addition to practices of reproductive health monitoring in CAH management universally, but particularly between General Endocrinology and subspecialty care settings. Lack of concrete outcome data supporting consensus guidelines remains an ongoing major contributor to such variability in clinical practice. Our observation of differences in practices of glucocorticoid prescribing, patient monitoring, and assessment of metabolic, cardiovascular and reproductive health sequelae, highlight the need for greater longitudinal assessment of outcomes for patients with CAH to guide future clinical practice guidelines. The launch of the upcoming CaHASE-2 consortium will aim to provide a springboard for further improvements in care for patients with CAH. Our results reinforce the current poor knowledge base surrounding care of patients with CAH, as indicated by the diversity of clinical practice observed in the UK and Ireland.

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## CONFLICTS OF INTEREST STATEMENT

MWOR is a guest editor for the dedicated CAH issue of *Clinical Endocrinology* and an editor with *Clinical Endocrinology*. JWT is a member of the scientific advisory board for Diurnal. DAR has undertaken clinical trials in Congenital Adrenal Hyperplasia sponsored by Diurnal Ltd and Neurocrine Biosciences, and is Senior Editor of *Clinical Endocrinology*. NPK has acted as consultant to Diurnal Ltd and Neurocrine Biosciences. SFA has received unrestricted research grants from Diurnal Ltd and Neurocrine Biosciences. The CaHASE2 project is funded by an Investigator Initiated Study Support Grant from Neurocrine Biosciences Inc.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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