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CLINICAL CASE SEMINAR

Dynamics of Ovarian Function in an Adult Woman with McCune-Albright Syndrome*

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McCune-Albright syndrome is a sporadic disease characterized by polyostotic fibrous dysplasia, *café-aux-lait* lesions, and a variety of endocrine disorders (1, 2). The molecular basis of this syndrome has recently been elucidated. Missense point mutations in the GNAS1 gene located on the long arm of chromosome 20 and encoding for the α subunit of G_s (the G protein that stimulates cAMP) of transmembrane glycoprotein receptors have been identified (3, 4). Mutations at codon 201 substituting Arg with either Cys or His give rise to abnormal Gsα proteins that reduce the intrinsic guanosine triphosphatase activity, thereby constitutively activating the Gs protein. The mutation is found in variable abundance in different endocrine and nonendocrine tissues, consistent with the mosaic distribution of abnormal cells generated by a somatic cell mutation early in embryogenesis. Severe disease may be associated with an earlier mutational event leading to more widespread distribution of mutated cells (5).

The most commonly encountered endocrine dysfunction in McCune-Albright syndrome is gonadal hyperfunction. Precocious puberty represents the usual initial manifestation of McCune-Albright syndrome in girls. Ovarian cysts may be found on pelvic ultrasound (6–8). Other endocrine abnormalities include hyperfunction of the thyroid and adrenal cortex, as well as excessive GH secretion. The majority of patients have abnormally elevated sex steroids with low or undetectable gonadotropin levels (5). Whereas pregnancies have been described later in life (9, 10), polymenorrhea and amenorrhea due to continued gonadotropin-independent estrogen production have also been reported (11). However, clinical information regarding ovarian dysfunction in McCune-Albright patients during adolescent and adult life is scant.

Case Report

A 22-yr-old patient previously diagnosed as McCune-Albright attended our outpatient clinic for fertility counseling. She exhibited the classical clinical triad of polyostotic fibrous dyplasia along with large *café-aux-lait* spots in the lumbosacral region and a history of precocious puberty and irregular menstrual bleeding.

Computed tomography scans showed fibrous dysplastic bone in the left humerus as well as in the sphenoid and maxillary sinus. The field of vision of the left eye was restricted due to facial bone involvement. Furthermore, she complained of recurrent maxillary sinusitis on the left side. At the age of 20 she underwent surgery in which dysplastic bone was removed from her maxillary and ethmoïd sinus on the left side. At age 21 she fractured her left clavicle following an accident with a horse. Healing was markedly delayed. Several typical *café-aux-lait* spots were located in the lumbosacral region, having a triangular shape, predominantly located at the left side and extending from L4 until S3, as well as in the neck and at the flexor surface of the lower left leg.

Menarche occurred at age 5 along with left-sided breast enlargement and development of pubic hair. At that time she exhibited low serum FSH and LH levels, whereas estradiol (E_2) was in the normal adult range. Bone age and height were normal at the onset of menstruation. Symptoms did not progress during 5 yr of treatment with cyproterone acetate (12). Sexual maturation started after cessation of cyproterone acetate at 10 yr of age and was completed at 15 yr of age. Thereafter, several combined steroid contraceptive pills were prescribed for irregular menstrual bleeding without success. As far as she could remember, her menstrual cycle had been irregular (bleeding interval, 1–2 weeks) throughout life. During several periods without hormonal contraception she had unprotected intercourse with different male partners without conceiving a pregnancy. Before consultation she also suffered from intermittent pelvic pain predominantly on the right side. On physical examination, her height was 175 cm

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and body weight 58 kg. Pubic hair and breast development, as well as the appearance of her external genitals, were according to Tanner stage V. On transvaginal pelvic ultrasound several cysts were observed only in the right ovary, together with a thickened endometrial lining of the uterus and engorged uterine veins. At the time of referral, increased serum E_2 (805 pmol/L), normal FSH (2.6 IU/L), LH (3.0 IU/L), PRL (3.6 μg/L), TSH (1.6 mU/L), androstenedione (9.4 nmol/L), and dehydroepiandosteronsulphate (2.4 μmol/L) levels were found.

Materials and Methods

Ultrasonography

Transvaginal ultrasound was carried out on initial screening and at 2-day intervals during two months. Ovarian volume, number of follicles and cysts, features of ovulation, and endometrial thickness (anterior and posterior layers measured in the longitudinal axis) were recorded. For sonographic imaging we used a 6.5-MHz vaginal transducer (model EUB-415; Hitachi Medical Corporation, Tokyo, Japan), as described previously (13, 14).

Source of tissue and preparation of cells

In the beginning of a bleeding period (day 3) laparoscopy and dilatation and curettage were performed to collect ovarian and endometrial biopsies. Before the laparoscopy, several ovarian cysts were punctured separately using transvaginal ultrasound guidance. Ovarian biopsies were taken from both ovaries for genetic analysis using monopolar scissors. Endometrial biopsies were taken using a Pipell microcurette (Laboratoire CCD, Paris, France). Samples were taken from the anterior and posterior endometrial wall. All tissue samples as well as the aspirates from cysts were placed in *in vitro* fertilization (IVF) medium immediately after collection. Aspirates were centrifuged at 3000 $\times$ *g* for 10 min, and the pellets of cells were reemerged into IVF medium. The remaining fluid was analyzed for its hormonal content.

Light microscopy

Sections of both ovaries and endometrium obtained by biopsy were prepared in neutral buffered formalin and embedded in paraffin. Thereafter, 10-μm thin sections were cut and subsequently stained with hematoxilin and eosin (15).

Hormone assays

Blood samples were obtained by venepuncture during the initial visit and at 2-day intervals during two monitored months. They were processed within 2 h after withdrawal. Serum and aspirates from the cysts was stored at −20 C. Serum was assayed for FSH, LH, E_2, progesterone (P), testosterone, androstenedione, sex hormone-binding globulin, inhibin A, and inhibin B as described previously (16, 17). Normal serum values were obtained from previous longitudinal studies in 42 normo-ovulatory volunteers (17, 18). Follicular fluid was assayed for E_2 and P. Normal follicular fluid values were obtained from normo-ovulatory volunteers (19).

DNA analysis

DNA was extracted from blood lymphocytes, endometrium, left and right ovarian tissues, and fluid obtained from ovarian follicles and cysts using commercial kits (QIAGEN, Courtaboeuf, France). PCR was performed on extracted DNAs. With the exception of minor modifications, we have used a method described previously (20) for selective enrichment of mosaic Arg 201 mutations.

Informed consent

The local Institutional Review Board was informed of the investigations being carried out. Because only one fully informed patient was involved, a research potocol approval was not required.

Results

Light microscopy

Microscopic analysis of ovarian biopsies showed primordial, primary, and secondary follicles along with Graaffian structures most pronounced in the right ovary. Although all stages of follicular development were present, larger follicles were luteinized. Secretory as well as proliferative elements were present side by side in the endometrium (Fig. 1, A and B).

Mutation analysis

Direct DNA sequencing showed the presence of a guanine to adenine transversion leading to an Arg-His substitution at position 201 in the anterior endometrial lining and right

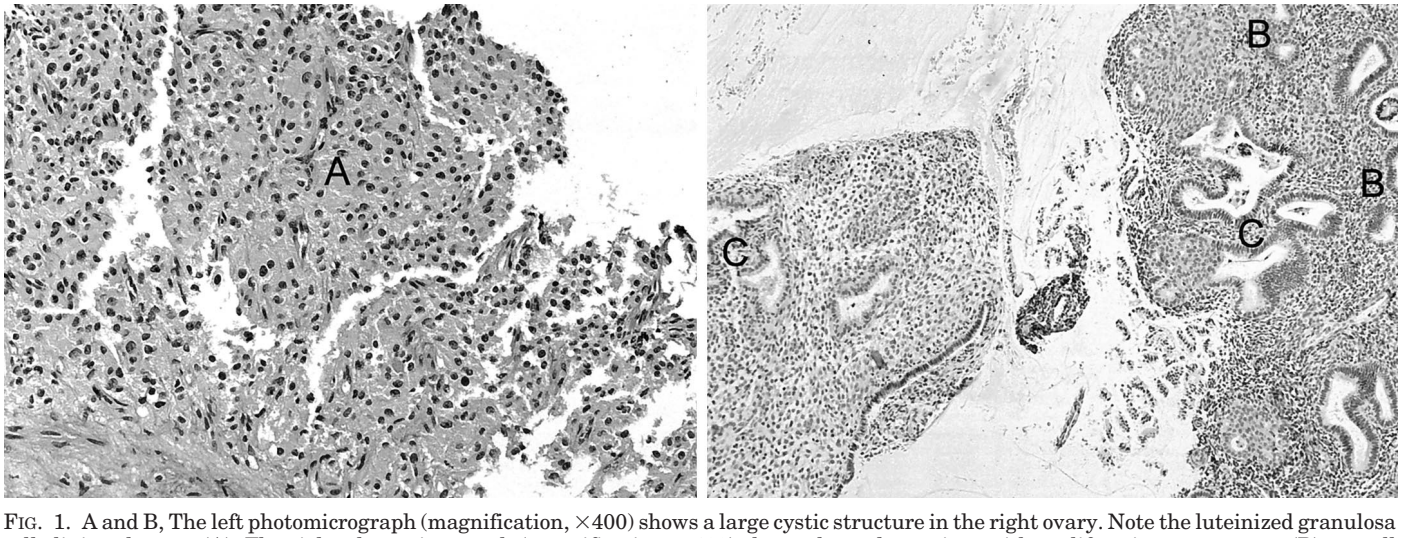

FIG. 1. A and B, The left photomicrograph (magnification, ×400) shows a large cystic structure in the right ovary. Note the luteinized granulosa cells lining the cyst (A). The right photomicrograph (magnification, ×400) shows the endometrium with proliferative components (B) as well as secretory elements (C).

ovary. The mutation was neither detectable in the left ovary nor in fluid obtained from ovarian cysts, in the posterior endometrial lining, or in blood lymphocytes.

Both canonical and mutant sequences were present. The latter with a weaker intensity, indicating a somatic mutation and, thus, a mosaicism of normal and abnormal cells as observed in McCune-Albright syndrome.

Cycle 1

In the beginning of this cycle the maximum FSH level observed was 4.0 IU/L (median during early follicular phase of normo-ovulatory controls, 5.2 IU/L; range, 2.5–11.2), whereas LH levels were increased at 15.5 IU/L (median during early follicular phase of normo-ovulatory controls, 3.2 IU/L; range, 1.9–10.1) (17, 18). The initial ultrasound investigation on day 5 showed four dominant follicles in the enlarged (58 mL) right ovary with a diameter ranging between 14 and 23 mm. Beyond day 9 these follicles ceased growing at a diameter beyond 25 mm. In contrast, single dominant follicle selection and normal development could be observed in the normal sized (18 mL) left ovary. At a follicle diameter beyond 20 mm signs of ovulation (a sudden decrease in follicle diameter and the appearance of free fluid in the pouch of Douglas) could be observed. This occurred once between the 10th and 15th day and once on day 23. E_2 levels were 971 pmol/L on cycle day 7 (median mid follicular phase in controls, 220 pmol/L; range, 91–462) and decreased to 467 pmol/L on day 16. Thereafter, an increase was observed up to 930 pmol/L before menses (median late luteal phase in controls, 169 pmol/L; range, 144–228). P levels were as high as 9.2 nmol/L in the beginning of the cycle (median early follicular phase in controls, 1.0 nmol/L; range, 0.2–9.0) and rose to a peak value of 30.2 nmol/L on day 12 (median mid luteal phase in controls, 49.5 nmol/L; range, 16.7–60.8). Subsequently, P levels decreased to a value of 4.5 nmol/L on cycle day 23. At day 23, LH and FSH levels were 4.3 IU/L and 3.4 IU/L, respectively. The total endometrial thickness was 10 mm on cycle day 10 and decreased to 4.5 mm on day 20. These results are depicted in Fig. 2A.

Cycle 2

During the second cycle, three distinctive rises in FSH were observed on cycle day 12 (6.8 IU/L), cycle day 24 (5.9 IU/L), and cycle day 39 (12.3 IU/L). Similarly, rises in LH were observed on days 12, 24, and 39, reaching values of 12.1 IU/L, 11.7 IU/L, and 50.0 IU/L, respectively. Inhibin B serum concentrations were only determined during the second cycle because the sample volume during the first cycle was insufficient. Inhibin B levels increased from early follicular phase levels of 76 ng/L (median early follicular phase in controls, 40 ng/L; range, 32–60) to a maximum of 220 ng/L on cycle days 15 and 17 (median late follicular phase in controls, 170 ng/L; range, 98–223). Thereafter, inhibin B fell to a nadir level of 45 ng/L on cycle day 30 with a subsequent rise to 96 ng/L on cycle day 37. Inhibin A levels were 28 ng/L on cycle day 3 (median early follicular phase in controls, 7 ng/L; range, 1.1–10.2) and gradually increased to a maximum value of 49 ng/L on cycle day 32 (median mid to late luteal phase in controls, 35 ng/L; range, 16–43). Thereafter, inhibin A decreased to a level of 4 ng/L on cycle day 39. In the right ovary, multiple dominant follicle development was observed and again growth was arrested at a diameter around 25 mm. In the left ovary, single dominant follicle growth was noted later during the cycle with a maximum diameter of 22 mm on day 32. E_2 levels were 521 pmol/L on cycle day 3 and remained fairly constant until cycle day 24. Thereafter, E_2 levels fell gradually to a nadir of 69 pmol/L on cycle day 37. P levels were 4.2 nmol/L on cycle day 3 and remained fairly constant during the follicular phase. On cycle day 24 a rise in P levels could be noted up to a peak value of 44.1 nmol/L reached on cycle day 32. A sharp decline was noted between days 32 and 39 in this cycle to a level of 5.8 nmol/L. Endometrial thickness was 3.7 mm at initial screening and increased gradually to 8.4 mm. On ultrasound examination a triple line was observed throughout the cycle. During menses the endometrium remained 8.4 mm thick. These results are depicted in Fig. 2B.

Follicular fluid

In the right ovary five follicles measuring 22, 13, 12, 10, and 10 mm were punctured whereas in the left ovary three follicles with a diameter of 5, 5, and 4 mm were aspirated separately. E_2 and P levels were compared with values obtained from similar follicles from regularly cycling women (19). Results are summarized in Fig. 3. Intrafollicular E_2 and P concentrations were increased in small follicles (<10 mm) but diminished in large follicles.

Discussion

Our findings represent the first longitudinal assessment of ovarian dysfunction in an adult patient suffering from McCune-Albright syndrome. The anticipated phenotype is the development of multiple dominant follicles as a result of increased FSH signaling. Indeed, FSH levels are increased in mothers of dizygotic twins resulting from multiple ovulations (21). Next to the development of multiple preovulatory follicles, premature luteinization and follicle maturation arrest may also be anticipated in this patient due to increased LH receptor signal transduction. This latter phenomenon may be comparable with a premature rise in serum LH observed during initial protocols for ovarian hyperstimulation for IVF without GnRH agonist cotreatment (22).

High FSH levels occurring during the luteo-follicular transition give rise to continued growth of a limited number (cohort) of follicles (23). Subsequent development of this cohort during the follicular phase is dependent on continued stimulation by gonadotropins. FSH levels decrease during the follicular phase due to negative feedback by ovarian inhibin B and E_2 synthesis. Except for the dominant follicle remaining, follicles enter atresia due to insufficient support by reduced FSH levels (24). During the late follicular phase, aromatase enzyme activity of granulosa cells from the dominant follicle is also stimulated by LH (25). Under normal conditions, a good correlation between dominant follicle diameter and follicle fluid or serum E_2 levels is observed (18, 19).

Increased FSH receptor signaling induced multiple dominant follicle development in the right ovary of the current

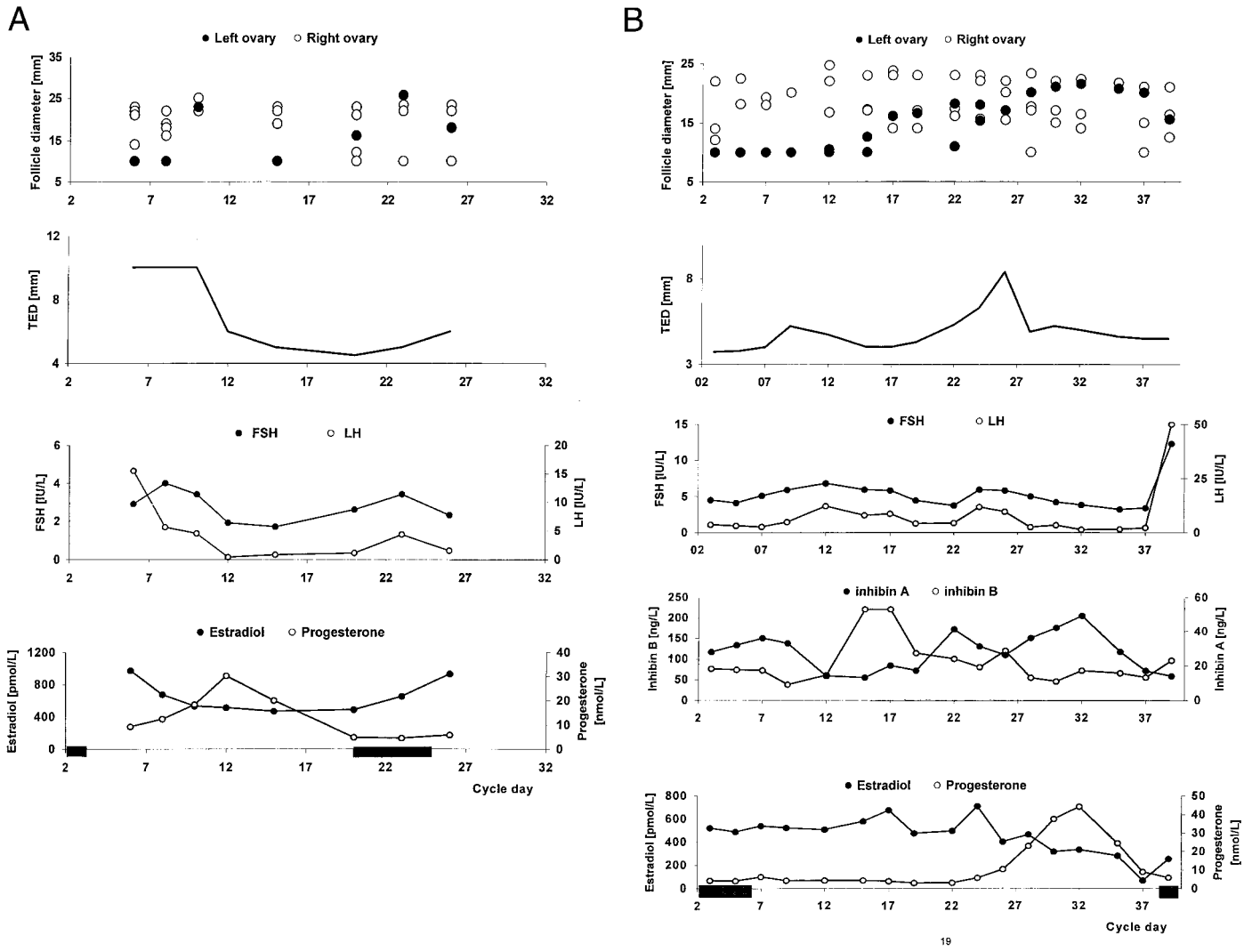

FIG. 2. A and B, Schematic presentation of ultrasound findings in both ovaries (*top*) and endometrium (*second panel*) during the first (A) and second (B) observation month. TED, Total endometrial diameter. FSH and LH concentrations are shown in the *third panel* of each figure. Inhibin A and inhibin B concentrations are summarized in the *fourth panel* of B. Finally, E_2 and P levels are depicted in the *bottom panels* of each figure. *Shaded areas* on the x-axis indicate periods of "menstrual" bleeding.

patient. Consequently, E_2 levels were increased at the beginning of the cycle. In McCune-Albright patients, cyst-like structures produce E_2 *in vitro* comparable with normal preovulatory follicles. In contrast, small follicles synthesize substantially more E_2 compared with these cysts (26). In the current study, follicular fluid E_2 levels were increased in small follicles and decreased in preovulatory follicles compared with normal control subjects. Because McCune-Albright patients respond well to treatment with aromatase inhibitors (12), it might be speculated that aromatase is overexpressed in granulosa cells of McCune-Albright patients due to constitutive FSH signaling resulting in supraphysiological intrafollicular E_2 concentrations.

Follicular fluid P levels were also increased in small follicles whereas in larger preovulatory follicles P concentrations were normal. Due to continuous LH receptor activation, P is synthetized prematurely by small follicles. Increasing P production is accompanied by decremental E_2 synthesis due to luteinization of granulosa cells. Consequently, growth is arrested, atresia occurs, and these follicles become cysts due to premature P exposure.

In the left ovary (without the mutation), normal single dominant follicle growth and normal intrafollicular steroid levels were found. The follicle reached a normal preovulatory diameter and subsequently showed signs of ovulation. In contrast to the luteo-follicular rise in FSH during the normal cycle, a dominant follicle emerged in our patient after a distinct rise in serum FSH during the midfollicular phase of the cycle. This rise was accompanied by a transient increase in inhibin B like in the normal cycle. While the dominant follicle is growing, E_2 output increases coinciding with the rise in inhibin A (27). Following ovulation, serum P levels increased along with an increase in inhibin A, suggesting normal corpus luteum function. Subsequently, P, inhibin A, and E_2 levels decrease, constituting a pattern comparable with luteolysis in the normal cycle. The overall hormonal pattern was virtually the same in both cycles monitored.

It seems that some negative feedback activity of inhibin B

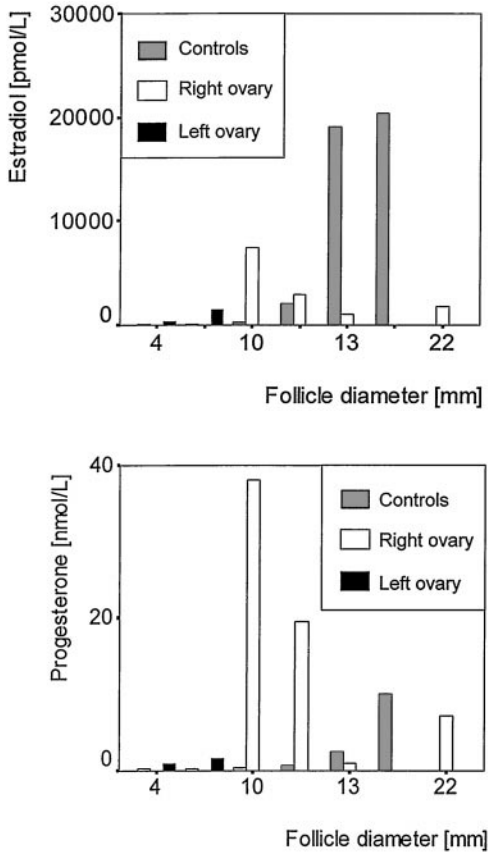

FIG. 3. Follicular fluid steroid concentrations in follicles of different diameters in normal regularly cycling women as well as follicles from both left and right ovaries from a patient with the McCune-Albright syndrome. Note that particularly estrogen and progesterone concentrations are increased in small follicles in the right ovary.

on endogenous FSH levels remains because FSH serum levels decreased after a rise in inhibin B levels during the midfollicular phase. LH levels were very low throughout the cycle. There is, however, no consistent relationship between LH concentrations and either E_2 levels or P levels indicating appropriate feedback. Collectively, these data suggest that the feedback mechanism of the pituitary gonadal axis for FSH is functioning properly in McCune-Albright patients.

Patients presenting with a Gsα "gain of function" mutation represent a "human model" to study increased signal transduction of gonadotropin receptors. The only activating FSH receptor mutation was identified in a hypophysectomized male who remained fertile despite undetectable gonadotropin levels (28). Activating LH receptor mutations have been described in male-limited precocious puberty, whereas they do not seem to have any particular phenotype in females (29). Hence, in females with McCune-Albright syndrome symptoms might be due mainly to increased FSH signal transduction. Although the effects of activating FSH receptor mutations in the context of normal pituitary function in the female are not known, they might resemble the phenotype of McCune-Albright patients. Indeed, enlarged ovaries with multiple cysts have been described in women with FSH-producing pituitary tumors (30). Finally, FSH receptor polymorphism seems to be associated with the amount of exogenous FSH required for adequate ovarian stimulation for IVF (31).

This patient showed a typical unilateral involvement of tissue. The mutation was only found in the right polycystic ovary. This might be due to the absence or a smaller number of mutated cells present in the left ovary not being detected by DNA analysis. This difference in expression of the mutation is compatible with "normal" monofollicular growth in the left ovary. This ovary might still be dysfunctional as a result of the abnormal endocrine environment induced by the right ovary. Removal of the right ovary might restore normal function of the remaining left ovary and should be considered. Similarly, differences were observed in distribution of mutated cells throughout the endometrium. Consequently, the endometrium was out of phase presumably due to elevated P levels throughout the cycle. This implies that endometrial receptivity is disturbed and natural fertility is compromised. This may represent an additional cause of infertility, even in case normal function of at least one ovary could be restored. This condition might also render future IVF procedures unsuccessful. Some women with McCune-Albright syndrome achieve normal menses and fertility, as well as pregnancies (9–11, 32–34). They might constitute a subgroup of patients in which the extent of the $G_s\alpha$-mutated cells is limited. On the contrary, other patients have persistence of autonomous gonadal function resulting in irregular cycles, metrorhagia, and other gynecological problems (8, 11, 34). These abnormalities might be underestimated because the vast majority of papers address clinical findings in younger patients.

In conclusion, the present report provides evidence for persistent autonomous unilateral ovarian dysfunction during early adulthood in McCune-Albright syndrome not compatible with normal fertility. Increased FSH and LH signaling gives rise to development of multiple dominant follicles, premature luteinization, anovulation, and cyst formation. Single dominant follicle development and normal ovulation and subsequent corpus luteum function could be observed on the contralateral unaffected ovary. Endometrial morphology is abnormal. The gynecological implications of these findings may include cycle disturbances and untreatable infertility. Extended suppression of endogenous FSH or unilateral ovariectomy should be considered when pregnancy is desired.

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