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Hypothalamic-Pituitary-Ovarian Function in Menstruating Women with Turner Syndrome (45,X)[1]

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ABSTRACT. The hypothalamic-pituitary-ovarian hormone secretion patterns were evaluated in two women with 45,X Turner syndrome, spontaneous sexual development, and monthly menstrual periods. Each woman had serum gonadotropin and sex steroid determinations during two or more menstrual cycles. During the follicular phase of a menstrual cycle, both women received 100 μg gonadotropin-releasing hormone (GnRH) s.c., and serum LH and FSH responses were determined. In addition, one woman collected daily overnight urine specimens for 40 consecutive days, spanning two menstrual periods, for the measurement of LH, FSH, estriol, and free progesterone. The randomly measured hormone results showed low serum progesterone concentrations during luteal phases, consistent with the interpretation of anovulation or inadequate corpus luteum function. At the time of the GnRH stimulation tests, baseline serum FSH concentrations and FSH responses to GnRH were within normal limits, whereas baseline LH levels and LH responses to GnRH were low. The pituitary gonadotropin secretion patterns were more consistent with patterns seen during early puberty than in the perimenopausal state. This interpretation was further confirmed by the urinary excretion patterns of gonadotropins, which were not significantly elevated. Furthermore, the urinary hormone profiles revealed that, although the intermenstrual period was of normal length, the follicular phase was prolonged, with normal levels of LH, FSH, and estriol excreted. The menstrual cycle studied was ovulatory but had a short luteal phase. The hormone results indicated that the dysgenetic ovary of women with 45,X Turner syndrome is capable of producing sufficient quantities of sex steroids and other regulatory factors to maintain gonadotropin secretion patterns that are reminiscent of early puberty. Some of the menstrual periods may be anovulatory, whereas others exhibit prolongation of the follicular phase, presumably due to difficulty in follicle recruitment, and short luteal phase due to inability to maintain normal corpus luteum function. (*Pediatr Res* 28: 514–517, 1990)

Abbreviations

GnRH, gonadotropin-releasing hormone
P, progesterone
E_2, estradiol
E_3, estriol

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In 1938, Turner described the syndrome of female sexual infantilism with multiple somatic features including short stature (1). The features of the syndrome were later associated with the 45,X karyotype described by Ford *et al.* (2). Subsequently, a variety of deletions or mosaic states involving the X chromosome have been associated with some or all of the phenotypic characteristics of the original syndrome (3).

It was suggested by Jones *et al.* (4) that the loss of a sex chromosome prevented primordial gonadal development, but in fetuses, infants, and young children with 45,X karyotypes, ovarian tissue can be demonstrated (5–7). There appears to be an accelerated loss of germ cells and follicular depletion leading to a hormonal imbalance reminiscent of premature menopause (8). In addition, about 8–10% of patients considered to have 45,X karyotypes demonstrate spontaneous sexual development (7, 9–15), and of a total of 12 reported pregnancies in women with Turner syndrome (16–27), two have occurred in women with convincingly nonmosaic karyotypes (17, 24).

We report detailed hormonal data in two women with nonmosaic 45,X Turner syndrome who had spontaneous sexual development and regular menstrual periods.

MATERIALS AND METHODS

Patient 1. At age 8, this young woman was discovered to have Hashimoto's thyroiditis with low serum thyroxine, elevated TSH, and elevated antimicrosomal antibodies. Replacement L-thyroxine was begun. Her menarche occurred at $10^{8}/_{12}$ y with regular monthly periods. Her growth continued along the 8th percentile until the age of $11^{10}/_{12}$ y and then plateaued at 140.5 cm. At this time, an i.v. pyelogram revealed a right double-renal collecting system. Her uterus sounded to 8 cm. On laparoscopy, the ovaries measured 2 × 2 cm on the left and 2 × 1 cm on the right. A recent corpus luteum cyst was present on the left. Both fallopian tubes appeared normal with fimbriated ends. Biopsies from both ovaries revealed no follicles on the right (biopsy size 5 × 4 × 2 mm) and two follicles (one atretic and one primordial) on the left (biopsy size 4 × 3 × 2 mm). Cell culture was successful only on the right-side biopsy.

Initially, her menstrual flow lasted from 7 to 10 d. From age 15, menses were regular and 5 d in duration with a 4-wk cycle until at least age 20. On physical examination, there were several of the characteristic features of Turner syndrome, such as squar-

ish head with prominent forehead, high-arched palate, short neck, small and firm thyroid, cubitus valgus, short digits, and several large pigmented areas of the cafe-au-lait type. Her blood pressure was 105/75 in the arms and 118/85 in her legs. She had achieved Tanner stage V sexual development with excellent breast size but sparse pubic and axillary hair. She weighed 47 kg at the time of study and denied recent weight loss, excessive participation in sports, or family stress.

Five d after the initiation of a menstrual period, serum LH was 11.1 mIU/mL (IU/L) (2nd IRP-hMG), FSH 15.8 mIU/mL (IU/L), total estrogens 137 pg/mL (503 pmol/L), and P 0.73 ng/mL (2.3 nmol/L). All of these values were within the normal follicular range for menstruating women at the Maine Medical Center Laboratory. Seventeen d after the onset of menstruation, the serum P was less than 1.0 ng/mL (3.2 nmol/L).

Cytogenetic studies. Over the years, the cytogenetic studies using standard trypsin-giemsa a staining (28) included chromosome studies, which showed 45,X in six blood lymphocyte studies (totaling more than 300 cells), fibroblasts obtained at laparoscopy from the area near the right ovary (50 cells), skin fibroblasts from the right and left forearms (50 cells each), and absence of Barr bodies in three buccal scrapings including both cheeks (200 cells each). In all preparations, no X,X cells were observed. Such nonmodal cells as were seen were consistent with random loss of chromosome material.

Patient 2. The patient grew along the 3rd percentile for the first 6 y of her life but her growth rate decelerated so that by age 9 y she was below the 3rd percentile. Ultimate height was 142.5 cm and weight 47 kg. Her parents were both 170 cm tall. Thyroid indices and i.v. pyelogram were normal. Breast development began at age 11 1/12, and menarche occurred at 13 4/12 years of age. At that time, her uterus sounded to 6 cm. At laparoscopy, the left fallopian tube appeared normal. The ovary was 2 × 2 cm and cystic. The right fallopian tube was thin and atrophic. In place of the right ovary, there was a yellowish-white streak gonad with a paraovarian cyst (0.5 × 0.8 cm). Biopsies from each ovary and round ligament were obtained. In the biopsy of the left ovary (6 × 4 × 3 mm), there were eight primordial and atretic follicles and a portion of a graafian follicle. The biopsy from the gonadal structure on the right (2 × 1 × 1 mm) revealed one atretic follicle. The patient's menstrual periods continued on a monthly basis until age 20 when she began to miss months and flow became scant. On physical examination, she was a normal appearing, short woman with short neck and digits, cubitus valgus, and a high-arched palate. Her blood pressure was 100/52 in her arms and 110/62 in her legs. Breast development was Tanner stage V and sexual hair was sparse. The genitalia were normally developed and cervix palpable.

At age 15, 2 d after a menstrual period, serum LH was 4.5 mIU/mL (IU/L), FSH 12.4 mIU/mL (IU/L), E_2 15 pg/mL (55 pmol/L), and P 0.69 ng/mL (2.2 nmol/L). Twenty d after the menstrual period, the serum progesterone was 1.07 ng/mL (3.4 nmol/L).

Cytogenetic studies. Cytogenetic studies included chromosome analysis on two separate preparations of blood lymphocytes (total 145 cells), fibroblasts from the right and left forearm (50 cells each), and three buccal smear studies from each cheek (200 cells each). No normal X,X cells were seen and no sex chromatin bodies were detected. The cell cultures from the ovaries and ligamentum failed.

Study Protocol. Response to exogenous GnRH. At the time of study, the patients were 15 and having regular menstrual cycles. Each patient was studied in early follicular phase 2 to 3 d after onset of her menses. Blood samples for LH and FSH were drawn 20 min and just before the s.c. injection of 100 μg of GnRH. Additional blood samples were obtained at 20, 45, 60, 80, 115, 175, and 300 min in patient 1 and 15, 30, 45, 60, 90, 120, 180, and 300 min in patient 2. Serum E_2 was measured at 0 and 300 min.

Urinary excretion of gonadotropins and sex steroids. Patient 1 collected daily overnight urine specimens for a total of 40 consecutive days. Menstrual flow was initiated on d 10 and 40 of the collection period. Each morning, the patient measured and recorded the urinary volume and stored an aliquot at −20°C for the measurement of urinary creatinine, LH, FSH, E_3, and free P. All of the samples from the entire study were processed within one assay for each hormone.

Hormone Measurements. Serum. Serum LH and FSH were measured by double antibody RIA, details of which have been previously described (29). E_2 was measured as previously described (30). All samples from each study were measured within one assay. The inter- and intraassay coefficients of variation were below 8.5%. The standard used was LER 907 for both LH and FSH, and the data are expressed as IU/L.

Urine. Urinary creatinine was measured by the Jaffe reaction. Urinary LH, FSH, E_3, and free P excretions were measured by means of previously described methods (30). For the measurement of urinary LH and FSH, the Second International Reference Preparation for Human Menopausal Gonadotropin (2nd IRP-hMG) was used as the standard.

RESULTS

Response of serum gonadotropins and E_2 to exogenous GnRH stimulation. The baseline concentrations of the patients' serum FSH, LH, and E_2 and responses of FSH and LH to exogenously administered GnRH (100 μg s.c.) are shown in Figure 1. Responses of E_2 could also be measured at 300 min, as shown.

The serum FSH and LH values for −6 and 0 min for the control group were not significantly different and therefore the mean values are shown. Compared with those of the normal women, the baseline serum FSH concentrations were within the normal range, whereas serum LH levels were low in patient 1 and more than 2 SD below the mean in patient 2. These low values were noted at a time when serum E_2 levels were also normal or low, 36 and 15 pg/mL (132 and 55 pmol/L), respectively. After exogenous GnRH stimulation, the changes in serum FSH were within the normal limits, whereas serum LH remained significantly below the responses for normal women at all time points. In response to GnRH stimulation, there was an increase in serum E_2 in both patients to 51 and 42 pg/mL (187 and 154 pmol/L).

Urinary excretion of pituitary gonadotropins and sex steroids throughout one menstrual cycle. The excretion of the urinary

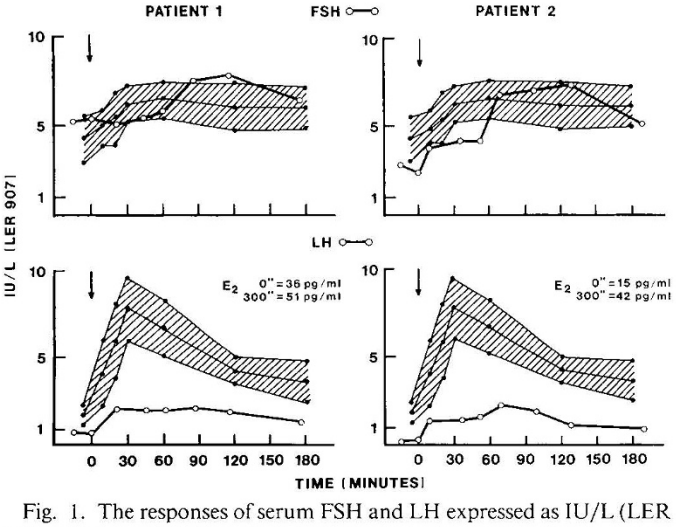

Fig. 1. The responses of serum FSH and LH expressed as IU/L (LER 907) to 100 μg of GnRH administered s.c. at time 0 (*arrow*) for patients 1 and 2 are shown by *open circles*. The ±SD for 15 normal cycling women studied during the follicular phase are shown in the *shaded areas*. Baseline and 5-h E_2 are given in pg/mL. In SI units, they are: patient 1, 132 and 187 pmol/L at 0 and 300 min; patient 2, 55 and 154 pmol/L.

gonadotropins (LH and FSH) and sex steroids (E_3 and free P) during a complete menstrual cycle of patient 1 is shown in Figure 2. The data are centered on the day of the LH surge with days in the follicular phase depicted as minus and days in the luteal phase as plus the day of the LH peak. Urinary free P estimates were determined on alternate day specimens only.

Even though the time between the two menstrual periods was 29 d, the distribution between follicular and luteal phases was abnormal. The follicular phase was prolonged to 20 d, whereas the luteal phase was shortened to 9 d. Based on the length of the luteal phase, it can be considered short by −2 SD of normal (14.0 ± 2.3 d).

The data for the first 10 d of the urine collections are not shown but are interesting. The LH peak occurred 4 d before the menstrual period. The baseline LH and FSH, preovulatory E_3 rise, and LH peak were within normal limits. The luteal phase was both short and inadequate. The duration of the luteal phase was 4 d and the urinary free P did not rise above preovulatory levels. Urinary E_3 excretion remained within 1 SD of normal throughout the short luteal phase. Therefore, we have documented two cycles with short luteal phases in this patient.

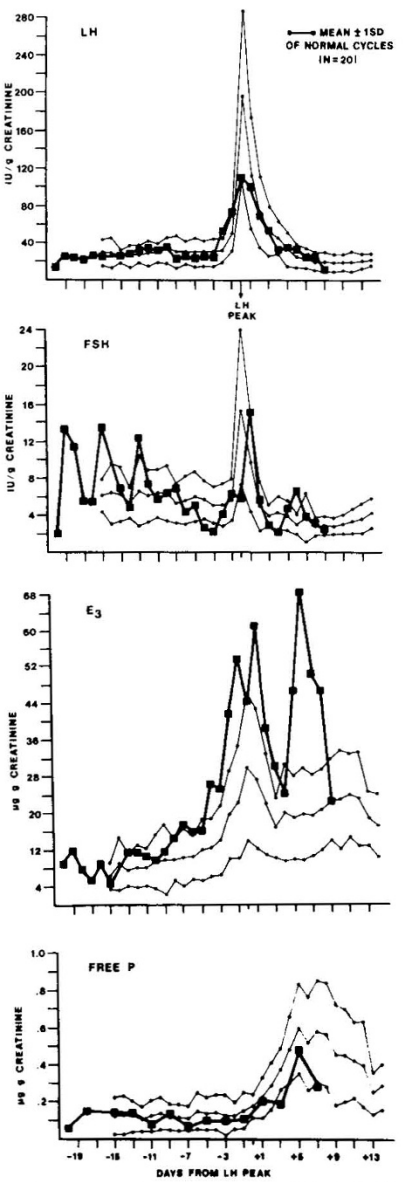

Fig. 2. The urinary excretion patterns for LH, FSH, E_3, and free P in daily overnight urine samples collected throughout one menstrual period in patient 1 are shown by *closed circles* and *heavy lines*. The data are centered on the day of the LH peak, which is considered d 0. The mean ±SD for the values obtained in 20 normal cycling women are shown by the *light lines*. Urinary LH and FSH are expressed as IU/g creatinine, whereas urinary E_3 and free P are expressed as µg/g creatinine. The conversion factor to nmol for µg E_3 is 3.468 and for µg free P is 3.18. To convert all of the excretion parameters from g to mmol of creatinine, results need to be divided by 8.84.

DISCUSSION

The menstruating patients described here have nonmosaic 45,X gonadal dysgenesis. This number of unambiguous cytogenetic studies convincingly indicates nonmosaicism (31), and the clinical picture and the histologic appearance of the ovaries are consistent. Loss of a 46,X,X cell line (32) in these patients is highly unlikely.

A better explanation of the occurrences of functional ovaries in nonmosaic Turner syndrome is that, as suggested by Singh and Carr (33), the early formation of ovaries in 45,X embryos is normal, but the follicular development from primitive germ cells is defective. Migeon and Jelalian (34) showed that both X chromosomes are active in the germ cells of the female before meiotic entry. Thus, primitive germ cells in a 45,X fetus may well form normally, but the process of meiosis would be expected to result in drastically reduced numbers of oocytes and follicles, hence, the observation of variable ovarian histology, sometimes bordering on the normal, in autopsies on fetuses, infants, and young children with 45,X karotypes (5, 6, 36–40). The ovarian dysfunction of Turner syndrome, therefore, results not from an absolute, chromosomally dictated block in ovarian development, but from an increased rate of decay in the number of germ cells in the ovary (7, 21, 24, 27, 41). Baker (42) has described the normal decay of germ cells in the human ovary. As a first approximation of the expectation in Turner syndrome, one might expect a decay of ovarian follicles with a rate constant double that of the normal. The expected number of follicles by the age of puberty would be very small, and of an order of magnitude comparable to that seen in the cases presented here.

There is thus some rationale for thinking of the endocrine disturbances of Turner syndrome as analogous to a markedly accelerated menopause. The normal gonadotropin values in our subjects are unusual in Turner syndrome, even among those who become pregnant, but are not unprecedented (24). The gonadotropin responses to GnRH in these patients reinforce the interpretation that there is substantial regulatory feedback from the ovaries. The significance of the subnormal LH response is unclear. This pattern of low LH responsiveness and greater serum FSH responses is classically seen in prepubertal girls (43) and adult women with hypothalamic amenorrhea (44). Under both circumstances, it is presumed that hypothalamic GnRH pulse frequency and/or amplitude are reduced. These results would imply that either the hypothalamic-pituitary axis has reverted to the state of increased sensitivity to low levels of circulating estrogens as evidenced by the low serum E_2 levels or that other neurosecretory or ovarian factors responsible for GnRH modulation are secreted in normal or even excessive amounts. These results are in contrast to those of typical women with Turner syndrome or premature ovarian failure, where serum gonadotropin levels are high with frequent low amplitude pulses and the response to exogenous GnRH exaggerated (45). E_2 responses to GnRH stimulation in both patients confirm the long-term significance of the acute challenge. They indicate ovarian responsiveness, which would not occur if the ovaries were chronically hyperstimulated by excessive GnRH and gonadotropins, as in developing ovarian failure.

To our knowledge, full cyclic hormone values have not been previously reported in a patient with Turner syndrome. Lisker *et al.* (14) studied serum gonadotropin levels in a patient over 40 d after induced menses. The gonadotropins were disassociated and noncyclic, but ovulation could be induced with clomiphene. A recent European report of a cycling 45,X woman showed, on

the basis of four blood samples, a preovulatory gonadotropin surge and a good E_2 and P response in a luteal phase of normal length (46). Our patient shows an ovulatory menstrual cycle with a long follicular phase of 20 d, with adequate FSH for 15 d before a rise in E_3. This suggests a need for prolonged follicular recruitment to obtain a dominant follicle. The luteal phase was short, but there were adequate quantities of excreted estrogen and free P and normal suppression of FSH, indicating normal hypothalamic-pituitary-ovarian interaction. Similar findings were obtained during the final 10 d of the preceding menstrual cycle in this patient, with the exception that, in addition to a short luteal phase, the excretion of sex steroids was inadequate. This suggests, if it is typical of her cycles, that the endometrium would be unlikely to support implantation and early embryonic development. This may relate to the relatively poor obstetrical history in patients with Turner syndrome (27). One might speculate that this pattern is a predictable outcome of the ovarian histology in the patients presented here. The follicular phase is a period during which follicle selection is occurring, with ultimate dominance of one follicle and degradation of the others (47). One would predict that in these ovaries with a reduced population of follicles from which to select, one might get a relatively incompetent dominant follicle, with resulting inadequacy of the luteal phase. We suggest that this process in patients with Turner syndrome can be viewed as analogous to acceleration of the follicular depletion leading to menopause in normal women (8).

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