High Prevalence of Reduced Fecundity in Men with Congenital Adrenal Hyperplasia

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Context: Testicular adrenal rest tumors (TARTs) are regarded to contribute to the high prevalence of subfertility in males with congenital adrenal hyperplasia (CAH).

Objectives: Our objectives were to evaluate reduced fecundity and its possible causes in well-controlled adult males with CAH, and to investigate diagnostic tools for improved treatment monitoring with respect to fertility outcomes.

Design: In a cross-sectional study at the Department of Endocrinology at the University Hospital München, Germany, 22 adult male CAH patients (15 salt wasting and seven simple virilizing, age 19–48 yr) were clinically assessed according to their hormonal control. We performed testicular ultrasound (22 of 22), magnetic resonance imaging (18 of 22), and a semen analysis (19 of 22) in the participants.

Results: All patients had a pathological semen analysis. TART prevalence was 10 of 22 (eight salt wasting, two simple virilizing). Poor therapy control was present in five patients, and all five had TARTs. Of the other 17 well-controlled patients with normal or suppressed adrenal androgens and 17-hydroxyprogesterone levels, five presented with TARTs. There was a significant correlation between sperm concentration and functional testicular volume ($r = 0.70$; $P = 0.002$), TART volume ($r = -0.70$; $P = 0.036$), as well as inhibin B levels ($r = 0.75$; $P < 0.0001$), respectively. In several men, hormonal control parameters suggested hypogonadism, with glucocorticoid overtreatment as a relevant factor for poor semen quality.

Conclusions: Poor semen parameters are common in male CAH patients. TARTs, most likely reflecting undertreatment, as well as inhibin B are important indicators of fecundity. On the other hand, long-term glucocorticoid overtreatment also seems to contribute to low semen quality. **(*J Clin Endocrinol Metab* 94: 1665–1670, 2009)**

Low childbirth rates and impaired fertility have been reported in congenital adrenal hyperplasia (CAH) patients of both sexes. High prevalence of testicular adrenal rest tumors (TARTs) in CAH males is thought to be associated with impaired fertility (1). Adrenals and gonads derive from a common adrenogonadal primordium during development (2). TARTs are thought to initiate from adrenocortical remnants that have descended with the testes. On a functional level, TARTs have been ACTH dependent (3) and expressed adrenal-specific steroidogenic enzymes, as well as ACTH and angiotensin II receptors (4, 5). High and prolonged ACTH levels in this situation may stimulate their growth, which can be reversed by suppressive glucocorticoid treatment (6).

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-1414 Received July 3, 2008. Accepted February 20, 2009.
First Published Online March 3, 2009

Abbreviations: CAH, Congenital adrenal hyperplasia; cor/ax, coronary/axial; HPG, hypothalamus-pituitary gonadal; MRI, magnetic resonance imaging; 17-OHP, 17-hydroxyprogesterone; TART, testicular adrenal rest tumor; WHO, World Health Organization.

However, Stikkelbroeck *et al.* (1) reported a high prevalence of TARTs also in adequately or even overtreated patients with suppressed ACTH levels. Chronic suppression of gonadotrophin secretion due to adrenal androgen excess has been suggested as another mechanism for infertility in male CAH patients (1).

In this study we evaluated fecundity and Leydig cell function in a well-defined and well-controlled cohort of adult male CAH patients. We investigated the underlying causes of reduced fecundity with the goal of defining diagnostic tools for improving treatment monitoring with respect to fertility outcomes.

Subjects and Methods

Patient population

The subjects were adult male patients with genetically confirmed classical CAH due to 21-hydroxylase deficiency with regular hormonal follow-up at the outpatient clinic of the Department of Endocrinology of the University Hospital München. The local ethics committee approved the study protocol. All subjects gave written informed consent. For individual patient characteristics, see Table 1. Exclusion criteria were other diseases with impairment of gonadal capacity, and other general and psychiatric diseases.

Study protocol

All patients were seen at the outpatient clinic by one experienced endocrinologist (F.B.). In each patient medical history, physical examination, blood drawing (between 0800 and 1000 h, 2 h after morning medication), 24-h urine collection, and testicular ultrasound were performed, and in 19 of 22 semen analysis and in 18 of 22 magnetic resonance imaging (MRI) of the testis were obtained.

Adequate hormonal control of CAH was defined if serum androgen levels were within the normal range and 17-hydroxyprogesterone (17-OHP) concentration in serum was 2.0–10 ng/ml (6–30 nmol/liter) 2 h after intake of morning medication and/or early morning salivary 17-OHP was between 500 and 4,000 pmol/liter (data not shown) and/or pregnanetriol in 24-h urine was less than 10,000 μg/d (data not shown). Possible overtreatment was defined as suppressed androgen levels and normalized to decreased 17-OHP concentration in serum or saliva or pregnanetriol in 24-h urine.

Testicular imaging

Grey-scale and color Doppler ultrasonography of the testis was obtained in longitudinal and transverse sections. MRI was performed in the Department of Radiology of the University Hospital München by dedicated testicular MRI using a 1.5T-Scanner (Magnetom Vision; Siemens, Erlangen, Germany). Thin-slice turbo spin echo series [3 mm T1w coronary/axial (cor/ax), T2w cor/ax, and two consecutive T1w cor/ax after administration of gadolinium contrast agent] were applied using a 14-cm loop flex coil placed on the surface of the elevated testicles with patients in prone position.

Semen analysis

Seminal fluid was collected by the subjects (19 of 22) after 3–7 d self-reported ejaculatory abstinence. Semen analysis was performed at the Department of Andrology at the University Hospital of Dermatology in München, and included assessment of semen volume (measured by graduated tube), sperm concentration (Neubauer Chamber, depth 0.1 mm, volume 0.0025 mm^3; Karl Hecht KG, Sondheim, Germany), total sperm count, motile and immotile spermatozoa according to World Health Organization (WHO) criteria of 1999 (7), and morphology evaluation [Tygerberg criteria (8)].

Hormone assays in blood and saliva samples

Circulating concentrations of Δ^4-androstenedione, testosterone, LH, FSH, ACTH, inhibin B, and 17-OHP were measured by commercially

TABLE 1. Clinical and genetic characteristics of the patient cohort

Patient no.	Phenotype	Genotype	Mutation group	Age (yr)	BMI (kg/m^2)	Height (cm)	GC dose equivalent/m^2 BSA (mg/m^2)	FC dose/m^2 BSA ($\mu g/m^2$)
I/9	SW	Del/Conv	Null	48	26.3	163.0	13.89	41.67
I/1	SW	Del/Del	Null	35	34.5	160.5	15.79	52.63
I/17	SW	Del/Del	Null	35	31.9	178.0	11.93	22.73
I/19	SW	Del/Del	Null	33	32.0	1585	16.67	83.33
I/10	SW	Del/Del	Null	23	25.4	172.0	26.32	39.47
I/13	SW	Del/sc	Null	20	23.9	173.5	15.79	65.79
I/6	SW	Del/Del	Null	19	18.6	178.0	14.71	58.83
I/16	SW	Conv/Conv	Null	19	32.9	177.0	27.27	56.82
I/4	SW	Del/I2G	A	31	27.6	184.0	15.91	45.45
I/3	SW	I2G/I2G	A	24	21.9	167.0	23.53	44.12
I/11	SW	Y97X/12G	A	22	19.6	180.0	18.06	41.67
I/22	SW	Conv/I2G	A	22	28.7	170.0	18.42	26.32
I/14	SW	Conv/I172N	B	41	27.3	167.0	15.79	26.32
I/20	SW	Del/I172N	B	40	27.3	174.0	20.00	50.00
I/18	SW	I2G/I172N	B	29	23.7	178.0	10.53	26.32
I/8	SV	Del/12G	A	44	27.3	164.0	19.44	
I/15	SV	R356W/I172N	B	39	30.1	163.0	15.79	
I/7	SV	I2G/I172N	B	37	21.3	176.0	16.67	
I/2	SV	Del/I172N	B	22	29.3	170.0	20.00	
I/12	SV	Del/P30L	C	36	25.9	174.0	10.53	
I/21	SV	Del/P30L	C	27	29.6	173.0	15.00	
I/5	SV			32	28.9	170.0	10.00	

Phenotype, genotype, mutation group (19), age, body mass index (BMI), height, glucocorticoid (GC) dosage, and fludrocortisone (FC) dosage were collected at the time of investigation in 22 adult male patients with CAH. Patient no. I/5 had been diagnosed outside of our center with no molecular study being performed yet. Glucocorticoid dose equivalent was calculated with: hydrocortisone, 1; prednisolone/prednisone, 4; and dexamethasone, 70 (20). SV, Classical simple virilizing; SW, classical salt wasting.

available assays. The GnRH stimulation test was performed by administering 100 μg GnRH (Aventis Pharma GmbH, Frankfurt, Germany) as an iv bolus. Serum FSH and LH levels were measured at 0 and 30 min after GnRH dose. An increase of 2-fold was considered normal.

Statistical analysis

For correlation analysis, Spearman's correlation coefficient was used. Means were compared using a *t* test. For group comparisons, statistical analyses were performed with the nonparametric Mann-Whitney *U* test. Two-sided *P* values are reported, and a *P* value less than 0.05 was regarded as significant. Statistical analysis was performed using SPSS for Windows 15.0 (SPSS, Inc., Chicago, IL).

Results

Hormonal control

Poor therapy control with elevated Δ^4-androstenedione in serum and 17-OHP in serum/saliva and/or pregnanetriol in urine was present in five patients. Eight patients presented with well-controlled CAH, and nine of 22 had low to suppressed serum Δ^4-androstenedione and low 17-OHP levels (serum/saliva) and/or pregnanetriol in urine, indicating possible overtreatment (for details see Table 1; data for salivary 17-OHP day profiles and pregnanetriol in urine not shown).

Leydig cell function (testosterone and LH levels)

In eight patients (36%), serum testosterone levels were below normal [median 416 ng/dl (14.4 nmol/liter)]. Basal LH levels were decreased in three patients. GnRH stimulation induced an adequate increase in all but one patient. All three patients with suppressed basal LH levels had elevated serum Δ^4-androstenedione levels, two of them with elevated estradiol. Three other patients with elevated Δ^4-androstenedione levels had normal LH levels, however, in the lower normal range. There was no correlation of serum testosterone, or estradiol and basal or stimulated LH levels; Δ^4-androstenedione was negatively correlated with stimulated LH levels ($P = 0.011$).

Semen analysis

Semen analysis was performed in 19 patients (Table 2).

Semen analysis, FSH, and inhibin B levels

In 15 of 22, serum FSH levels were within the reference range, in four of 22 elevated, and in three of 22 decreased. All patients with elevated basal serum FSH levels had a normal FSH response with GnRH stimulation. In two patients with low basal FSH levels, stimulated FSH responses were insufficient. All three patients with FSH levels below the normal range also had suppressed basal LH levels. Six patients with normal basal FSH levels showed inadequately stimulated FSH levels. FSH levels were negatively correlated with all semen parameters except motility (total sperm count $r = -0.56$, $P = 0.012$; sperm concentration $r = -0.57$, $P = 0.011$; sperm morphology $r = -0.53$, $P = 0.019$). FSH levels were correlated negatively with inhibin B levels ($r = -0.65$; $P = 0.001$). Serum inhibin B levels were 99.3 pg/ml (median; range 24.2–301.1 pg/ml). Three patients had inhibin B levels below the reference range; all three had oligoasthenoteratozoospermia. Serum inhibin B levels showed a strong positive correlation with all semen parameters (total sperm count $r = 0.74$, $P < 0.0001$; sperm concentration $r = 0.75$, $P < 0.0001$; sperm morphology $r = 0.60$, $P = 0.008$; motile sperm $r = 0.48$, $P = 0.038$).

TARTs

Of 22 TARTs, 10 were detected by ultrasound, and all were bilaterally. In 18 of 22 patients, MRI was performed that confirmed the ultrasound findings in all cases (Table 2).

Relationship of TARTs, hormonal control parameters, and phenotype

Neither TART presence nor volume showed a significant correlation with any marker of hormonal control. TART volume was significantly higher in salt-wasting patients compared with simple virilizing patients ($P = 0.037$).

Relationship of TARTs, inhibin B, and sperm parameters

In patients with and without TARTs, inhibin B levels differed significantly ($P = 0.03$), and there were higher total sperm counts and concentrations in patients without TARTs ($P = 0.027$, $P = 0.021$).

Tumor volume negatively correlated with sperm concentration ($r = -0.70$; $P = 0.036$), sperm morphology ($r = -0.70$; $P = 0.038$), functional testicular volume (total testis volume minus tumor volume), sperm concentration ($r = 0.70$; $P = 0.002$), and total sperm count ($r = 0.69$; $P = 0.002$).

Discussion

Semen quality of CAH patients

Our data show a surprisingly high prevalence of impaired spermatogenesis in adult male CAH patients. Conventional techniques for spermiogram evaluation have been standardized by the WHO (7). Nevertheless, there is no general agreement which parameter is best in predicting fertility (9). In a prospective study on first pregnancy planners, Bonde *et al.* (10) suggested that the lower limit of a normal sperm concentration is close to 40 million/ml. Applying this reference only 42% of our patients were above this limit. A European study of fertile men indicated a longer waiting time to pregnancy, with sperm concentration less than 55 million/ml and morphologically normal spermatozoa less than 19% (11). Only three (16%) of our CAH patients had semen parameters above this threshold. Although semen quality in the general German population is declining, the median sperm concentration in this population is still 44 million/ml (12), whereas it ranged at 31 million/ml in our CAH cohort. This provides indirect evidence that even for the least affected men, the time to pregnancy is likely to be prolonged, although *in vivo* fertility of our patients cannot be predicted with certainty. Four of our patients have fathered children at a time point when no information on semen parameters or TARTs were available. However, one (patient no. I/15) additionally fathered a child during the study period (natural conception). Interestingly, his

TABLE 2. Endocrine parameters of the patient cohort

	Hormone profile							
	LH basal (U/liter)	LH peak (U/liter)	FSH basal (U/liter)	FSH peak (U/liter)	Inhibin B (pg/ml)	Androstenedione (ng/ml)	Testosterone (ng/dl)	17–OHP in serum (ng/ml)
Patient no.								
I/9	8.2	56.2	18.0	35.9	26.9	0.6	431	1.8
I/1	4.2	48.7	13.3	33.7	24.2	0.6	552	1.5
I/17	2.5		7.1		41.6	1.3	328	9.2
1/19	4.9	23.1	5.9	9.1	133.5	2.2	478	0.3
I/10	0.1	1.0	0.3	0.5	76.9	7.4	566	103.5
I/13	2.1	25.8	3.3	6.7	136.5	0.6	448	1.7
I/6	0.7	3.6	0.7	0.7	179.1	25.1		90.0
I/16	2.0	38.9	7.5	18.3	77.2	0.6	279	2.2
I/4	1.4	15.9	1.5	3.1	99.3	6.0	359	56.0
I/3	3.4	28.5	2.4	5.5	150.5	1.3	711	2.2
I/11	3.0	30.6	12.0	23.5	97.6	0.7	464	0.9
I/22	1.9	31.5	3.9	9.3	135.2	0.6	416	2.6
I/14	2.9	16.0	2.7	4.5	172.4	0.4	229	1.1
I/20	3.7	29.7	9.0	14.4	83.2	0.9	328	1.7
I/18	3.7	30.2	4.7	10.6	147.7	8.6	454	0.1
I/8	11.3	67.8	20.6	44.1	<10.0	2.6	141	18.0
I/15	2.7	20.2	2.4	3.4	301.1	0.9	255	2.9
I/7	3.1	31.9	6.8	15.1	52.2	0.4	366	0.2
I/2	5.8	32.9	7.7	13.3	90.9	1.0	490	3.6
I/32	2.3	24.3	6.2	12.9	81.9	2.7	501	62.0
I/21	0.8	16.6	0.7	2.8	136.8	5.8	238	38.9
I/5	2.0	139	30	3.7	205.0	7.2	239	16.8
Median SW (range)	2.7 (0.1–8.2)	29.1 (1.0–56.2)	4.7 (0.3–18.0)	9.2 (0.5–35.9)	99.3 (24.2–179.1)	0.9 (0.4–25.1)	439.5 (229.0–711.0)	1.8 (0.1–103.5)
Median SV (range)	2.7 (0.8–11.3)	24.3 (13.9–67.8)	6.2 (0.7–20.6)	12.9 (2.8–44.1)	113.9 (52.2–301.1)	2.6 (0.4–7.2)	225.0 (141.0–501.0)	16.8 (0.2–62.0)
Median total (range)	2.8 (0.1–11.3)	28.5 (1.0–67.8)	5.3 (0.3–20.6)	9.3 (0.5–44.1)	99.3 (24.2–301.1)	1.15 (0.4–25.1)	416.0 (141.9–711.0)	2.4 (0.1–103.5)
Normal values	1.0–10.0	>2-fold	1.0–10.0	>2-fold	>40.0	1.2–4.8	350–900	0.1–1.6

Basal and stimulated serum levels of LH and FSH, baseline serum levels of inhibin B, androstenedione, testosterone, and 17-OHP were determined at the time of investigation. Testicular volumes, TART volumes, and functional testis volumes measured by MRI (18 of 22) and results of semen analysis (19 of 22). Conversion factors: androstenedione × 3.49 nmol/liter; testosterone × 0.0347 nmol/liter; and 17-OHP × 3.026 nmol/liter.

[a] TART volume was significantly higher in salt-wasting patients compared with simple virilizing patients ($P = 0.037$).

[b] Total sperm count, sperm concentration, motile sperm, and viability were assessed according to WHO criteria of 1999 (7).

[c] Morphology was performed according to Tygerberg's criteria (8).

semen analysis revealed a sperm concentration in the upper range of 177.8 million/ml with no TARTs being present.

Leydig cell dysfunction

Decreased testosterone levels [median 416 ng/dl (14.4 nmol/liter)] compared with the general German population [median 640 ng/dl (22.2 nmol/liter)] (12) and reduced semen volume also indicate impaired Leydig cell function in our CAH cohort. These findings could be explained either by disease or treatment-related effects on the hypothalamus-pituitary axis or through direct, intratesticular mechanisms. In the first instance, inadequately controlled adrenal androgen production and its conversion to estrogens can suppress gonadotropin secretion. Such an effect is likely to contribute to the Leydig cell impairment in five of 19 of our patients who presented with high Δ^4-androstenedione serum levels, whereas LH levels were in the lower normal range (n = 1) or below normal (n = 4), and testosterone was either in the lower normal range (n = 4) or below (n = 1). Furthermore, low basal LH levels could also be explained by LH suppression through estradiol, which was elevated in four of our patients. On the other hand, five of 19 patients were characterized by normal LH serum levels with concomitant low-serum testosterone and normal estradiol and normal Δ^4-androstenedione levels. Two of these patients had TARTs, suggesting a local effect on Leydig cell function either mechanically or by local steroid production, hereby confirming the data published by Stikkelbroeck *et al.* (1). The fact that all except one patient had normal GnRH stimulation tests suggests that hypothalamus-pituitary gonadal (HPG) dysfunction can be overcome via stimulation and, thus, should be reversible.

Influencing factors of spermatogenesis

Although we and others (1, 13) could not demonstrate a correlation of hormonal control and semen parameters or TART prevalence or size, this does not exclude its potential causal relationship. It has been shown that TARTs are ACTH dependent, and a decrease in TART size can be achieved through dexamethasone therapy (6). Thus, because TARTs might have developed over a longer period of time, they could be regarded as a more sensitive indicator of the long-term endocrine control than single hormonal measurements in a cross-sectional study design. The same holds true for the relationship of semen parameters and hormonal control, which is further complicated by the fact that sperm production takes 70–80 d, whereas endocrine control parameters reflect the current hormonal situation when the patients were examined.

In fact, several men in the study had low LH, FSH, and testosterone levels, and inadequately stimulated FSH in the GnRH test, which might reflect glucocorticoid-induced suppression of the HPG axis due to overtreatment. This interpretation could explain some of the seminal fluid abnormalities. One may argue that glucocorticoid overdosage is contradicted by the simultaneous finding of TARTs, which rather would suggest inadequate ACTH suppression. Although it is intriguing to speculate that

TABLE 2. Continued

Testicular morphology				Semen parameters			
Total testicular volume (ml)	Total TART volume (ml)	Functional testicular volume (ml)	Total sperm count ($\times 10^6$)	Sperm concentration ($\times 10^6$/ml)	Motile sperm (%)	Normal morphology (%)	Viability (%)
26.13	9.74	16.39	7.8	11.2	50	6.0	62
29.10	5.58	23.52	57.9	18.7	50	4.0	72
17.04	3.53	13.51	0.8	0.3	0	0	0
24.40	2.19	22.21	97.4	40.6	50	9.0	79
48.12	21.56	26.56	0	0	0	0	0
			487.5	195.0	55	7.0	72
21.95	4.88	17.07					
35.29	1.25	34.04	463.1	165.4	55	28.0	82
			227.2	59.8	50	30.0	64
29.38	0	29.38	48.7	20.3	40	4.0	54
35.25	0	35.25	131.0	62.4	60	7.0	70
28.17	0	28.17	92.0	92.0	50	7.0	71
21.10	2.90	18.20	19.5	7.8	50	8.0	72
14.93	3.07	11.86	0.9	0.9	0	0	0
33.01	0	33.01	497.8	177.8	60	19.0	78
21.19	0.37	20.82	48.3	19.3	50	7.0	64
21.52	0	21.52	33.6	14.0	30	9.0	52
25.36	0	25.36	114.8	32.8	60	10.0	66
26.02	0	26.02	262.1	187.2	50	21.0	70
21.76	0	21.76	127.9	31.2	50	9.0	80
28.2 (17.0–48.1)	4.2 (1.3–21.6)[a]	23.5 (13.5–35.3)	75.0 (0.0–487.5)	30.5 (0.0–195.0)	50 (0–60)	7.0 (0.0–30.0)	70.5 (0–82)
21.8 (14.9–33.0)	1.7 (0.4–3.1)[a]	21.8 (11.9–33.0)	114.8 (0.9–497.8)	31.2 (0.9–187.2)	50 (0–60)	9.0 (0.0–21.0)	66 (0–80)
25.4 (14.9–48.1)	3.3 (0.4–21.6)	22.9 (11.9–35.3)	92.0 (0.0–497.8)	31.2 (0.0–195.0)	50 (0–60)	7.0 (0.0–30.0)	70 (0–82)
			>40[b]	>20[b]	>50[b]	>14[c]	>75[b]

these findings might reflect differences in responsiveness of the HPG axis and testicular adrenal rest tissue to glucocorticoid treatment, overall, only longitudinal investigation with close follow-up of individual patients could provide indirect evidence for a causal relationship.

A major supposed cause of subfertility through TARTs is the mechanical obstruction of the seminiferous tubules by the tumor (14). Mechanical obstruction by TARTs would explain the negative correlation of TART volume with semen parameters, and the absence of a correlation between TART volume and any hormone levels, including inhibin B. Inhibin B, a reliable marker of Sertoli cell function (15), in our patients was highly correlated with sperm concentration, as well as functional testicular volume and tumor volume. Inhibin B levels have correlated positively with Sertoli cell number (16) and negatively with seminiferous tubules damage (17). This supports both the hypothesis of testis parenchyma damage leading to a reduced number of Sertoli cells and mechanical obstruction of seminiferous tubules via TARTs, as well as impaired testis development and, thus, Sertoli cell development in CAH patients independent from TART presence. This is in line with the Chilean finding (18) of lower inhibin levels in CAH already in prepubertal boys also in the absence of TARTs.

In conclusion, we hypothesize that the most important determinant factors of impaired fecundity in male CAH patients are the development of TARTs on the one hand and gonadal axis suppression on the other. Most likely, both mechanisms represent complex long-term consequences of insufficient hormonal control that are not reflected adequately by routine hormonal pituitary-gonadal axis parameters. Inhibin B serum levels correlate with Sertoli cell function, and seem to be an adequate diagnostic tool that could be of benefit to monitor and improve fertility outcome in CAH patients.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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