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Infertility

Familial Partial 17,20-Desmolase and 17α-Hydroxylase Deficiency Presenting as Infertility

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***Purpose*:** Females with 17α-hydroxylase/17,20-desmolase deficiency normally present with amenorrhea, sexual infantilism, hypertension, and hypokalemia. We report on a new clinical presentation of this combined enzymatic defect.
***Methods*:** Four Jewish women from two unrelated families presented with primary infertility. All patients exhibited a normal phenotype, blood pressure, and serum potassium levels, with abnormally high follicular phase serum progesterone and low E_2 levels. In order to characterize the underlying defect, the following steps were undertaken: 1) ovarian suppression by GnRH agonist, 2) adrenal suppression by dexamethasone, 3) ovarian stimulation by gonadotropins, 4) adrenal stimulation by ACTH, 5) hormonal assessment of follicular fluid aspirates, and 6) assessment of in vitro E_2 production by luteinized granulosa cells.
***Results*:** The clinical characteristics and endocrine testing results support the diagnosis of a partial deficiency in 17α-hydroxylase/17,20-desmolase activities, shared by the adrenal gland and the ovaries.
***Conclusions*:** Female infertility can be the first and sole clinical manifestation of this enzymatic defect. Its exact nature and prevalence remain to be determined.

KEY WORDS: 17α-hydroxylase; 17,20-desmolase; deficiency; dysmucorrhea; infertility; steroidogenesis.

INTRODUCTION

Ovulation disorders are among the main causes of infertility. They can result either from a primary ovarian defect or from derangement of the hypophyseal–ovarian axis, which controls follicular growth and development. Even though the diagnosis of anovulation is relatively simple, the underlying etiologies are often obscure. It has been shown that partial derangements of steroidogenesis in either the adrenal gland or the ovary underlie a significant proportion of these cases (1).

Sex hormone steroidogenesis begins with the conversion of cholesterol to pregnenolone by a side-chain cleavage catalyzed by 20,22-desmolase. Further synthesis in the ovary proceeds by one of two pathways: the Δ^4-3-ketone pathway or the Δ^5-3β-hydroxysteroid pathway. In the former, pregnenolone is dehydrogenized to progesterone (P) and then converted by 17α-hydroxylase and 17,20-desmolase to androstenedione (ADD), while in the latter it is converted to dehydroepiandrosterone (DHEA) by 17-α-hydroxylase and 17,20-desmolase. These two latter steps in both pathways are catalyzed by a single polypeptide from the cytochrome P-450 group of oxidases designated as P-$450_{17\alpha}$. The DNA sequence encoding this peptide is located on chromosome 10 (2,3). DHEA and ADD serve as precursors

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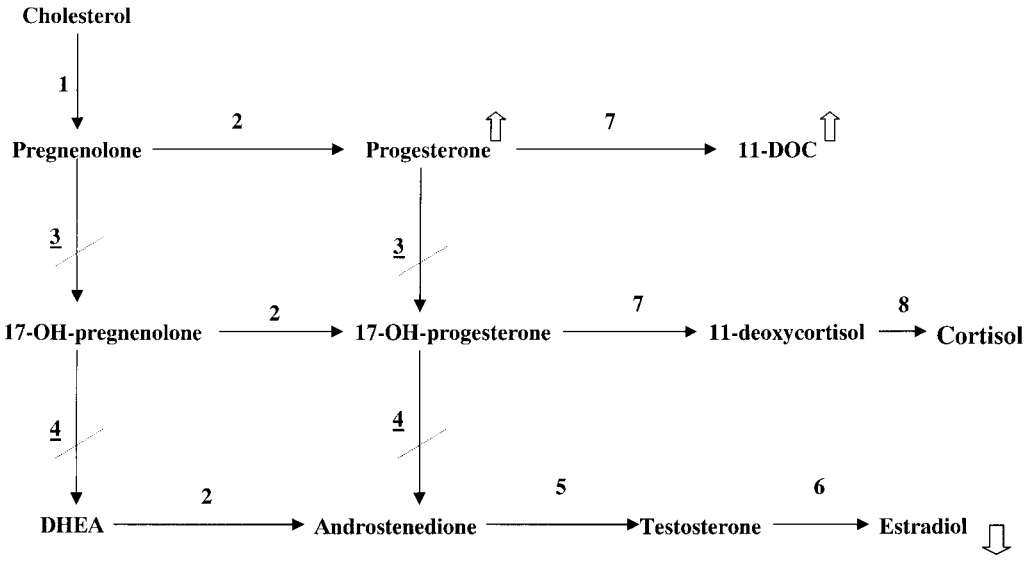

Fig. 1. A scheme of steroidogenic pathways in the ovary and adrenal gland with special reference to 17, 20-desmolase and 17a-hydroxylase (underlined numbers). The partial blocks are demonstrated by dotted lines. Changes in ovarian steroids levels are demonstrated by open arrows.

for testosterone and estrogens in the ovary, and 17-hydroxyprogesterone (17OH-P) serves as the precursor for 11-deoxycortisol and cortisol in the adrenal gland (Fig. 1).

Several reports have appeared in the literature on severe (probably complete) deficiency of 17α-hydroxylase and 17,20-desmolase activities, presenting early in life as either male pseudohermaphroditism or primary amenorrhea with sexual infantilism in the female, accompanied by hypertension and hypokalemia (4–8). A diagnosis of the complete form of 17α-hydroxylase deficiency can be readily assumed in the female patient with primary amenorrhea, hypertension, and hypokalemia (9).

A combined defect in ovarian 17α-hydroxylase and 17,20-desmolase activities would be expected to result in low serum and follicular fluid levels of ADD, testosterone, and E_2, which are subsequent to the synthetic block, and high levels of P, which accumulate because of a block in its further conversion. Because of the biosynthetic block, 17OH-P, 17-hydroxypregnenolone, and androgens are virtually absent. In the adrenal gland, the pathway of cortisol production also involves 17-hydroxylation by the same enzyme; thus, if the above defect is expressed by the adrenals, cortisol production in response to stimulation would be lower than normal and 11-deoxycorticosterone (11-DOC) response higher than normal, for the same reasons, respectively. In several cases of partial defects in one or both activities of P-$450_{17\alpha}$, hypertension and hypokalemia (resulting from the accumulation of 11-DOC) accompanied the clinical presentation, which was mainly some degree of sexual infantilism (10,11).

To the best of our knowledge, this is the first description of familial occurrence of combined partial 17,20-desmolase and 17α-hydroxylase deficiency in phenotypically normal, normotensive women, who presented with primary infertility, anovulation, and persistent cervical dysmucorrhea.

MATERIALS AND METHODS

Four women, two sisters and two cousins, from two unrelated families were referred to our clinic because of primary infertility. The first pair of patients was two cousins who belonged to a Jewish family originating in Egypt. The father of one cousin and the mother of the second cousin were brother and sister. Each cousin had two fertile sisters (Fig. 2). The second pair of patients was two sisters, born to Jewish parents of Yemenite origin. They had four brothers, all fertile, and two more sisters with primary unexplained infertility who were never investigated.

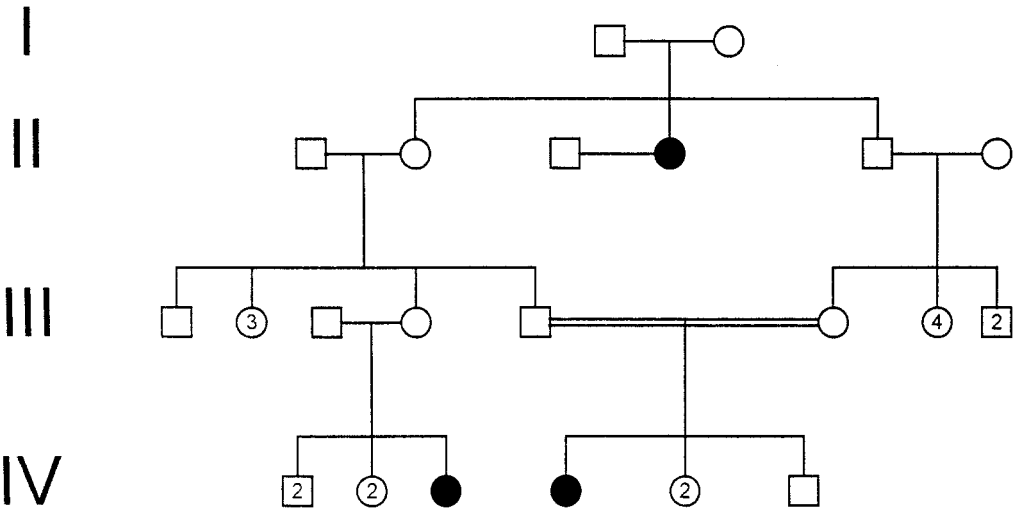

Fig. 2. Pedigree of family 1. It is a Jewish family originating in Egypt and the two cousins in the fourth generation are the subject of our investigation.

Thus, all four sisters suffered from primary infertility, and two of them became the subject of our investigation.

All four patients exhibited a normal adult female phenotype and had regular menstruation with scanty bleeding (hypomenorrhea). All had undergone several courses of treatment with clomiphene citrate and human menopausal gonadotropin (hMG) with presumed ovulation but no conception. Basal body temperature charts in each case revealed a biphasic pattern, but the luteal phase was uniformly short (9–12 days). Physical examination revealed a normal adult female appearance, including well-developed secondary sexual characteristics, in all four cases. Blood pressure values were normal. Preovulatory cervical mucus was poor in amount and quality, consistent with dysmucorrhea. Serum potassium levels were within the normal range. The serum levels of basal (Day 3) gonadotropins during spontaneous cycles were within the normal range for all four patients (FSH mean 7.85 ± 2.32, range 4.8–10.1 IU/L; LH mean 6.5 ± 1.65, range 4.4–7.8 IU/L). Follicular phase P levels were repeatedly elevated in the range of 4.8–17.3 nmol/L (1.5–5.4 ng/mL; normal values <0.5 ng/mL) and E_2 levels no higher than 296 pmol/L (80 pg/mL; normal values >200 pg/mL). Ultrasound monitoring during spontaneous cycles revealed normal ovarian morphology and follicular growth. Luteal phase P was in the range of 12.8–25.6 nmol/L (4.0–8.0 ng/mL).

In summary, all four patients exhibited abnormally elevated serum P levels and lower than normal serum E_2 levels during the follicular phase of the menstrual cycle, which were suggestive of a possible derangement in sex steroid biosynthesis.

A battery of dynamic endocrine and laboratory testing was performed in an attempt to define the exact nature of the derangement and to determine whether it was confined to the ovary or also shared by the adrenal gland.

The first stage of tests was aimed at evaluation of the relative contributions of the ovary and the adrenals to the elevated P levels.

Suppression Tests

(a) The gonadotropin-releasing hormone agonist (GnRHa) triptorelin (Decapeptyl, Ferring, Malmo, Sweden) was administered daily at a dose of 0.5 mg in order to suppress the pituitary–ovarian axis. This treatment is expected to achieve complete suppression of ovarian steroidogenesis within 8–14 days, as evidenced by serum E_2 and P at the menopausal range with a marked decrease in serum gonadotropins levels (12) and the failure of gonadotropin levels to rise following further GnRHa injections (13). Once suppression was confirmed, serum levels of DHEA-sulfate (DHEA-S), ADD, E_2, P, 17OH-P, and 11-DOC were measured.

(b) Dexamethasone (Rekah, Israel), 0.5 mg daily for 5 days, was added on the 14th day of the ongoing GnRHa course in order to achieve

concomitant suppression of the pituitary–adrenal axis. All hormone assays were repeated on the morning after completion of the dexamethasone course.

Stimulation Tests

(a) Ovarian stimulation: hMG (Pergonal, Teva, Netanya, Israel), 150–300 IU/day, was administered concomitantly with dexamethasone, 0.5 mg/day. Serum levels of E_2, P, ADD, DHEA-S, and testosterone were measured daily. Follicular development was monitored by vaginal ultrasonography.
(b) Adrenal: Adrenocorticotropic hormone (ACTH) (Synacthen, Novartis Pharma, Bern, Switzerland), 0.25 mg, was administered during the follicular phase of a spontaneous cycle, and serum concentrations of all the above hormones plus cortisol were sampled every 30 min for 90 min. A normal response to the ACTH test includes a rise in cortisol levels by at least 7 μg/dL to values greater than 18 μg/dL by 1 h (14).

The second stage of tests was aimed at ruling out peripheral target organ failure as the cause of the dysmucorrhea observed in all four women. Following complete suppression of P overproduction (GnRHa + dexamethasone therapy), 2 mg of estradiol valerate (Progynova, Schering, Germany) was administered daily for 10 days, after which the cervical mucus was clinically assessed in each patient.

The third stage of testing consisted of two steps: 1) controlled ovarian hyperstimulation with subsequent oocyte retrieval, also yielding follicular fluid for hormonal evaluation and 2) laboratory determination of the steroid production capacity of luteinized granulosa cells. Ovarian stimulation was accomplished by the administration of hMG (225 IU/day) from the 3rd day of the menstrual cycle. Human chorionic gonadotropin (10,000 IU) was given when at least two follicles larger than 18 mm were observed, and oocyte retrieval was performed 32–36 h later. In vitro fertilization resulted in fertilization of more than 70% of the retrieved oocytes, with subsequent normal cleavage.

Luteinized granulosa cells, pooled from 10 follicles after centrifugation of follicular fluid at 1000 $\times$ *g*, were resuspended in Ham's F-10 medium (Biological Industries, Kibbutz Bet Haemek, Israel) supplemented with L-glutamine, antibiotics (1 mg/mL streptomycin, 10 U/mL penicillin and 1 U/mL mycostatin), and 5% heat-inactivated calf serum. The cells were layered onto 4 mL of 50% Percoll (Pharmacia, Uppsala, Sweden) and centrifuged at 1000 $\times$ *g* for 30 min. Granulosa cells were collected from the interface, washed, and counted in a hemocytometer. About 9×10^5 viable cells, as assessed by 0.1% trypan blue, were obtained. Cells were cultured in eight replicates at a density of 10^5 cells/ml well in 16-mm plastic culture wells (Nunc, Copenhagen, Denmark) at 37°C in an atmosphere of 95% air–5% CO_2. After 24 h, cells were washed, and reincubated for a further 24 h. The medium was then collected, frozen at −20°C for hormone assays (basal steroid production), and fresh medium containing 10^{-7} M 17OH-P, ADD, DHEA, or testosterone (Makor, Israel) was added. Following incubation for 8 h, the medium was collected and frozen at −20°C for steroid assays. Granulosa cells from controls (10 women undergoing IVF treatment for tubal factor infertility) were subjected to a similar procedure.

Estradiol, P, and testosterone concentrations in the extracts were determined by radioimmunoassay (RIA), using reagents supplied by WHO Special Program for the Provision of Matched Assay Reagents for the RIA of Hormones in Reproductive Physiology. In the E_2 assay, antibody cross-reactivity was less than 0.02% for estrone, P, and testosterone, and the sensitivity was 74 pmol/L, with interassay and intraassay variations of 7 and 10%, respectively. In the P and testosterone assays, the interassay variation was 6%, and the intraassay variations were 12 and 10%, respectively. Following extraction with benzene/ethyl acetate (2:1), ADD was determined by RIA with an antibody (Serono, Milan, Italy) that has a cross-reactivity of 0.4% with testosterone and less than 0.01% with P and E_2. Following ether extraction, 17OH-P was determined using a kit purchased from CIS (Sorin, France); cross-reactivity was 5.8% with P and less than 0.001% with E_2 (15).

Follicular fluid was tested for all of the above substances using the same methods as were used for the culture medium of the granulosa cells.

Results are presented as means ± SD. Statistical analysis was conducted using the Student's *t* test. A *P* value of <0.05 was considered statistically significant.

RESULTS

By the 14th day of GnRHa administration, the serum P levels in all four women had declined to a

Table I. Infertility History and Current IVF Cycle Outcome for the Study Patients

Patient	Age (years)	Infertility duration (years)	Number of previous IVF cycles	Number of oocytes retrieved in current cycle	Fertilization rate (%)	Number of embryos cleaved (%)
1	41	20	4	13	7 (54)	5 (71)
2	38	7	9	34	26 (76)	17 (65)
3	38	19	1	2	1 (50)	1 (100)
4	33	2	2	22	20 (91)	19 (95)

mean value of 4.8 nmol/L (range 3.84–5.76 nmol/L; 1.2–1.8 ng/mL). The addition of dexamethasone was followed by a further decline in serum P to below the detection limit of 0.064 nmol/L (<0.02 ng/mL), indicative of an adrenal contribution to the abnormally high P levels.

Following ovarian stimulation with hMG, an abnormal sex steroid output pattern was noted, characterized by abnormally high follicular phase P levels, exceeding 6.68 nmol/L (2.1 ng/mL) in all cases, and attenuated E_2 secretion, with levels not higher than 844 pmol/L (230 pg/mL), along with an adequate growth of 6–18 follicles. Clinical characteristics and embryology data for the study patients during the current IVF cycle is given in Table I. None of the patients conceived.

Basal serum cortisol levels were within the normal range, i.e., 342.1–491.1 nmol/L (12.4–17.8 μ/dL). However, following adrenal stimulation by ACTH, cortisol levels rose by less than 193 nmol/L (7 μ/dL). An increase in serum P from 8.64–12.6 to 19.2–34.24 nmol/L in response to this test was observed in all four patients but not in the controls. No increase was observed in ADD, DHEA-S, or testosterone. Basal levels of 11-DOC were 1.2 nmol/L (range 1.33–2.66), which is higher than normal (range 0.09–0.6 nmol/L), and rose to 14.6 nmol/L (8.3–17.1) after 60 min (normal 1.8–4.5 nmol/L).

Following the administration of exogenous estrogen in combination with suppression of P overproduction (GnRHa + dexamethasone), the quality and quantity of cervical mucus was excellent, thus ruling out end-organ failure.

Sex steroid concentrations in the follicular fluid obtained during oocyte retrieval are given in Table II. Relative to the control values, E_2 and ADD levels were low and P was high in all patients, while levels of 17OH-P was not significantly different from those for controls.

Basal 24 h production of E_2 by luteinized granulosa cells (expressed as E_2 concentration in the culture medium) was 6.24 ± 3.67 nmol/L (1.7 ± 1.0 ng/mL), which was significantly lower than in controls (13.1 ± 1.85 nmol/L; 3.6 ± 0.5 ng/L) ($p < 0.01$). Progesterone production was 3870 ± 1273 nmol/L (1046 ± 344 ng/mL) compared to 2235 ± 196 nmol/L (604 ± 53 ng/mL) in controls ($p < 0.001$). Levels of 17OH-P in the culture medium did not differ from control values, i.e., 1.347 vs. 1.368 nmol/L (44.9 vs. 45.6 ng/mL), respectively. Levels of sex steroids production following the addition of various precursors to the culture medium are summarized in Table III. Addition of 17OH-P, a substrate for 17, 20-desmolase, resulted in lower than normal E_2 production, while the addition of substances normally present beyond this metabolic stage resulted in significantly increased E_2 production.

DISCUSSION

Numerous enzymatic defects are known to cause derangements in either adrenal or ovarian steroidogenesis. Among these, the complete blocks result in obvious clinical syndromes that are readily detected early in childhood. Partial blocks, leading to moderate

Table II. Steroid Concentrations in Follicular Fluid Obtained from the Study Patients and Normal Controls

Substance	Patients	Controls
Estradiol, nmol/L (ng/mL)	$859 \pm 720^{**}$ (234 ± 196)	3873 ± 815 (1055 ± 222)
Progesterone, μmol/L (μg/mL)	$51.5 \pm 7.95^{**}$ (16.2 ± 2.5)	20.1 ± 3.18 (6.2 ± 1.0)
17OH-P, nmol/L (ng/mL)	$2090 \pm 496^{**}$ (643 ± 155)	3130 ± 538 (978 ± 168)
ADD, nmol/L (ng/mL)	$48.5 \pm 32.5^{*}$ (13.9 ± 9.3)	74.7 ± 19.5 (21.4 ± 5.6)

Note. 17OH-P: 17-hydroxyprogesterone; ADD: androstenedione.
$^{**}p < 0.001$;
$^{*}p < 0.01$.

Table III. Estradiol Production in 24 h by Luteinized Granulosa Cells from Four Women with Combined Partial 17,20-desmolase and 17α-hydroxylase Deficiency Following the Addition of Several Steroid Precursors

Basal rate	6.24 ± 3.67 (1.7 ± 1.0)
17-hydroprogesterone	6.24 ± 3.67 (1.7 ± 1.0)
Dehydroepiandrosterone	112 ± 1.1 (30.5 ± 0.3)
Androstenedione	152 ± 81.1 (41.4 ± 22.1)
Testosterone	73.8 ± 11 (20.1 ± 3.0)

Note. Results are given in nmol/L, whereas values in brackets are ng/mL.

alterations in steroidogenesis, may sometimes present as female infertility in adult life. It has been recently shown that in Jews, where partial deficiencies of 21-hydroxylase, 11-hydroxylase, and 3-hydroxysteroid dehydrogenase are relatively common, unexplained infertility was the only complaint in 31/170 (18%) of the patients studied (1).

Various forms of P-$450_{17\alpha}$ deficiency have been identified and extensively investigated (16). The enzyme is bound to the smooth endoplasmatic reticulum, and is regulated by a gene on chromosome 10 (2,3). The molecular basis for deficiency of P-$450_{17\alpha}$ is due to a variety of mutations, which result in multiple base deletions and duplications in the *CYP17* gene on chromosome 10q24-25. Over 15 different P-$450_{17\alpha}$ mutations have been described in patients with P-$450_{17\alpha}$ deficiency, including nonsense mutations, deletions, and small duplications, indicating that mutations in this gene are due to random events (2,3,17–23).

The P-$450_{17\alpha}$deficiency syndrome is usually recognized at the time of puberty in young adults through the presence of hypertension or hypokalemia associated with hypogonadism (primary amenorrhea and sexual infantilism) in the female or pseudohermaphroditism in the male. Approximately 10–15% of reported patients with P-$450_{17\alpha}$deficiency are not hypertensive or hypokalemic at the time of diagnosis (16). The syndrome is believed to be rare, with only a few hundreds of patients reported in the literature so far (16). Studies in several families where familial occurrence has been detected are suggestive of an autosomal recessive trait as a mode of inheritance (16).

Traditionally, 17α-hydroxylase and 17,20-desmolase were regarded as separate enzymes. These two different functions of a single enzyme, P-$450_{17\alpha}$, are not genetic or structural but represent different activities, probably influenced by local factors (24). Three forms of enzymatic deficiency related to an abnormal P-$450_{17\alpha}$ gene have been reported (16): 1) combined deficiencies of 17α-hydroxylase and 17,20-desmolase (the most common form) 2) isolated 17α-hydroxylase deficiency, and 3) isolated 17,20-desmolase deficiency.

The four women described herein presented with a previously unreported form of partial deficiency of 17,20-desmolase and 17α-hydroxylase activities in both the ovaries and the adrenal gland. The primary reason for characterization of this deficiency as partial is the presence of normal secondary sexual development, with detectable, though subnormal, peak serum E_2 levels. This is also the main point of difference with respect to previously reported variants. The higher than normal P levels during the follicular phase provided the clue, suggesting a synthetic block. The decrease in P levels upon suppression of the hypothalamic–ovarian axis, followed by its complete disappearance only after the addition of dexamethasone, indicates that both the adrenal gland and the ovary share the block. The stimulation tests, on the other hand, further revealed the nature of this defect, where under GnRHa suppression, the ACTH stimulation test caused a sharp rise in P secretion, a subnormal rise in cortisol levels, and a mild rise in 11-DOC with no rise in ADD levels. An increase in ADD concentration would be expected in participant with the adrenogenital syndrome, and its absence specifically indicates that 17α-hydroxylase activity in the adrenal gland is lower than normal, resulting in an accumulation of P.

A unique feature of this variant is the relatively mild rise in 11-DOC, from 2.1 nmol/L to 14.36 nmol/L, in response to ACTH stimulation. Yanase *et al.* (25) described a patient with partial deficiency of 17α-hydroxylase and 17,20-desmolase, in whom the baseline 11-DOC serum level was 9.05 nmol/L, compared to 2.1 nmol/L in our patients. The ACTH-induced rise in 11-DOC supports the existence of a synthetic block. The rise is mild, which explains why our patients, unlike previously reported individuals with partial block and markedly elevated 11-DOC, do not have either hypertension or hypokalemia. In addition, gonadotropin stimulation did not raise the E_2 serum level above 844 pmol/L (230 pg/mL), but it did cause a rise in P levels, thus demonstrating that the partial block in both 17α-hydroxylase and 17,20-desmolase activities exists in the ovary.

Conclusive evidence of a synthetic defect comes from the demonstration of lower than normal production rate of E_2 by luteinized granulosa cells following the addition of preblock precursors and normal

production rate when postblock precursors are supplied. Addition of 17OH-P did not raise the subnormal basal rate of E_2 production; this rate was however increased by 10- to 20-fold upon the addition of ADD, DHEA, or testosterone.

Although the prevalence of P-450$_{17\alpha}$ deficiency in the general population is yet unknown, its clinical implications may be relatively wide. In view of the familial occurrence in our patients, and since their parents had emigrated from different parts of the world, there is good reason to suspect that the genomic defect responsible for the syndrome is not rare. In fact, its frequency has been estimated as twice the frequency of 11 β-hydroxylase deficiency (16). As mentioned above, P-450$_{17\alpha}$ activity is regulated by a gene on chromosome 10 (2,3) and examination of the family history and pedigrees in our two families is suggestive of autosomal recessive inheritance (Fig. 2). Moreover, three of the women had been undergoing treatment for infertility for many years before their disorder was properly characterized, and there might be quite a few others as yet undiagnosed. In our opinion, every infertile woman with cervical dysmucorrhea despite a normal appearing uterine cervix and regular menstruation should be evaluated for this defect. Thus, partial deficiency of 17α-hydroxylase and 17,20-desmolase activities should be included in the differential diagnosis of cervical dysmucorrhea.

In addition to cervical dysmucorrhea, which may interfere with sperm transport, infertility in subjects affected by this partial enzymatic defect may also result from raised P levels during the follicular phase that may cause asynchronous endometrial development, and from the consistently observed short luteal phase. Arrest of follicular development has been observed in complete 17α-hydroxylase deficiency (26), but is unlikely with the partial defect in view of the apparently normal follicle growth and development, as well as the normal oocyte fertilization and embryo cleavage observed.

For clinical diagnosis of women thought to have this syndrome, we suggest the use of the ACTH-stimulation test. This should result in a rise in progesterone in these patients, while ADD, unlike in women with partial forms of the adrenogenital syndrome, should remain low. A concomitant mild rise in 11-DOC can then be used to distinguish these women from more severely affected patients.

The therapeutic approach in cases with P-450$_{17\alpha}$ deficiency remains a dilemma. As demonstrated by our series of patients, as well as by Rabinovici *et al.* (27) and Pellicer *et al.* (10), fertilizable oocytes can be obtained following controlled ovarian hyperstimulation and IVF, but implantation failure is repeatedly observed. This may result from the combination of attenuated E_2 secretion and overproduction of P during the follicular phase of the cycle, which may interfere with endometrial preparation for implantation. As also suggested by Pellicer *et al.* (10), endometrial preparation with exogenous steroids (28) and subsequent transfer of frozen–thawed embryos might be undertaken in order to overcome the problem of endometrial receptivity. In cases with 17,20-desmolase and 17α-hydroxylase deficiency, complete suppression of endogenous sex steroid production (GnRHa + dexamethasone) would be required prior to exogenous E_2 and P administration. We have recently attempted this approach in one of the two cousins from the first family (Fig. 2). Following controlled ovarian hyperstimulation under gonadal and adrenal suppression with dexamethasone and GnRHa, IVF was performed and all the resulting embryos were frozen. Frozen embryos were subsequently thawed and transferred under the same suppression regimen, while the endometrium was prepared with exogenous estrogen and progesterone. A triplet pregnancy was achieved, which resulted in the live birth of three healthy babies. In our opinion, this is the preferred therapeutic approach in partial 17,20-desmolase and 17α-hydroxylase deficiency.

In summary, the possibility of combined partial 17,20-desmolase and 17α-hydroxylase deficiency should be actively investigated in infertile women who present with abnormally high follicular phase P levels, attenuated E_2 secretion, and cervical dysmucorrhea. The exact mutation in the *CYP17* gene on chromosome 10q24-25 in our patients and their families is currently under investigation.

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