Hormonal Profile after Removal of the Dominant Follicle and Corpus Luteum in Women

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Abstract

The present experiments were performed to elucidate the mechanism of the selection and maturation of a dominant follicle in women. Eight normally menstruating women undergoing myomectomy or tubal surgery volunteered for the present study. In 3 patients who were operated on Day 9-11, a visual dominant follicle was removed. The other 5 patients underwent the removal of a newly developing corpus luteum on Day 15-21. After taking 3 or 4 preoperative blood samples in the morning after their hospitalization, blood was obtained at 3 or 6 h intervals for the first 36-45 h and at 1-3 day intervals thereafter for 21-34 days. Serum FSH, LH, estradiol and progesterone were measured by radioimmunoassay.

Follicleectomy was followed by a sudden drop in estradiol and a minor increase in progesterone. FSH increased for a few days and then declined. There was a drastic, but short-term increase in LH following follicleectomy which was performed before a preovulatory gonadotropin surge. A LH surge occurred 10.7 ± 1.2 days (mean ± S.E.) after follicular ablation followed by a luteal phase.

In contrast, there was no remarkable LH release in 4 out of 5 patients who underwent luteectomy. A slightly higher level of FSH was sustained for 2-7 postoperative days. "Luteal phase" rises in estradiol and progesterone terminated promptly following luteectomy. A LH surge was observed 14.2 ± 1.7 days after surgery followed by a luteal phase. After either type of operation, a sustained increase in FSH was followed by a gradual increase in estradiol which preceded a gonadotropin surge. These hormonal sequences resemble those seen in the normal follicular phase.

The present data demonstrated that follicleectomy and luteectomy bring on some characteristic hormonal changes which may exert stimulatory or suppressive effects on the selection and maturation of a dominant follicle after the removal of a main ovarian cyclic structure culminating in ovulation at a certain interval.

It is well known that in normal women there is an early "follicular phase" rise in circulatory FSH which is probably necessary for selection and maturation of a dominant follicle (Ross et al., 1970; Araki, 1979). Our earlier data, also indicated that increased secretion of FSH sustained for several days may be a key event in the recruitment of follicular growth and subsequent ovulation following ovarian wedge resection in patients with polycystic ovary syndrome (Araki et al., 1982).

On the contrary, some experimental results support the theory that an inhibitory effect on folliculogenesis is exerted via intraovarian mechanisms in the presence of a dominant follicle (diZerega and Hodgen, 1980). Based on the hormonal analysis in

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a sequence of follicular maturation and subsequent ovulation following the removal of a dominant follicle or corpus luteum in monkeys, Goodman and his co-workers (1977) insisted that local factors rather than gonadotropins act to influence the development of a dominant follicle. Resko et al. (1974) reported that exogenous progesterone administered after spontaneous luteolysis delayed the next ovulation in monkeys even in the absence of FSH suppression. Since the intervals from follicleectomy and luteectomy to the subsequent ovulation were similar in women, Nilsson and others (1982) speculated that a preovulatory gonadotropin surge may not have any discernible effects on new follicle growth.

**Materials and Methods**

Eight normally menstruating women undergoing myomectomy or tubal surgery volunteered for the present study. Judging from the basal body temperature curves of the last 3 consecutive cycles, the lengths of the follicular phases and the luteal phases were 12-16 days and 11-14 days, respectively. The menstrual period lengths were 26-30 days. Surgery was performed in the late follicular phase or in the early luteal phase. On visual inspection of both ovaries, the largest follicle or a newly developing corpus luteum was removed by incising from surrounding tissue and the incision was sutured with 3-0 catgut.

In 3 patients (#1, 2 and 3) who were operated on Day 9-11, a dominant follicle with hyperemic changes on its surface was removed. The remaining 5 patients (#4, 5, 6, 7 and 8) underwent the removal of a newly developing corpus luteum on Day 15-21.

Three or four preoperative daily blood samples were obtained in the morning after their hospitalization. An intravenous cannula with a three-way stopcock was inserted into the brachial vein shortly prior to the operation for frequent blood collections. Postoperative blood samples were obtained at 3 or 6 h intervals for the first 36-45 h and at 1-3 day intervals thereafter until the next menses following the first ovulation which was confirmed by daily postoperative hormonal patterns.

Serum FSH, LH, estradiol and progesterone were measured by radioimmunoassay of which detailed procedures were reported previously (Araki et al., 1978 a, b).

**Results**

Since hormonal levels of following the operation varied from case to case, each set of individual results was illustrated in separate figures.

**Hormonal changes following follicleectomy**

Case 1: Follicleectomy was performed on the 9th day of the cycle. Hormonal patterns for 3 preoperative days and for the first 45 h after the operation are illustrated in Fig. 1a. The preoperative level of LH was 13-20 mIU/ml. It rose remarkably to 228 mIU/ml 6 h after the operation followed by a steep decrease by 12 h and thereafter declined gradually. The preoperative level of FSH was low (5-13 mIU/ml). It started to increase shortly after follicleectomy and the higher level of FSH (23-43 mIU/ml) was sustained from 6 to 45 h after the operation. The concentration of estradiol 3 h before the operation was 145 pg/ml and this level decreased for the first 9 h. The lower level of this steroid was maintained until the end of frequent samplings. The preoperative progesterone level was low (0.3-0.6 ng/ml). However, it increased markedly to 4.4 ng/ml within the first 6 h followed by a rapid decrease.

Daily hormonal patterns are illustrated in Fig. 1b. FSH increased after surgery reaching a peak level around 40 mIU/ml on the 2nd and 3rd days. Thereafter, it decreased gradually. A minor increase in LH was observed for the first 2 postoperative days. A preovulatory gonadotropin surge was seen on the 10th day following an increase in estradiol one day previously. The mid-cycle hormonal changes were followed by a remarkable increase in progesterone which was comparable to that seen in the normal luteal phase.

Case 2: Follicleectomy was performed
Fig. 1a and b: Serial hormonal changes before and after follicleectomy performed on Day 9 in case #1. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 45 h and at 1-3 day intervals for 23 postoperative days, respectively.
on the 10th day for the cycle. Hormonal patterns for 3 preoperative day and for the first 42 h after the operation are illustrated in Fig. 2a. The preoperative level of LH (10–13 mIU/ml) increased sharply to a peak of 89 mIU/ml at the 12th h and thereafter declined rapidly. FSH increased gradually during the 42 h period of frequent samplings. The concentration of estradiol was 170 pg/ml just prior to follicleectomy. It declined rapidly after surgery. The lower level of the steroid was maintained between 6 and 42 h postoperatively. The preoperative level of progesterone was low (0.4–0.7 ng/ml). It rose to a higher level (2.4 ng/ml) at the 12th h followed by a rapid drop.

Daily hormonal patterns are illustrated in Fig. 2b. The preoperative level of FSH was 5–8 mIU/ml. It increased approximately 3–4 fold on the 1st and 2nd postoperative days and then declined gradually. A gonadotropin surge occurred on the 9th postoperative day after an increase in estradiol one day previously. A remarkable increase in progesterone appeared after the hormonal changes that usually happened in the normal mid-cycle.

Case 3: Blood samples were obtained for 32 days after the operation. Hormonal patterns for the 3 preoperative days and the first 45 h after follicleectomy are illustrated in Fig. 3a. LH concentrations in the blood samples obtained shortly before the operation were markedly elevated (118–190 mIU/ml). It decreased gradually with some fluctuations reaching a basal level 21 h later. FSH level was also high (32 mIU/ml) at the beginning of the operation. The elevated level was maintained until the end of frequent samplings. The concentration of estradiol was 370 pg/ml shortly prior to follicleectomy, but this level promptly dropped by 12 h after surgery. The lower level of the steroid (50–100 pg/ml) was maintained thereafter. There was a slight elevation in the progesterone level (1.8 ng/ml) at the beginning of the operation. It increased slightly for 9 h and then promptly dropped to the basal level.

Daily hormonal patterns are illustrated in Fig. 3b. A higher level of FSH was seen on the day of operation and on the next day (32 and 30 mIU/ml). Thereafter, FSH declined and remained at lower levels (8–14 mIU/ml) for 3 to 12 days. A preoperative increase in LH was followed by a sudden decrease on the 1st day after the operation. A low level of LH continued until the postoperative day. A gonadotropin surge occurred on the 13th day concomitantly with an increase in estradiol on the same day. An increase in progesterone was seen after the characteristic hormonal changes which were similar to those observed at the mid-cycle of the normal menstrual cycle.

Hormonal changes following luteectomy
Case 4: A spontaneous gonadotropin surge was observed 2 days before laparotomy in which a fresh corpus luteum was enucleated from the ovary. Blood samples were obtained for 21 days after the operation. Hormonal patterns for 3 preoperative days and for the first 36 h of frequent samplings are shown in Fig. 4a. There was no discernible change in LH until 36 h. On the contrary, FSH started to increase at the 12th h reaching a level approximately 4 times higher than that seen shortly before the operation. Then it declined gradually.

Estradiol concentrations were 250 and 245 pg/ml 72 and 48 h before surgery, respectively. At the time of the operation it declined to a basal level and thereafter remained at a low level until 36 h later. In contrast, the progesterone level was elevated (4.4 ng/ml) at the beginning of the operation. It declined and reached the basal level (0.8 ng/ml) by 12 h postoperatively.
Fig. 2a and b; Serial hormonal changes before and after follicleectomy performed on Day 10 in case #2. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 42 h and at 1-3 day intervals for 25 postoperative days, respectively.
Fig. 3a and b; Serial hormonal changes before and after follicleectomy performed on Day 11 in case #3. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 45 h and at 1-3 day intervals for 32 postoperative days, respectively.
Fig. 4a and b: Serial hormonal changes before and after luteectomy performed on Day 15 in case 24. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 36h and at 1-2 day intervals for 21 postoperative days, respectively.
Daily hormonal patterns are shown in Fig. 4b. Preoperative hormonal patterns including a gonadotropin surge and a preceding increase in estradiol indicates that the operation was performed at the early stage of a luteal phase. There was a minor increase in FSH on the 1st and 2nd days after the operation. It returned to a lower level on the 3rd day. Postoperative LH levels fluctuated around the basal level until the 10th day at which time a preovulatory gonadotropin surge was observed after a preceding increase in estradiol. These hormonal changes characteristic of the mid-cycle were followed by a remarkable increase in progesterone.

Case 5: Laparotomy was carried out on the 17th day of the cycle. A newly developing corpus luteum with blood clots was removed from the ovary. Blood samples were collected for 27 days postoperatively. Hormonal patterns for 3 preoperative days and for the first 36 h are shown in Fig. 5a. The preoperative concentration of LH and FSH were 11–20 mIU/ml and 10–14 mIU/ml, respectively. FSH levels started to rise at the 18th h and then stayed at a slightly higher level (15–22 mIU/ml) during the latter period of frequent samplings. There were no apparent changes in LH until 39 h later. The preoperative level of progesterone showed a gradual rise. Its concentration on the day of surgery was 7.8 ng/ml which was comparable to that seen in an early luteal phase. The progesterone level decreased after luteectomy reaching the basal level (1.0 ng/ml) 18 h after surgery. The preoperative estradiol level ranged between 100 and 175 pg/ml. There was only a minor decrease postoperatively.

The daily hormonal patterns are shown in Fig. 6b. FSH increased 2 fold on the 1st day, but returned to the preoperative level on the 3rd day. LH showed only minor fluctuations until the 18th postoperative day at which time a mid-cycle gonadotropin surge occurred. The preoperative higher level of progesterone declined to the basal level on the next day after luteectomy. A remarkable increase in estradiol was observed on the same day as a gonadotropin surge which was followed by an increase in progesterone.

Case 7: A fresh corpus luteum was observed by laparotomy which was carried out on the 19th day of the cycle. The preoperative concentrations of progesterone were 13–16 ng/ml which was comparable
Fig. 5a and b: Serial hormonal changes before and after luteectomy performed on Day 17 in case #5. Fig. a and b show hormonal levels in the blood samples obtained frequently for the 36h and at 1-3 day intervals for 27 postoperative days, respectively.
Fig. 6a and b; Serial hormonal changes before and after luteectomy performed on Day 18 in case #6. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 39 h and at 1-3 day intervals for 34 postoperative days, respectively.
Fig. 7a and b: Serial hormonal changes before and after luteectomy performed on Day 19 in case 7. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 39 h and at 1-3 day intervals for 34 postoperative days, respectively.
Fig. 8a and b; Serial hormonal changes before and after luteectomy performed on Day 21 in case #8. Fig. a and b show hormonal levels in the blood samples obtained frequently for the first 39h and then daily for 30 postoperative days, respectively.
Blood samples were obtained for 34 days following the luteectomy. The hormonal patterns for 3 preoperative days and first 38 h after luteectomy are shown in Fig. 7a. The preoperative levels of LH and FSH were 7–15 mIU/ml and 7–8 mIU/ml, respectively. Postoperative levels of FSH rose gradually reaching a higher level (20 mIU/ml) 33 h later. LH increased to a peak level of 60 mIU/ml at the 6th h. Thereafter it declined to the basal level rapidly and stayed at lower levels with some fluctuations during the rest period of the frequent samplings. The concentration of estradiol which was 300 pg/ml at the beginning of the operation declined rapidly after luteectomy. The preoperative high level of progesterone also dropped steeply to the basal level which was similar to that seen in a normal follicular phase.

Daily hormonal patterns are shown in Fig. 7b. FSH increased twice on the day after the operation and then stayed at slightly higher levels than the preoperative level. There was no discernible change in LH after luteectomy until a gonadotropin surge. LH and FSH were markedly increased on the 18th postoperative day with a concomitant elevation of estradiol. These preovulatory hormonal patterns were followed by a luteal phase which was proved with a significant increase in progesterone.

Case 8: A fresh corpus luteum was removed on the 21st day of the cycle. Hormonal patterns for 3 preoperative days and for 39 h after the operation are shown in Fig. 8a. There were no apparent changes in LH until the end of frequent samplings. FSH showed only a minor increase following surgery. The preoperative level of progesterone was 10–14 ng/ml. It decreased gradually reaching a nadir within 24 h after the operation. Estradiol, also declined rapidly after surgery.

Daily hormonal changes until the 30th day after the operation are shown in Fig. 8b. The postoperative level of FSH rose gradually reaching approximately twice as high as the level on the 5th day. It declined to close to the control level on the 7th day. LH remained around the preoperative concentration until the 14th day at which time a characteristic preovulatory gonadotropin surge occurred following an increase in estradiol for several days. A luteal phase with a remarkable elevation of progesterone followed the gonadotropin surge.

Discussion

In our preliminary studies we found that ovulation occurred approximately 2 weeks after follicleectomy or luteectomy in normally cycling women. The present experiments were designed to elucidate the mechanisms of selection and maturation of a dominant follicle following the removal of a main cyclic structure of the ovary. In order to avoid the removal of a false dominant follicle or corpus luteum the operations were performed on subjects who had an apparent singular dominant follicle with hyperemic changes or a newly developing corpus luteum. In addition, follicleectomy was carried out in patients with high levels of estradiol which were comparable to those seen in a normal preovulatory phase. A rise in progesterone as a sign of a luteal phase was recognized in all cases with luteectomy.

In the present study the development of a new dominant follicle and a subsequent ovulation occurred at a certain interval after either operation in accordance with the results reported by Nilsson and others (1982). The intervals between the operation and a subsequent preovulatory LH surge were 10.7±1.2 days (mean±S.E.) and 14.2±1.7 days (mean±S.E.), respectively. Both of them are considered to be comparable with the length of a normal
follicular phase.

Nilsson and his co-workers (1982) reported that the length of time required for the recruitment of follicular development and subsequent ovulation following surgery was similar in both follicleectomy and luteectomy. However, no exact identification of a gonadotropin surge was reported by them. In monkeys the period required for initiation of a gonadotropin surge after follicleectomy or luteectomy was approximately 12 to 14 days which was close to the length of a normal follicular phase (Goodman et al., 1977).

Based on the data obtained from the experiments in women (Nilssen et al., 1982) and in monkeys (Goodman et al., 1977, 1979a and 1979b), it was suggested that the difference in the hormonal environment around the time of surgery may not result in an apparent influence on postoperative follicular development and subsequent ovulation. Since no appreciable changes in gonadotropins were observed following the removal of a main cyclic structure of the ovary in monkeys (Goodman et al., 1977), they claimed that local factors rather than gonadotropins may influence the recruitment of follicular growth. Although their observation does not coincide with our results, the disagreement may be due to the difference in species or surgical procedures. Goodman and Hodgen (1979a, b) reported that the differences in ovarian manipulation and experimental animals affected postoperative changes in circulating gonadotropin levels.

The present data obtained by a precise hormonal analysis in frequently collected blood samples demonstrated that some characteristic gonadotropin changes in addition to significant changes in ovarian steroids occurred following the operation. The postoperative hormonal changes were different between the 2 types of the operations.

For estradiol there was a rapid decline in the steroid from its elevated level in a preovulatory or luteal phase. A rise in estradiol observed in the periovulatory phase seemed to represent mainly a secretion from the single dominant follicle or from the corpus luteum. Since progesterone decreased to the basal level rapidly after surgery, most of this steroid appeared to be secreted from the corpus luteum. These observations on ovarian steroids are consistent with those reported by Aedo et al. (1980a, b) who found a significant drop in circulating steroids after the enucleation of the largest follicle or corpus luteum in women.

It is reasonable to consider that the significant increase in FSH observed after the operation might play a role in the development of a new dominant follicle through a similar mechanism which operates in a normal menstrual cycle (Ross et al., 1970). After either type of operation, a sustained increase in FSH was followed by a gradual increase in estradiol which preceded a gonadotropin surge. These hormonal sequences resemble those seen in the normal follicular phase. Variations in the duration and magnitude of FSH increases which varied from case to case might depend on the maturational degree of the follicle which develops to a leading follicle.

A short-term but remarkable increase in LH was found shortly after the removal of a preovulatory follicle, whereas such a change in LH was not recognized after luteal ablation. In a previous study, we reported that withdrawal of estradiol from general circulation provokes a release of LH (Araki et al., 1978a) and that LH levels rise following the administration of progesterone in women pretreated with estradiol (Araki et al., 1978b). A short-term but significant increase in LH after follicleectomy may be elicited by the action of slightly increased in progesterone in addition to the withdrawal of estradiol. The mechanism of the postoperative increase
in progesterone remains unknown. However, surgical manipulation of the ovaries may enhance the release of the steroid by squeezing and disrupting the ovarian tissue (Araki et al., 1982).

Since HCG treatment in an early follicular phase disturbs the process of follicular maturation resulting in the delay of ovulation (Tamada and Matsumoto, 1969; Friedlich et al., 1975), an increase in LH after follicleectomy may impair a group of partially matured follicles. This hypothesis can explain the reason why no follicle serves as a surrogate for the removed dominant follicle. A mid-cycle LH surge preceding to luteectomy may elicit a similar effect on a cohort of growing follicles. These possible effects of LH on folliculogenesis could account for the fact that a similar time length is required for the maturation of a dominant follicle and subsequent ovulation following either follicleectomy or luteectomy.

Minor changes in circulatory gonadotropins seem to exert profound effects on follicular growth in the normal menstrual cycle (Ross et al., 1970). Even if basal levels of gonadotropins show no discernible changes, there may be some changes in the magnitude and frequency of the episodic gonadotropin release (Yen et al., 1972; Santen and Bardin, 1973). In the present study, frequent measurements of FSH and LH over the prolonged period after removal of the follicle or the corpus luteum made it possible to find definite hormonal changes which probably account for the recruitment of follicular growth. Further in-depth studies will be necessary to define the physiological role of gonadotropins and intraovarian factors in the selection and maturation of a dominant follicle.

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References


