0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 3
Printed in U.S.A.

Reproductive Aging: Accelerated Ovarian Follicular Development Associated with a Monotropic Follicle-Stimulating Hormone Rise in Normal Older Women*

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ABSTRACT

Women experience a decline in fertility that precedes the menopause by several years. Previous studies have demonstrated a monotropic rise in FSH associated with reproductive aging; however, the mechanism of this rise and its role in the aging process are poorly understood. The purpose of this study was to characterize ovarian follicular development and ovarian hormone secretion in older reproductive age women.

Sixteen women, aged 40–45 yr, with regular ovulatory cycles were studied. The control group consisted of 12 ovulatory women, aged 20–25 yr. Serum obtained by daily blood sampling was analyzed for FSH, LH, estradiol (E), progesterone, and inhibin (Monash polyclonal assay). Follicle growth and ovulation were documented by transvaginal ultrasound.

Older women had significantly higher levels of FSH throughout the menstrual cycle. E, progesterone, LH, and inhibin levels did not differ between the two age groups when compared relative to the day of the LH surge. Ultrasound revealed normal growth, size, and collapse of a dominant follicle in all subjects. Older women had significantly shorter follicular phase length associated with an early acute rise in follicular phase E, reflecting accelerated development of a dominant follicle.

We conclude that older reproductive age women have accelerated development of a dominant follicle in the presence of the monotropic FSH rise. This is manifested as a shortened follicular phase and elevated follicular phase E. The fact that ovarian steroid and inhibin secretion were similar to those in the younger women suggests that elevated FSH in women of advanced reproductive age may represent a primary neuroendocrine change associated with reproductive aging. (*J Clin Endocrinol Metab* **81:** 1038–1045, 1996)

WOMEN EXPERIENCE a marked decline in fecundity that precedes the menopause by many years (1). An accelerated decline in fertility has been consistently observed near the end of the fourth decade. Whereas regular ovulatory cycles usually continue during this period of advanced reproductive age, the endocrinological profile of these women has been incompletely characterized. The ovary becomes increasingly gonadotropin resistant due to aged, diminished, or resistant follicles with advancing reproductive age (2). The most consistent finding from previous investigations has been a subtle rise in the concentration of FSH unaccompanied by a rise in LH (3–6). Whether this monotropic FSH rise represents a primary neuroendocrine change or a response to changes in feedback signals from the aging ovary is controversial. It has been demonstrated that the concentration of primordial follicles in the ovarian cortex undergoes steady depletion with chronological age, primarily through atresia, with eventual follicular exhaustion occurring subsequent to the time of menopause (7–9). The rate of decline in follicle number follows a biexponential pattern, with the onset of the rapid phase occurring around age 38 yr (8, 9), which is the approximate age of onset of the accelerated loss of reproductive capacity (1, 10, 11).

A number of theories have been proposed to account for the monotropic FSH rise. Considering the disparity between the pituitary secretion of LH and FSH, it has been postulated that the FSH elevation is primarily due to a decrease in the ovarian secretion of inhibin. Preliminary reports of decreased inhibin concentration in older perimenopausal women and the absence of inhibin production after menopause appear to support this theory (12–14). However, studies in natural cycles of premenopausal women have been limited by small sample size, inclusion of anovulatory subjects, and/or infrequent blood sampling. The role of altered feedback due to changes in ovarian estradiol (E) and progesterone (P) secretion remains controversial. Previous investigators have reported that E production in older ovulatory women is similar (4, 6, 15), decreased (5), or even increased (16) compared to that in younger women. Similarly, P secretion has been reported to be either decreased (4, 5, 17) or unchanged (6, 15, 18) in these older women. An alternative theory for the monotropic FSH rise is an age-related primary neuroendocrine change in the pulsatility of GnRH or in the hypothalamic set-point to ovarian steroid feedback. Reduced bioactivity of the FSH molecule is another mechanism that could result in an increased FSH requirement to sustain follicle development. Considering the current lack of knowledge regarding the physiological alter-

Received June 19, 1995. Revision received September 7, 1995. Accepted October 12, 1995.

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* Previously presented in part at the 50th Annual Meeting of the American Fertility Society, November 5–10, 1994, San Antonio, TX. This work was supported by NIH Grants RO1-HD-18967 (to M.R.S.), P50-HD-12629 (to W.J.B.), and MO1-RR-00037 (to C.R.C.).

ations associated with reproductive aging, the current study was undertaken to more thoroughly examine age-related changes in the hypothalamic-pituitary-ovarian axis in normal ovulatory women.

Subjects and Methods

Subjects

Twenty-eight normally cycling women, age 20–25 yr [group Y (younger); n = 12] and 40–45 yr [group O (older); n = 16], were recruited for this study. To qualify for the study, all subjects were required to 1) have regular 25- to 35-day menstrual cycles, 2) be in good health (normal medical history and physical examination), 3) be of normal weight for height (body mass index of 18–24 kg/m^2), 4) be taking no medications (including no exogenous hormones within 6 weeks of the study), 5) have no past or current reproductive endocrine problems (*e.g.* galactorrhea or hirsutism) or infertility, 6) participate in no more than 5 h/week of aerobic exercise, 7) consume a standard balanced diet, and 8) be ovulatory, as evidenced by a biphasic basal body temperature graph, a midluteal serum P level greater than 10 nmol/L, a serum PRL level below 20 μg/L, and a testosterone level below 3.5 nmol/L in a cycle preceding the study cycle. Written consent was obtained to participate in the study. The study protocol was approved by the University of Washington human subjects committee. Monetary compensation was provided for study participation.

Experimental design

In the study cycle, daily blood samples were obtained between 0700 and 1000 h by venipuncture, beginning with the first day of menstrual bleeding and continuing for 5 days into the subsequent menstrual cycle. Serum was separated and frozen in aliquots at −20 C for subsequent analysis.

Twelve older and all younger subjects received daily transvaginal ultrasound beginning in the mid- to late follicular phase and continuing until evidence of ovulation. The maximum diameter of the largest follicle was recorded in three perpendicular planes during each examination. Twice daily ultrasound studies were performed once the lead follicle reached 14 mm in mean diameter. Criteria for ovulation included two or more of the following signs: 1) disappearance of the dominant follicle or significant decrease in size, 2) thickened irregular follicle borders, 3) free pelvic fluid, and/or 4) increased echogenicity within the follicle (19).

Hormone assays

Serum concentrations of FSH, LH, E, P, and inhibin were determined in daily blood samples. All samples from an individual were analyzed in a single assay. Samples were analyzed in duplicate for LH and FSH by an immunoradiometric method (MAIA clone, Serono Laboratories, Geneva, Switzerland). The interassay variabilities were 12% and 14%; the intraassay variabilities for LH and FSH were 5% and 9%, respectively.

The double antibody RIA for E was performed in duplicate using reagents supplied by ICN Biomedicals (Costa Mesa, CA). The antibody cross-reacts 20% with estrone, 1.5% with estriol, and less than 1% with all other steroids. The inter- and intraassay coefficients of variation were 16% and 7%, respectively.

Serum P concentrations were determined in duplicate by solid phase RIA using reagents supplied by Diagnostic Systems Laboratories (Webster, TX). The antibody cross-reactivity is less than 5% with all other steroids. The inter- and intraassay coefficients of variation were 13% and 11%, respectively.

Bioactive FSH was determined throughout the cycle in seven older and six younger randomly selected subjects. Sera collected on days −9, −6, −3, 0, 3, 6, and 9 relative to the LH surge (day 0) were analyzed using a rat granulosa cell culture aromatase bioassay, as previously described (20). Inter- and intraassay coefficients of variation were 17% and 12%, respectively.

Daily serum samples were assayed for inhibin using a heterologous double antibody RIA based on purified 31-kDa bovine follicular fluid inhibin (Monash assay) as standard, as previously described (21). This assay uses a polyclonal antibody directed primarily to the α-subunit. Inter- and intraassay coefficients of variation were 13.8% and 6.8%, respectively.

Statistical analysis

Results are expressed as the mean ± SEM. Two-way ANOVA with repeated measures was used to test for differences between groups over the menstrual cycle. Differences between cycle lengths were assessed by a Mann-Whitney U test. All other comparisons between mean values in the two groups were accomplished by an unpaired two-tailed *t* test. To test for within-subject consistency in intercycle hormone secretion, mean hormone levels were calculated for each subject over cycle days 1–5 for two consecutive cycles. For each hormone, corresponding pairs of means for each subject were used to calculate a group correlation coefficient (Pearson's) for that hormone. In all instances, a $P < 0.05$ was considered indicative of a significant difference.

Results

Cycle length and follicle development

The mean ages for group O and Y subjects were 42.8 ± 1.6 yr (n = 16) and 22.6 ± 1.8 yr (n = 12), respectively. The results for cycle lengths and follicular ultrasounds are shown in Table 1. All women demonstrated a midcycle LH surge and ovulatory levels of luteal phase P (minimum P, >16 nmol/L). The follicular phase was designated as the number of days from the onset of menses up to and including the day of peak serum LH (day of LH surge = day 0). There was a tendency for older subjects to have a shorter total cycle length, but the difference did not reach statistical significance ($P = 0.06$). This tendency for a shorter cycle length was entirely attributable to a significantly decreased follicular phase length in group O (11.4 ± 0.4 *vs.* 14.6 ± 1.0 days; $P < 0.01$). In contrast, luteal phase length was slightly longer in the older group, but the difference was not statistically significant.

Twelve subjects in group O and all subjects in group Y had daily transvaginal ultrasound examinations performed over the period that included the LH surge, revealing the development of a dominant follicle in each woman. Three women in group O did not complete the ultrasound examinations secondary to scheduling difficulties. Results could not be interpreted in one older subject due to the presence of an ovarian cyst. All but one of the older women and all younger subjects had ultrasound evidence of ovulation within 36 h of the peak serum LH concentration. There were no differences in either the rate of follicle growth or the maximum follicle diameter between the two age groups (Table 1).

Gonadotropins

Mean values for LH and FSH, normalized to the day of the LH surge (day 0), are depicted in Fig. 1, A and B. There was

TABLE 1. Cycle length and dominant follicle characteristics in younger and older reproductive age women

	Age 40–45 yr	Age 20–25 yr	*P*
Cycle length (days)	25.5 ± 0.4 (16)	27.8 ± 1.1 (12)	0.06
Follicular phase length (days)	11.4 ± 0.4 (16)	14.6 ± 1.0 (12)	0.01
Luteal phase length (days)	14.1 ± 0.3 (16)	13.2 ± 0.6 (12)	0.19
Maximum follicle diameter (mm)	19.8 (12)	21.9 (12)	0.07
Mean follicular growth rate (mm/day)	1.9 (6)	2.2 (8)	0.25

The number of subjects is in *parentheses*.

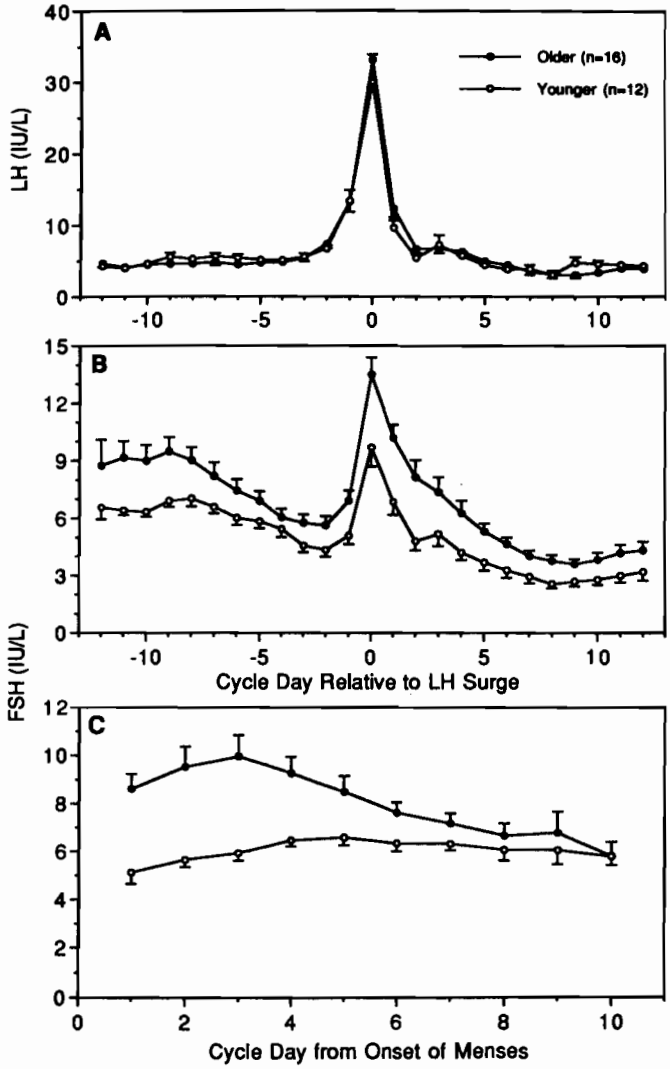

FIG. 1. A and B, The mean ± SE LH (A) and FSH (B) concentrations across the menstrual cycle in older and younger reproductive age women according to the day of the LH surge (day 0). Data are shown for days −12 to +12 only. The pattern of secretion for both hormones is similar in the two age groups. Mean LH does not differ between the two groups, whereas FSH is elevated throughout the cycle in older subjects ($P < 0.01$). C, The follicular phase FSH concentration according to the cycle day from onset of menses, illustrating that the most marked numerical difference in FSH concentration occurs during the first 4 cycle days.

no difference in serum LH throughout the menstrual cycle between the two groups, including the LH surge (Fig. 1A). FSH was significantly elevated in the older reproductive age women throughout the menstrual cycle ($P < 0.001$; Fig. 1B). There was no age-related difference in the pattern of FSH secretion (interaction) across the menstrual cycle. Follicular phase serum FSH levels are shown in Fig. 1C according to the cycle day from the onset of menses (day 1).

To evaluate the intercycle rise in FSH, the day of onset of the intercycle FSH rise was identified as the day in the luteal or menstrual phase when the FSH level exceeded the mean for the preceding 2 days by at least 25% and when this increase was sustained until at least the fifth day of the second cycle. Using these criteria, group O demonstrated an intercycle FSH rise significantly earlier than group Y (day −1.13 ± 0.3 *vs.* day 0.17 ± 0.3, $P = 0.004$, when day 0 = onset of menses for this analysis).

Bioactive FSH was also significantly elevated in group O throughout the menstrual cycle ($P < 0.001$; Fig. 2A). However, there was no significant difference in the bioactive/immunoactive FSH ratio across the cycle between the two groups (Fig. 2B).

Ovarian steroid secretion

P secretion across the cycle was compared using analysis of variance with repeated measures, revealing no significant differences in pattern or concentration between the older and younger subjects (Fig. 3A). Integrated luteal phase P was 359 ± 35 nmol/day·L for group O and 308 ± 41 nmol/day·L for group Y ($P = 0.33$).

There were no differences between the two age groups in E secretion throughout the menstrual cycle when data were compared relative to the LH surge (Fig. 3B). However, when follicular phase E levels were compared according to the cycle day from onset of menses, E was significantly elevated in group O ($P = 0.03$; Fig. 3C).

To further evaluate the early rise in follicular phase E in group O, the day of onset of the acute rise in E was identified as the day when E exceeded the mean for all preceding days

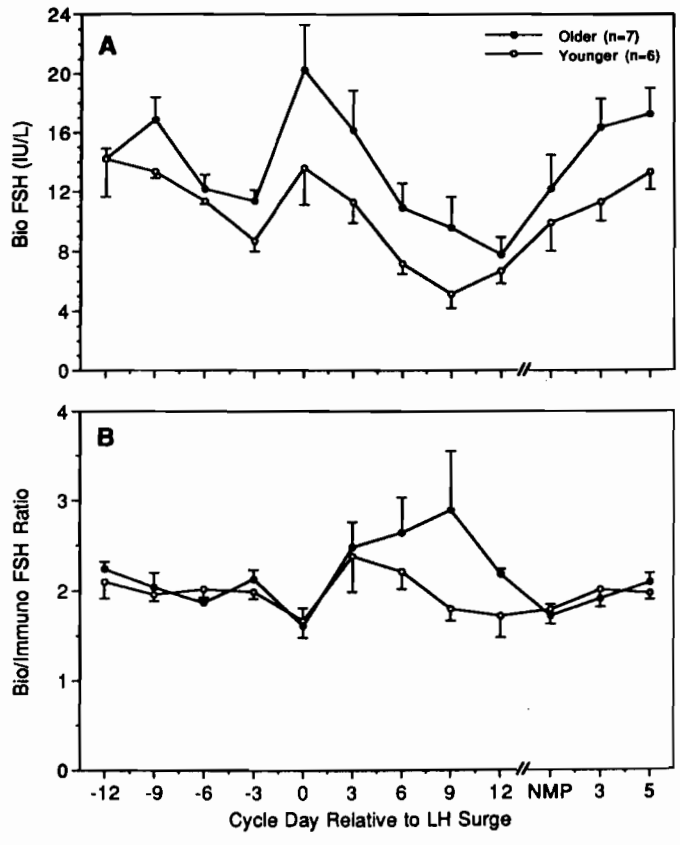

FIG. 2. A, The mean ± SE bioactive FSH concentrations across the menstrual cycle relative to the LH surge in older and younger women. B, The mean ± SE bioactive/immunoactive FSH ratio across the menstrual cycle according to the cycle day relative to the LH surge, revealing no differences between older and younger subjects ($P = 0.12$).

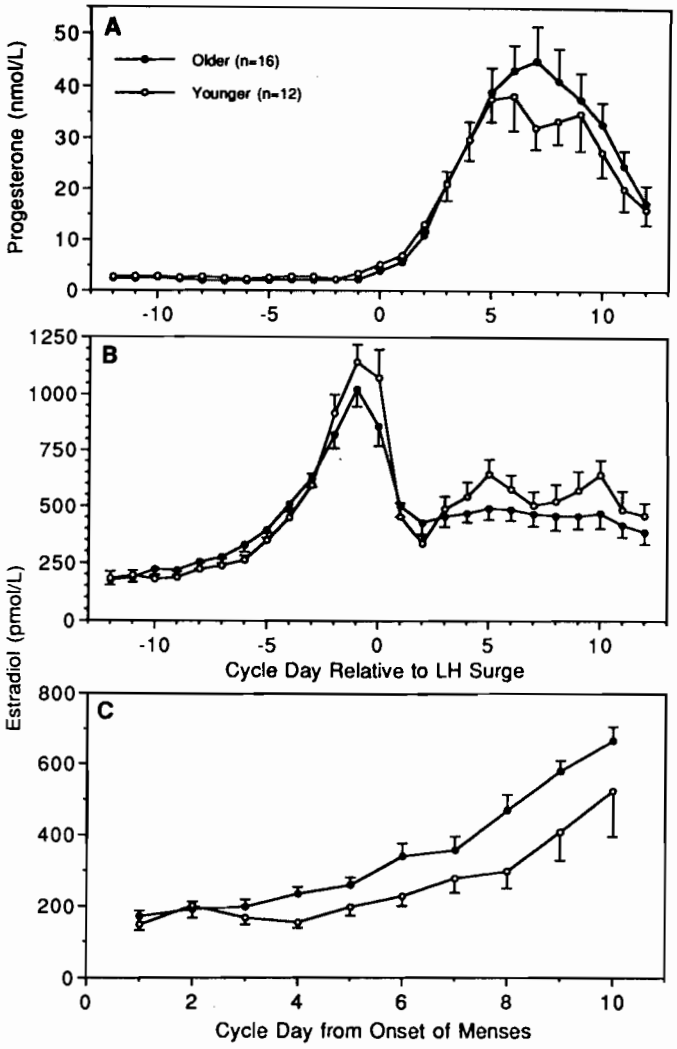

FIG. 3. A and B, The mean ± SE concentrations of P (A) and E (B) relative to the LH surge, revealing similar patterns of secretion with no significant differences throughout the cycle ($P > 0.05$). In contrast, C illustrates higher follicular phase E secretion in older women when data are compared according to the cycle day from the onset of menses ($P < 0.05$).

by 50% and when this increase was sustained for at least 2 consecutive days. The period before the onset of the acute rise was designated the resting phase. For each subject, the mean E level was calculated from the daily values during the resting phase. Whereas there was no difference in mean resting phase E concentration between the two groups, the onset of the acute E rise occurred significantly earlier in older subjects ($P < 0.01$; Table 2). The three E values midway between the day of onset of the acute rise and the midcyle peak were used to calculate the slope of the acute E rise. As shown in Table 2, the slope of the E rise was significantly less steep in group O ($P < 0.05$). Therefore, the acute rise occurred an average of 4 days earlier in older subjects, but due to the difference in slope, the follicular phase was shortened by an average of only 3.2 days.

Inhibin

There was a significant variation (pattern) in daily inhibin concentrations across the menstrual cycle, with both age groups demonstrating a similar pattern (Fig. 4A). However, there were no differences in inhibin levels between groups O and Y when compared according to the cycle day relative to the LH surge. Follicular phase inhibin levels also did not differ when compared according to the cycle day from the onset of menses (Fig. 4B).

Intercycle variability

Mean values for cycle days 1–5 of the two consecutive cycles were determined for FSH, E, and inhibin for each individual, and a correlation coefficient was determined for each group. There was a significant correlation between cycles 1 and 2 for FSH ($r = 0.552$; $P < 0.05$), E ($r = 0.649$; $P < 0.01$), and inhibin ($r = 0.652$; $P < 0.01$) in the older subjects. In contrast, the mean correlation coefficient in the younger group was statistically significant for FSH ($r = 0.755$; $P < 0.01$), but not for E ($r = 0.459$; $P > 0.05$) or inhibin ($r = 0.288$; $P > 0.05$). Therefore, the older subjects demonstrated more consistency in their early follicular phase hormone profiles than the younger women.

Follicular development according to basal FSH concentration

A moderate degree of variability in the FSH concentration existed among subjects in both groups. Therefore, based on early follicular FSH levels, group O appeared to consist of women who were at various stages of reproductive aging. To assess whether our results were significantly affected by the heterogeneity of the study population, we identified those subjects who, based on early follicular FSH concentrations, exhibited more overt signs of reproductive aging. The mean FSH level on cycle day 3 was 5.9 ± 1.1 IU/L for the younger (control) group. A day 3 FSH level of more than 8.0 IU/L was 2 SD above the mean for the younger subjects, and none of the FSH values in younger women exceeded this level. Eleven of the older women had a FSH measurement on cycle day 3 greater than 8.0 IU/L (group $O_{High\ FSH}$), and five had a FSH measurement on day 3 below 8.0 IU/L (group $O_{Low\ FSH}$). When data from group $O_{High\ FSH}$ were analyzed

TABLE 2. Estradiol secretion in younger and older reproductive age women

	Age 40–45 yr (n = 16)	Age 20–25 yr (n = 12)	P
Integrated follicular estradiol (pmol/day · L)	4165 ± 371	5347 ± 444	0.79
Integrated luteal estradiol (pmol/day · L)	6745 ± 701	7179 ± 914	0.83
Peak estradiol (pmol/L)	1039 ± 77	1222 ± 95	0.11
Day of onset of acute estradiol rise	7.0 ± 0.4	10.8 ± 1.2	<0.01
Slope of acute estradiol rise (pmol/L/day)	119 ± 13	189 ± 28	0.04
Mean resting phase estradiol (pmol/L)	215 ± 20	197 ± 24	0.56

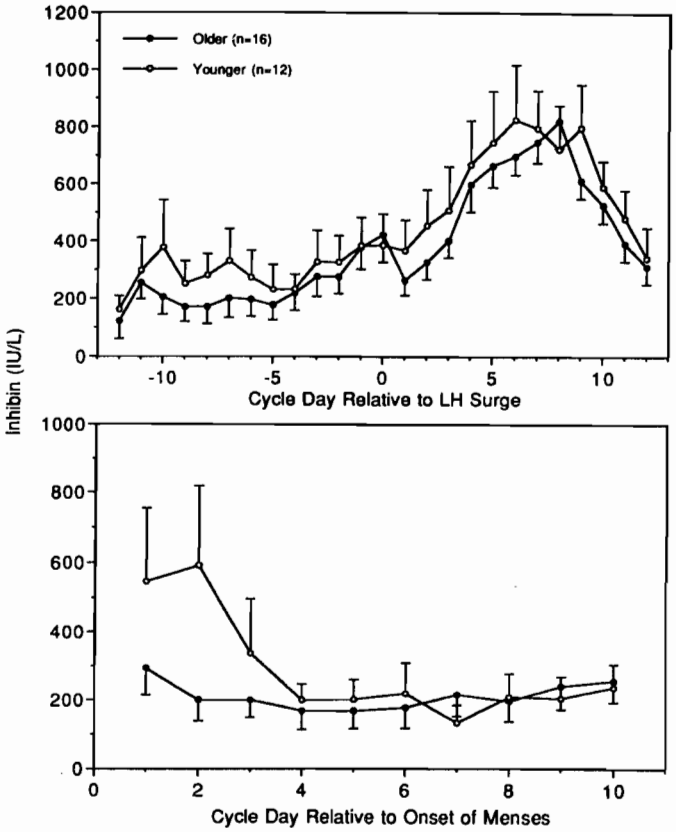

FIG. 4. Shown are the mean ± SE concentrations of inhibin for older and younger subjects according to the cycle day relative to the LH surge (A) and relative to the onset of menses (B). There were no significant differences between age groups in inhibin secretion across the menstrual cycle ($P > 0.05$).

separately and compared to those from the younger group, all of the previous findings were confirmed; there were no significant differences in LH, E, P, or inhibin concentrations throughout the menstrual cycle. Compared to group Y, group $O_{Low\ FSH}$ had significantly higher mean FSH and shorter follicular phase length, with numerical values intermediate between those of group Y and group $O_{High\ FSH}$ (data not shown). Therefore, it is unlikely that potential differences in steroid or inhibin secretion between the older and younger subjects are obscured due to those older subjects who followed a younger pattern.

Intercycle phase

Because FSH rises earlier in the older women and because the onset of menstrual flow is an indirect approximation of the onset of follicular development, we compared data for older and younger women beginning with the last 4 days of the luteal phase through day 4 (resting phase) of the subsequent cycle. We designated this period the intercycle phase. Two-way ANOVA with repeated measures detected a significant elevation in FSH in group O, with no significant difference between the two groups in either E or inhibin secretion (Fig. 5).

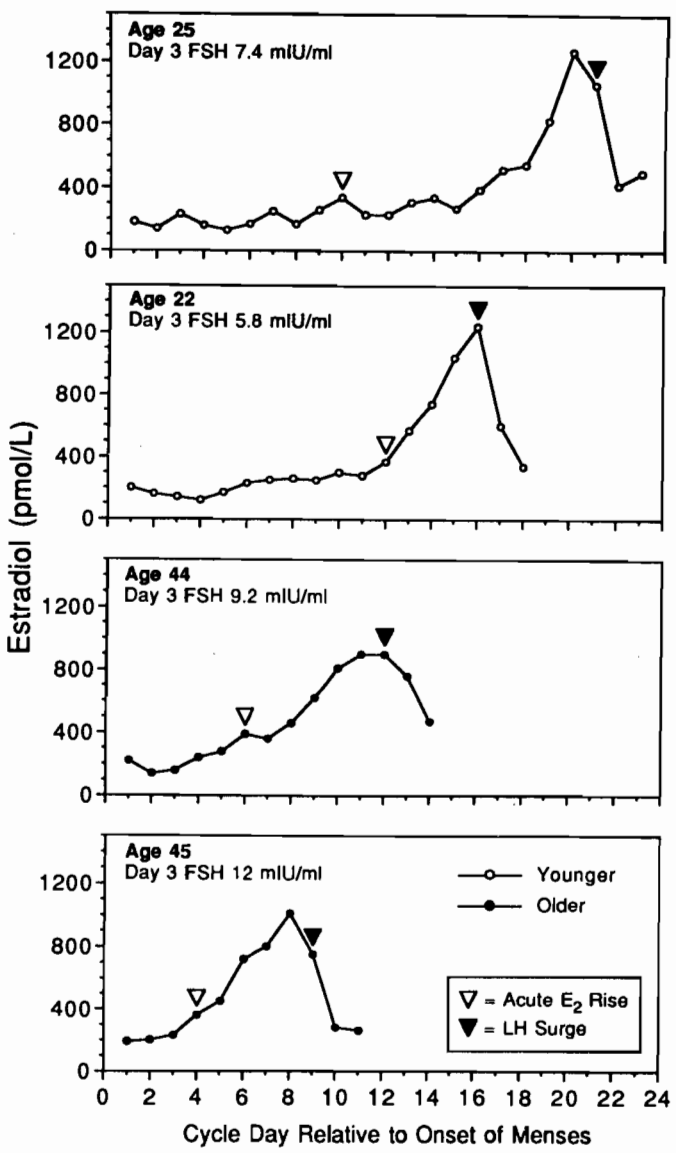

FIG. 5. A–C, The mean ± SE concentrations of FSH, E, and inhibin for the intercycle phase, beginning 4 days before the day of the onset of menses (MP). The FSH concentration was significantly higher in the older subjects, whereas there were no differences between groups in E or inhibin. two older subjects, illustrating the decreased follicular phase length and earlier onset of the acute E rise in older subjects.

Summary

In summary, most of our older reproductive age women demonstrated a monotropic rise in FSH associated with normal follicle size and ovarian hormone secretion. Changes in neither E nor inhibin were detected to account for this rise in FSH. In addition, older women had accelerated follicular development, with earlier onset of the intercycle FSH rise, earlier onset of the acute follicular phase E rise, earlier LH surge, and earlier ovulation. These findings were manifested clinically as a shortened follicular phase and a shortened total menstrual cycle length. Examples of the follicular phase E pattern in representative older and younger subjects are shown in Fig. 6.

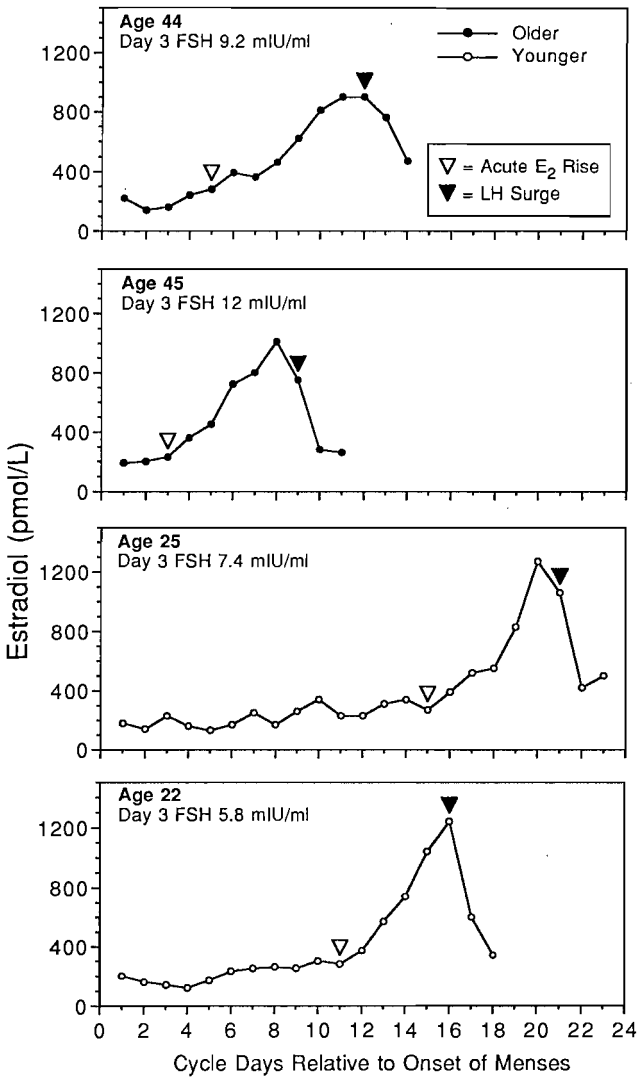

FIG. 6. Shown are follicular phase concentrations of E in two younger and two older subjects, illustrating the decreased follicular phase length and earlier onset of the acute E rise in older subjects.

Discussion

These data demonstrate that the monotropic FSH rise in older reproductive age women is associated with accelerated recruitment and ovulation of a dominant follicle. The FSH secreted in older women has the same biological activity as that in younger women, as indicated by similar bioactive/immunoactive FSH ratios in both groups. Together with the findings of normal ovarian secretion of E, P, and inhibin, this argues against the concept that the aging ovary is somehow resistant to endogenous gonadotropin signals. On the other hand, it is possible that slight decreases in ovarian inhibin and steroid secretion in response to a given level of FSH may lead to FSH elevation, which, in turn, stimulates the ovary to increase the secretion of these hormones (*i.e.* a compensatory mechanism).

Histological quantitation of primordial follicle numbers has established that the rate of follicle atresia is biexponential, with an accelerated phase that begins at about 37 yr of age (9). The same influences that control this increased rate of atresia may be responsible for the shortened follicular phase and early ovulation we observed in our older subjects. Longitudinal studies of menstrual calendars encompassing data from about 60,000 cycles demonstrated a decline in cycle length that occurs in the later reproductive years preceding the onset of perimenopausal menstrual irregularity (22). A progressive shortening of the follicular phase with age has also been demonstrated through a cross-sectional study of women aged 18–50 yr, in whom the time of the LH surge was determined with daily blood sampling (23). We have demonstrated by concurrent follicle measurement and endocrinological surveillance that the increase in E observed in the early follicular phase of older women corresponds to an accelerated recruitment and ovulation of the dominant follicle. We speculate that early ovulation and/or follicular atresia may be a direct result of the monotropic FSH rise.

E and P secretion across the menstrual cycle was normal in the older subjects. This confirms reports by others suggesting that E and P productions are unaltered in the early stages of reproductive aging (*i.e.* after a FSH rise becomes apparent, but before the cessation of menstrual regularity) (4, 6, 15). Previous reports had shown decreased production of E and/or deficient luteal phase P production in older women (4, 5, 17); however, these studies did not clearly limit their study population to women with regular ovulatory cycles. The E assay we used has up to 20% cross-reactivity with estrone, which has been demonstrated to be decreased in older reproductive age women (16). Whereas this cross-reactivity could obscure a subtle rise in E secretion in older women, given that estrone does not increase, we can be confident that E secretion is at least maintained. Therefore, the follicular apparatus remains competent, and the steroid milieu is maintained in older reproductive age women, albeit at the expense of elevated FSH secretion, implying that their reduced fecundity is derived from mechanisms unrelated to inadequate steroid secretion.

In the presence of elevated FSH, the onset of significant E secretion is advanced in the early follicular phase, such that E levels in the earliest phase of the cycle are actually higher in the older subjects. It is unclear to what degree this early E rise may be due to the contribution of secondary follicles, reported previously to be increased in patients with elevated FSH (24). In the present study, monofollicular development was consistently observed in both age groups. However, the fact that both age groups had similar integrated follicular E despite discrepant follicular phase lengths together with the decreased slope of the E rise observed in older subjects may reflect an ancillary contribution of secondary follicles to early follicular phase E production. Our findings of a normal rate of follicle growth and preovulatory follicle size are in contrast to previous reports (15, 24). It is possible that the trend we observed toward smaller follicle size in older subjects is a real difference, but obscured due to our relatively small sample size. However, we have demonstrated in a parallel study of unstimulated cycles of normal women (selected according to the same criteria as the present study) that follicular fluid from the dominant follicles of older women is equal or superior to that of younger subjects with regard to androgen and estrogen content (25). Therefore, we do not believe that

the slight difference in follicle size we observed is of biological significance.

Clinical data from an *in vitro* fertilization study reveal that the decreased implantation rates observed in older women can be overcome by using oocytes from younger women (26). This suggests a defect in the oocytes from older women that is not manifested by either abnormal ovarian hormone production or growth of the dominant follicle. In fact, studies in our laboratory confirm that the majority of oocytes obtained from the dominant follicles in unstimulated cycles from older women have abnormalities of the meiotic spindle (27). Whether the acceleration of follicle growth, E production, and ovulation contributes to the abnormal development of the oocytes or whether they are intrinsically abnormal is unknown.

A widely held view considers that follicular exhaustion leads to decreased inhibin production, which, in turn, causes the monotropic FSH rise. The peripheral inhibin concentration has been reported to represent the contribution of the entire follicle pool rather than secretion by the dominant follicle alone (28) and might, therefore, be expected to decrease in parallel with declining numbers of primordial follicles. Furthermore, inhibin levels are undetectable in postmenopausal women. In the present study, inhibin was not significantly different in the older subjects despite a consistent elevation of FSH throughout their cycles. This is in contrast to earlier reports of decreased ovarian inhibin production in older perimenopausal women (12, 13). A negative correlation between inhibin and FSH has been demonstrated in women with intermittent ovarian failure (13). However, these studies included women with menstrual irregularities suggestive of oligoovulation and a more advanced state of reproductive aging, and both sampling frequency and sample sizes were limited. We observed a slight trend toward lower inhibin levels in the older subject group, and it is possible that a significant age-related decline in inhibin production is obscured due to the degree of intersubject variability and/or small sample size.

Failure to detect an age-related difference in inhibin secretion may be attributable to the relatively nonspecific nature of the Monash inhibin assay. This assay uses a polyclonal antibody to the α-subunit that has significant cross-reactivity with the free α-subunit and its precursors (29, 30). An age-dependent increase in α-subunit messenger ribonucleic acid expression in rat granulosa cells unaccompanied by a similar increase in the active dimer has been reported (31). If such an increased subunit production occurs in humans, cross-reactivity with the subunit or its precursors could mask a true reduction in the biologically active dimeric form. However, as the Monash inhibin assay has been shown to correlate well with inhibin measured by a sheep pituitary cell bioassay (21), our results should provide a reliable indicator of inhibin bioactivity. Furthermore, previous reports of decreased inhibin in older reproductive age women used the same assay (12, 13). A recently developed inhibin two-site monoclonal enzyme-linked immunosorbent assay is specific for dimeric inhibin A (32). The classic menstrual cycle pattern reported for inhibin with the Monash assay was demonstrated in both of our subject groups and is also observed using the more specific dimeric assay (32). However, further studies using such assays are warranted to further evaluate the role of inhibin in older reproductive age women.

In conclusion, the fact that we could detect no differences in ovarian steroid or inhibin secretion supports the possibility that the monotropic FSH rise represents a primary neuroendocrine change associated with aging. Further studies using more specific assays for dimeric inhibin will more clearly address the role of this hormone. Also, other central or ovarian modulators could play a role in the FSH rise. In a parallel study, we were unable to detect any differences in pulsatile LH secretion, presumably reflective of an unaltered pattern of hypothalamic GnRH release (33). However, a change in hypothalamic/pituitary sensitivity to steroid or inhibin feedback has not been excluded. Thus, the possibility remains that the monotropic FSH rise may be the cause, rather than simply an effect, of the accelerated loss of the follicular pool observed in older reproductive age women.

Acknowledgments

We would like to acknowledge Drs. Kris Dahl for performing the FSH bioassay and David Robertson for performing the inhibin assay in their respective laboratories. We thank Ms. Florida Flor, Ms. Elizabeth VanGaver, Ms. Dorothy McGuinness, and Mr. Arlen Sarkissian for their technical assistance with the other assays; Ms. Jan Hamanishi and Mr. Patrick Clarke for their assistance with the illustrations; and Ms. Angela Hovey and Ms. Julie Siemion for preparation of the manuscript. We also thank the nursing staff of the Clinical Research Center and the sonographers of the ultrasound department of the University of Washington Medical Center for their expert patient care.

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