Functional life-span of the dominant follicle in pharmacologically induced anovulatory cycles

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With the purpose of measuring the duration of the functional life-span (FLS) of the anovulatory follicle in women under continuous low-dose progestogen treatment, the oestradiol curve of Norplant implant users was retrospectively analysed. From all the data collected during the previous 5 years at the Department of Biomedical Research at the Family Planning Clinic of Profamilia, Santo Domingo, Dominican Republic, data from all 29 Norplant implant users showing follicular activity without luteal activity were selected for this retrospective analysis. Serial blood sampling twice or three times a week for 5 or 6 consecutive weeks had been taken in all subjects. The duration of the FLS of the dominant follicle in anovulatory cycles was defined as the period from the first day of ascending oestradiol curve until the day preceding onset of menses. The mean FLS of the dominant follicle in anovulatory cycles under continuous low-dose progestogen administration was 21.1 ± 4.2 days, independently of the length of the menstrual cycle. The duration of the FLS of the anovulatory dominant follicle appears not to be different from the duration of a normal follicle/corpus luteum unit.

Key words: anovulation/functional life-span of dominant follicle/length of cycle

Introduction

The endocrine profile of women under continuous low-dose progestogen treatment mimics practically every dysfunction of the ovarian cycle, from ovarian rest with no follicle development and low oestradiol, through ovulation with luteal phase defect (Croxatto et al., 1982; Brache et al., 1990; Faúndes et al., 1991b; Shaaban et al., 1993). Clinically, persistently low oestradiol usually corresponds to periods of amenorrhoea, while ovulation, even if with luteal phase defect, coincides with menstrual cycles of normal length (Weiner and Johansson, 1976; Brache and Alvarez-Sanchez, 1990). Clinical cycles of normal length can also be observed among women apparently without ovulation as judged by very low progesterone levels in the second phase, but with an above normal and monophasic rise and fall of oestradiol, usually interpreted as follicular development without ovulation (Faúndes et al., 1991a).

Follicle development without ovulation, and exceptionally with ovulation, can also be observed in menstrual cycles longer than 35 days, during use of Norplant implants (Faúndes et al., 1991a). In the latter case there is a prolonged period of low oestradiol followed by a rise, which appears to be similar to that observed in anovulatory cycles of normal length. We recently called attention to the fact that the time span from the moment oestradiol reached pre-ovulatory peak serum concentrations until menses was not different in ovulatory and anovulatory cycles in women under continuous low-dose progestogen treatment (Faúndes et al., 1991b). This finding was inconsistent with the observation that the enlarged anovulatory follicle may last for several weeks before involuting, possibly leading to an incorrect diagnosis of a permanent ovarian cyst (Peralta et al., 1990; Shaaban et al., 1993).

All the above observations led us to raise the hypothesis that once a dominant follicle is selected and becomes functional, the time period in which it will remain endocrinologically active is predetermined and is independent of ovulation and whether the anatomical structure of a dilated follicle persists.

In order to test this hypothesis, we did a secondary analysis of the endocrine profiles of Norplant implant users who had been studied in our centre during the previous few years. All anovulatory cycles were identified in order to measure the duration of the functional life-span (FLS) of the dominant cycle.

Methods and materials

All oestradiol and progesterone concentrations from serial blood samples taken twice or three times a week during 5–6 consecutive
The calculated means were compared using Student's t-test. Analysis was repeated separating menstrual cycles of normal length (25 through 35 days) from prolonged cycles (36 through 71 days). The mean FLS in prolonged menstrual cycles was only 1.3 days longer than in normal cycles, while the difference in the mean length of the clinical cycle was 18.1 days (Table I). The variability in the total length of the FLS was greater in the long cycles. The three FLS of 30 days or longer corresponded to menstrual cycles of 35, 54 and 58 days. In addition, the two shorter FLS, of 15 days, corresponded to prolonged menstrual cycles of 36 and 71 days.

Results

Mean oestradiol of the 29 cycles followed a curve which was very similar to that already described (Faundes et al., 1991b), with levels compatible with a normal pre-ovulatory peak around day -14 but which continued rising up to about 400 pg/ml on day -8 before next menses (Figure 1). Counting backwards from the first day of the following menses (day 0), the time of the initial rise of the oestradiol varied within a wide range, from day -31 to day -15, but clustered around day -20 ± 2, in 19 of the 29 cycles.

The average FLS was 21.1 days. Though the duration of the rising and declining phases of the FLS were similar (10.9 and 10.2 respectively), there was a greater variance in the latter (Table I). The mean FLS in prolonged menstrual cycles was only 1.3 days longer than in normal cycles, while the difference in the mean length of the clinical cycle was 18.1 days (Table I). The variability in the total length of the FLS was greater in the long cycles. The three FLS of 30 days or longer corresponded to menstrual cycles of 35, 54 and 58 days. In addition, the two shorter FLS, of 15 days, corresponded to prolonged menstrual cycles of 36 and 71 days.

No significant correlation was found between the highest oestradiol level and the length of the FLS of the follicle ($r = 0.3708$).

In the three cycles in which ultrasound was performed, a single dominant follicle developed, parallel to the increase in oestradiol, but rupture did not occur. At day -8 from menses the mean oestradiol levels for these three subjects was 480 pg/ml with a mean follicular diameter of 27.6 mm. From then on, oestradiol levels dropped, reaching a mean level of 61.0 pg/ml on day -1/0 from menses. However, the follicular structure persisted with minimal changes in size, up to the time of menstruation (Figure 2). In one subject the follicle diameter had already diminished more than 20% by day 2 of the next cycle. In the other two a similar reduction was observed after only 2 weeks.

Discussion

The ovarian cycle is regulated by several elements and signaling systems. Of the approximately $7 \times 10^6$ oocytes present in the human fetal ovary, less than 250 000 remain at menarche and less than 500 will eventually ovulate during the 35–36 years of menstruation. In the human, the development of a primordial follicle into a dominant one takes about 10 weeks. Approximately 300 follicles per cycle are recruited initially for growth and development, 30 of which are likely to become gonadotrophin-dependent and enter competition for...
dominance; finally, only one will achieve ovulation (Lunenfeld and Insler, 1993). The number of growing follicles per cycle with an enlarged oocyte and two or more layers of granulosa cells, declines with age from around 50 at age 24–25 to only one at age 50. The decrease is much more rapid after age 39 (Faddy and Gosden, 1995).

It is generally accepted that the serum levels of ovarian steroids, particularly oestradiol and progesterone, are reasonably good indicators of the functional capacity of the follicle and the corpus luteum in a normal ovulatory cycle. Similarly, the absence of a rise in progesterone in the second half of the cycle is accepted as a good indicator of anovulation, and oestradiol levels signal the endocrine functional capacity of the anovulatory follicle.

The FLS of the follicle/corpus luteum unit has been thoroughly studied. There is general agreement that follicle selection is completed around day 7 of a 28 day cycle, meaning that the life-span of the ovulatory follicle lasts about 21 days. However, we did not find any previous results estimating the FLS of the dominant follicle in anovulatory cycles, although there is a general belief that it could be longer, based on the more prolonged duration of the clinical cycle and the persistence of the anovulatory follicle for more than 3 weeks.

In this study of pharmacologically induced anovulatory cycles, we used the oestradiol profile as an indicator of the time when the dominant follicle initiates accelerated synthesis of oestrogen, and used the first day of next menses, preceded by a drop in oestradiol, as an indicator of the end of its capacity for steroidogenesis. Using these two indicators of initiation and end of follicle endocrine function, we calculated what we called the FLS of the dominant follicle, in pharmacologically induced anovulatory cycles.

The results described here indicate that the duration of the FLS of the anovulatory follicle is not different from that of a normal follicle/corpus luteum unit, regardless of the length of the menstrual cycle, at least among women under continuous low-dose progestogen treatment.

These results, obtained under the artificial pharmacological conditions of the study subjects, may be seen to be limited and not necessarily applicable to non-pharmacologically induced anovulation. Even if anovulation in this group of women was not physiologically different from naturally observed anovulation, continuous administration of levonorgestrel may have other consequences. It is possible, for example, that our marker of the end of FLS, the first day of the following menses, may be affected by the direct influence of levonorgestrel on the endometrium, although we have previously shown that bleeding is usually associated with a decline in oestradiol during use of Norplant implants (Faúndes et al., 1991a).

In spite of such limitations, these observations suggest that, at least during continuous low-dose progestogen treatment, the length of cycle is relatively fixed once the dominant follicle selection has been completed, and that most of the variation in menstrual cycle length reflects differences in duration of follicle recruitment and selection.

The apparent contradiction between the persistence of a dilated follicle and a drop in serum oestradiol to levels similar to those observed after luteal atresia appears to indicate that the functional capacity of these large follicles is exhausted long before their macroscopic anatomical structure starts to decline. The drop in oestradiol levels at the expected time, in spite of the persistence of the follicle, suggests that the granulosa cells of the dominant follicle have a limited life-span, after which they lose the capacity to synthesize oestradiol, independent of the ultrasonographic anatomical appearance of the follicle.

Further studies, ideally on naturally occurring oligomenorrheic and eumenorrheic anovulatory cycles, are necessary to confirm whether these observations also pertain to women who are not under the same pharmacological influences.

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