# Non-classical 21-hydroxylase deficiency: prevalence in males with unexplained abnormal sperm analysis

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**Objective:** To evaluate the prevalence of nonclassical 21-hydroxylase deficiency (NC-21OHD) in men with abnormal sperm parameters of unexplained etiology compared with males with normal sperm analysis.
**Design:** Case control study.
**Setting:** Major tertiary medical center.
**Patient(s):** Of 484 healthy men being followed at a fertility clinic, 222 (mean age 33.8 ± 6.1 [±SD] years) presented with abnormal findings on sperm analysis (1999 WHO criteria) of unknown cause and 262 (mean age 34.8 ± 6.5 [±SD] years) with a normal sperm analysis.
**Intervention(s):** Random mid-morning blood sampling to test for 17-hydroxyprogesterone (17-OHP) levels. Subjects with levels of ≥ 6 nmol/L underwent a standard adrenocorticotropic hormone (ACTH) stimulation test.
**Main Outcome Measure(s):** NC-21-OHD, defined as a stimulated ACTH level of ≥45 nmol/L.
**Result(s):** A serum 17-OHP level of ≥6 nmol/L was detected in 11 study patients (5.0%) and 14 control subjects (5.3%). Seven study patients and 8 controls subsequently underwent ACTH stimulation test, and none had levels compatible with a diagnosis of NC-21OHD. Mean 17-OHP levels were similar in the two groups (3.3 ± 1.4 [±SD] nmol/L and 3.3 ± 1.5 [±SD] nmol/L, respectively). There was no correlation between sperm parameters and serum 17-OHP levels.
**Conclusion(s):** Until larger studies are performed, the routine measurement of 17-OHP in the evaluation of male infertility is not recommended. (Fertil Steril® 2010;93:1887–91. ©2010 by American Society for Reproductive Medicine.)

**Key Words:** NC21-OHD, male, sperm analysis, infertility

Congenital adrenal hyperplasia (CAH) is a family of disorders resulting from a defect in cortisol biosynthesis. The most common cause is deficient activity of 21-hydroxylase (CYP21), an enzyme required for the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, which leads to reduced cortisol production and consequent overproduction of corticotropin and adrenal androgens. The disorder is inherited as a monogenic autosomal recessive trait and has traditionally been divided into three types according to severity of expression. The two more severe types, salt-wasting and simple virilizing CAH, are collectively referred to as classical steroid 21-hydroxylase deficiency (C-21-OHD) and are the consequence of null or severe mutations in the *CYP21* gene. The third type, nonclassical 21-hydroxylase deficiency (NC-21-OHD), is associated with different degrees of postnatal virilization and is a consequence of mild mutations (1–4). NC-21-OHD is one of the most common genetic inborn errors of metabolism, with a reported prevalence of approximately 0.1%–0.4% in the general population (1, 4–6) and, 3.2%–3.7% among Ashkenazi Jews (5, 6). The phenotypic expression is heterogeneous: either premature pubarche or precocious puberty with accelerated growth and advanced bone age leading to compromised adult height (in both sexes) (7, 8) or polycystic ovary syndrome (PCOS) with hirsutism, menstrual irregularities, and impaired fertility in females (9, 10). NC-21-OHD is widely underdiagnosed in children and adults, especially in male subjects (1, 4, 8), probably because of its subtle signs.

Most of the large cohort studies of NC-21-OHD were performed in virilized or infertile females (9–12); data on males have been derived thus far from small series or case reports (13–17). Studies of males treated with large doses of exogenous testosterone combined with progesterone have reported findings of suppressed gonadotropin levels and spermatogenesis and consequent oligospermia (18).

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Accordingly, it has been speculated that the infertility associated with untreated CAH in men might be attributable to overproduction of adrenal androgens, leading to suppressed gonadotropin secretion and a hypogonadotropic state (19). However, the reported data on fertility in males with CAH are conflicting (20–22). In the classical form of the disorder, infertility was documented mainly in men with adrenal rests (21). In anecdotal case reports, the nonclassical form in men was associated with an improvement in sperm quality after treatment with hydrocortisone, resulting in spontaneous conception (14–17).

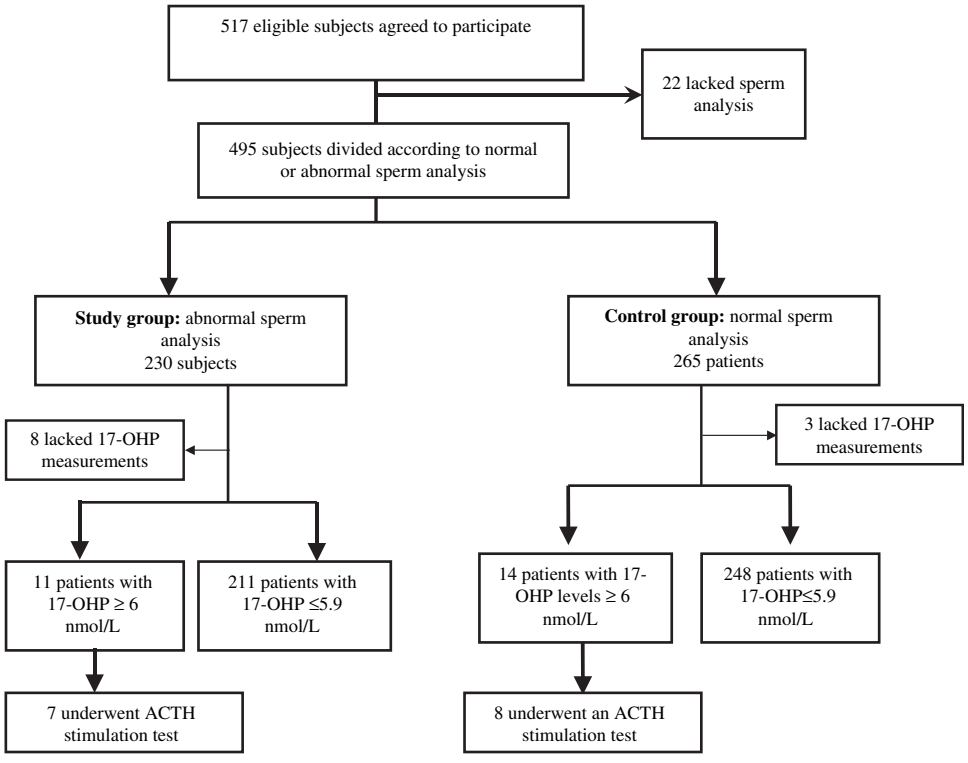
Given that NC-21-OHD is common and easily treatable, and its diagnosis and treatment might theoretically spare patients with infertility from more elaborate tests and interventions, studies of the prevalence of undiagnosed NC-21-OHD in men with unexplained abnormal sperm parameters are warranted. Furthermore, there is no consolidated policy for continued therapy in men with NC-21-OHD following cessation of growth. However, should an increased rate of NC-21-OHD be found in infertile men in whom glucocorticoid therapy had proved effective, its continuation might be justified to preserve fertility. The aim of the present study was to compare the rate of NC-21-OHD between a large group of otherwise healthy infertile men with unexplained abnormal sperm parameters and a matched group, retrieved from infertile couples, with normal semen.

## MATERIALS AND METHODS

The study population was recruited consecutively from couples with male and female factor infertility undergoing in vitro fertilization (IVF) at the Infertility and IVF Unit of Rabin Medical Center from 2000 to 2007. Inclusion criteria were age 18 to 50 years (23) and Jewish origin. Exclusion criteria were known male causes of infertility such as chromosomal abnormality, primary gonadal failure, obstructive azoospermia (congenital or acquired), severe chronic illness, chemotherapy, radiation, drug abuse (24), and daily alcohol consumption of 40 g or more (25). Figure 1 presents the flow diagram of subject inclusion. Of the 517 eligible men who agreed to participate, 22 were excluded because of a lack of sperm analysis. The remaining men were divided into two groups according to their sperm analysis findings, as documented in the clinical files. The study group included 230 men who failed to meet at least two criteria of the World Health Organization reference values for normal sperm (26), as follows: count $\geq 20 \times 10^6$/mL, motility $\geq 50\%$, and normal morphology $\geq 30\%$ or $\geq 14\%$, based on the strict criteria (27). The cutoff for morphology differed because of the different methods used for its determination in the laboratories that conducted the sperm analysis. In 88% of the patients, all three parameters were abnormal. The control group consisted of 265 men with normal sperm parameters.

**FIGURE 1**

Flow diagram of the study subjects.

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All study participants completed a short questionnaire on background data: age, ethnic origin, age at which they started shaving, height, alcohol and drug consumption, and number of children. Ethnic origin was defined as Sephardic, Ashkenazi, Asiatic, Yemenite, mixed, or unknown.

A random mid-morning blood sample was drawn for 17-OHP measurement. The plasma was separated and stored at −20°C until assayed. Patients with a serum 17-OHP level of ≥6 nmol/L (28) underwent a standard adrenocorticotropic hormone (ACTH) stimulation test. Plasma 17-OHP and cortisol levels were measured in the morning before and 30 and 60 minutes after administration of an intravenous bolus of 250 μg of ACTH (Synacthen, Ciba-Geigy, Basel, Switzerland). A commercial radioimmunoassay kit was used (DPC, Los Angeles, CA). The intraassay and interassay coefficients of variation for 17-OHP were, respectively, 8.1% and 9.3% with a 17-OHP level of 1.23 nmol/L, 5% and 6.2% with a 17-OHP level of 7.6 nmol/L, and 4.7% and 5.4% with a 17-OHP level of 30 nmol/L. NC-21-OHD was defined as a 17-OHP value of ≥45 nmol/L at 60 minutes (29). The study protocol was approved by the local ethics committee of Rabin Medical Center and all participants signed an informed consent form.

### Sample Size

As data on the frequency of NC-21-OHD in infertile men are lacking, our calculation of the required sample size for this study was based on the reported frequency of NC-21-OHD in the general population (1%) (4–6) and in females with hyperandrogenism (6%–10%) (9, 10). Based on these proportions, sample size analysis showed that to achieve a significance level of 0.05 (alpha) with 80% power and a difference in proportions of 5% (0.01 vs. 0.06) on two-tailed test, we would need a sample size of 211 for each group.

### Statistical Analysis

The data were analyzed using BMDP Statistical Software (30). Continuous variables were compared between groups with analysis of variance (ANOVA), and discrete variables with Pearson's chi-square test or Fisher's exact test, as appropriate. We also applied Pearson's correlation between various continuous variables. Data are presented as mean ± SD unless otherwise indicated. A $P$ value of ≤ 0.05 was considered statistically significant.

## RESULTS

Eleven subjects (eight of the study group and three of the control group) lacked 17-OHP measurements and therefore were excluded from the study.

Table 1 presents the demographic data of the two groups. There were no between-group differences in age, age at which they started shaving, height, alcohol or drug consumption, or number of children. The only significant difference was in ethnicity because of the higher rate of subjects of Yemenite origin in the study group (14.2% vs. 4.2%, $P$=0.004). Gonadotrophins and testosterone levels of the study group were within the normal range follicle stimulating hormone [FSH] 5.5 ± 2.8 IU/L, luteinizing hormone [LH] 4.2 ± 1.9 IU/L and testosterone 15.8 ± 6.3 nmol/L).

Table 2 shows the sperm parameters of the two groups. Sperm count and percent motility were significantly lower in the study group than in the controls ($P$<0.001 for both parameters).

Table 3 shows the 17-OHP measurements. Of the 484 men, 25 (5.2%) had serum 17-OHP levels equal to or greater than 6 nmol\L: 11 (5.0%) from the study group and 14 (5.3%) from the control group ($P$=1.0). Fifteen of the men, 7/11 (63.6%) from the study group and 8/14 (57.1%) from the control group ($P$=1.0), underwent the ACTH test. None

**TABLE 1**

**Demographic characteristics of the study population.**

| Parameter | Study group (n = 222) | Control group (n = 262) | *P* value |
|---|---|---|---|
| Age (y) | 33.8 ± 6.1 | 34.8 ± 6.5 | 0.07 |
| Origin (%) | | | |
| Ashkenazi | 34.9 | 41.7 | 0.004* |
| Sepharadi | 19.7 | 20.8 | |
| Asiatic | 18.3 | 15.4 | |
| Yemenite | 14.2 | 4.2 | |
| Mixed | 11.9 | 17.0 | |
| Unknown | 0.0 | 0.4 | |
| Age started shaving, y | 15.9 ± 1.9 | 15.9 ± 1.6 | 0.74 |
| Height (cm) | 176.8 ± 7.0 | 177.6 ± 6.8 | 0.22 |
| Number of children | 0.5 ± 0.9 | 0.4 ± 0.7 | 0.55 |

* Difference is due to the between group difference in rate of patients of Yemenite origin.

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**TABLE 2**

**Sperm parameters by group.**

| | Study group (n = 222) | Control group (n = 262) | *P* value |
|---|---|---|---|
| Sperm concentration ($10^6$) | 12.7 ± 13.7 | 71.4 ± 54.3 | < 0.001 |
| Sperm motility (%) | 29.2 ± 17.2 | 54.8 ± 12.8 | < 0.001 |

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had stimulated levels of 17-OHP that fit the diagnosis of NC-21-OHD. The mean levels of 17-OHP were similar in the two groups (3.3 ± 1.4 and 3.3 ± 1.5 nmol/L, respectively, *P*=0.85), as were the peak 17-OHP levels in response to ACTH stimulation (9.6 ± 3.9 and 10.6 ± 2.4, p=0.59; range: 6.3–17.4 nmol/L). No correlations were found between sperm parameters and levels of serum 17-OHP.

## DISCUSSION

The present study was initiated to determine whether NC-21-OHD is a significant cause of abnormal sperm parameters of unexplained etiology in mixed-ethnicity Jewish males. We found that none of the men with normal or abnormal sperm parameters in our study had NC-21-OHD. We were prompted to perform the study for three reasons: [1] the published anecdotal case reports of improved sperm quality and achievement of spontaneous pregnancy in couples in whom the male partner with NC-21-OHD was treated with glucocorticoids (14–17); [2] the reported underdiagnosis of NC-21-OHD in male subjects (1, 4, 7, 8); and [3] the reported effect of chronic elevations of serum androgen concentrations on menstrual disturbances, acne, slowly progressive hirsutism, PCOS, infertility (9–12, 31), early pregnancy loss, and recurrent miscarriages in women with and without PCOS (12, 32). Previous studies have suggested that these disturbances may be attributable to the conversion of excess adrenal androgens to estrogens, which then disrupt gonadotropin secretion (33, 34).

Our negative results may have several explanations. As there are no previous data relating to this issue, our sample size (with 80% power and 0.05 alpha) was calculated on the basis of the assumption of a 1% prevalence in a mixed Jewish population, as previously reported (6), and a presumed 6% prevalence among males with unexplained abnormal sperm parameters, as based on the prevalence figures of NC-21-OHD in females with hirsutism or PCOS (9, 10). However, in a recent survey study of NC-21-OHD, Dr. Shoshana Israel of Haddassa Ein-Karem, Jerusalem (unpublished data) reported a carrier frequency of 1:10 in Ashkenazi Jews living in Israel and 1:20 in Moroccan Israeli Jews, for a disease frequency of 1:400 (0.25%) and 1:800 (0.13%), respectively. These new data place into question the case frequency values of 3.2%–3.7% reported by Spieser at al. (5) in Ashkenazi Jews and the 1% prevalence reported by Zerah et al. (6) in a heterogenous population from New York City. Therefore, much larger groups may be needed to determine whether NC-21-OHD occurs more frequently in infertile males than in the general population.

A second potential reason for our negative findings is the high percentage of subjects (40%) with 17-OHP levels of ≥6 nmol/L who refused to undergo the ACTH test. However, both the total number of subjects with 17-OHP levels of ≥6 mmol/L and the number of them who refused the follow-up test were similar in the two groups.

A third explanation might be the heterogeneity of our population. NC-21-OHD is more frequent in Ashkenazi Jews (4–6), although in our study sample, less than 40% of the subjects were of Ashkenazi origin. Had we studied only Ashkenazi males, the results might have been different. However, the mixture of ethnicities in Jewish Israeli society makes this type of study almost impossible.

The rationale to define the study population according to abnormal sperm analysis was based on the reported subjects with

**TABLE 3**

**17-OHP levels by group.**

| | Study group (n = 222) | Control group (n = 262) | *P* value |
|---|---|---|---|
| Random 17-OHP levels (nmol/L), mean ± SD | 3.3 ± 1.4 | 3.3 ± 1.5 | 0.85 |
| Number of subjects with 17-OHP level ≥6 nmol/L | 11 | 14 | 1.0 |
| Number of subjects who underwent ACTH test | 7 | 8 | 1.0 |
| Stimulated 17-OHP (nmol/L), mean ± SD (range) | 9.8 ± 3.8 (6.3–17.4) | 10.6 ± 2.4 (8.4–16) | 0.59 |

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NC-21-OHD and infertility. These cases (14–17) had low sperm count, which reversed to normal after glucocorticoid therapy.

It is noteworthy that in the case reports of males with NC-21-OHD in whom infertility was reversed by glucocorticoid therapy (14–17), gonadotropin levels were suppressed by the elevated adrenal androgen levels. Yet in the small cohort studies of males with C-21-OHD who have markedly increased adrenal androgen levels (19–22), infertility was limited to those with testicular adrenal rests. In addition, a small Finnish study reported that males with 21-OHD had similar levels of gonadotropins and inhibin B to age-matched controls (22). Given that, of the sex steroids, $E_2$ is the predominant negative-feedback regulator of follicle-stimulating hormone (FSH) secretion in males (34) and that inherited and acquired aromatase efficiency varies in men (35), it is possible that different degrees of aromatization lead to variable FSH responses in different subjects. Therefore, 17-OHP measurements should probably be limited to males with unexplained abnormal sperm parameters combined with suppressed gonadotropin levels.

Our results suggest that NC-21-OHD is not a frequent cause of abnormal sperm quality. Until a larger cohort of males is studied, measuring 17-OHP level as part of the evaluation of infertile males is not recommended.

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